

HEPATOCELLULAR CARCINOMA

Editors: Shuyou Peng, Ghassan K. Abou-Alfa, Patrick Pessaux



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Hepatocellular carcinoma: a new century and a new optimism

It was not long ago that the incidence rate of hepatocellular carcinoma (HCC) approximated the mortality rate. Due to the causative relationship between chronic viral infection, chronic inflammation, hepatotoxins, and hepatocellular carcinoma, this cancer is responsible for nearly one million deaths yearly worldwide. The last years have seen tremendous progress in diagnosis and treatment of this common cancer. The current book edited by Professor Xiujun Cai comprehensively summarizes the current understanding of this disease within the context of patient treatment and outcome.

The broad impact of this cancer on the entire world is highlighted in Section 2: “*Current Status of HCC in Different Countries and Regions*”. It is not just a cancer ravishing Asia, its impact in the Middle East, Europe, and Americas is well presented. The world context of this disease is appropriately accompanied by a discussion of the evolution and current status of the languages used by clinicians and researchers to communicate. The language of “staging systems” and “clinical pathways of care” are presented in Chapters in Section 1. This is truly an intersection of the fields of hepatology, infectious disease, and oncology, where surgeons, interventional radiologists, radiation oncologists, and medical oncologists now stand. The common vocabulary of these fields as well as the scientific concepts encompassing cellular metabolism, cellular proliferation, infectious diseases, and homeostatic pathways are well articulated in this book.

Liver transplantation clearly would be an optimal therapy, treating simultaneously the cancer and the underlying cause of infection and inflammation in the diseased liver. The limited availability of organs for transplantation and the cost of maintaining transplantation programs have limited the use of this wonderful technology to only a small proportion of patients. In Asia, where cadaveric organs are particularly hard to come by, most procedures in liver transplantation involve grafts from living donors. In China, where a national policy limiting the number of offsprings has been in place, living-related transplantation means that two-thirds of a nuclear family will be undergoing surgery, posing another deterrent to transplantation.

Over the past decades, the greatest progress involves improvements in techniques of surgical resection that now allow for safe removal of cancers from livers using partial hepatectomy (Section 5). Such surgeries have clearly proven to be potentially curative. Needle based thermal ablations now allow for effective cancer killing, and particularly durable killing of small tumors (Section 6). These needle-based therapies afford safe treatments in patients with advanced cirrhosis by minimizing amount of liver parenchyma resected or damaged. For small tumors, ablation is also proving to be as potentially curative and equivalent cancer treatment as partial hepatectomy, with the advantage of less morbidity (1). Finally, minimally invasive liver resections now also allows less morbid surgery for patients, allowing rapid recovery and less ascitic leak and complications (Section 5) (Leung and Fong, p225) (Herman and Coelho, p222) (2). Overall, treatment using partial hepatectomy, thermal ablation, and minimally invasive resections including robotic surgery allow for increasingly less morbid therapies that extend life and provide potential cure.

Great progress is being made in the understanding of the pathogenesis of HCC, giving promise to better markers for early diagnosis (Song *et al.*, p193), and in time, better systemic therapies. Diagnosis is certainly improving rapidly. Due to increasingly sensitive markers, and increasingly higher resolution of scanning techniques, smaller and smaller tumors are being detected for effective killing by percutaneous ablative (Section 6) and transcutaneous radiation techniques (Section 7). Equally impressive is the rate of progress in treatment of liver inflammation and infection. Treatment of viral hepatitis can now cure hepatitis C (3), and eliminate viremia and inflammation from hepatitis B. Treatment of liver fluke and public education to decrease consumption of the raw fish leading to this parasitic infection should decrease another cause of liver cancer (4).

In summary, progress in public health and infectious disease is decreasing the incidence of HCC. Transplantation remains a most attractive therapy for those patients with HCC and moderate or advanced cirrhosis. Partial hepatectomy and ablative therapies provide for life prolonging and potential curative therapies for the majority of treatable patients. These are also now

being increasingly less invasive to optimize patient outcome. It is certainly a new day in the treatment of this disease. The world community of surgeons, oncologists, and scientists has combined forces to provide for “More Cures, Less Invasive”.

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Hepatocellular carcinoma (HCC), which accounts for more than 90% of all primary liver cancers, affects more than 800,000 individuals annually and stands as the second cause of cancer-related death, worldwide. Unique of this typically inflammatory tumor, is its development in the context of readily identifiable environmental risk factors, like viral hepatitis B and C, alcohol and obesity, which theoretically would allow this lethal cancer to be curbed by strategies of primary and secondary prevention. This notwithstanding, HCC is on the rise in many geographical regions, often reflecting epidemics of viral hepatitis associated to either risk behaviors or poor sanitation, whereas, due to a lack of awareness, most patients are still detected with an advanced cancer disease that effects delivery of potentially curative therapies. Fighting against liver cancer, therefore, relies on an integrated approach that spans from the pillar represented by the implementation of strategies of primary prevention to the development of user friendly, effective drug regimens for patients with advanced HCC. In the last decade, many efforts have met with little success in developing therapies tailored upon the genetic profile and molecular subclass of the tumor, not to speak about the many failures to identify performant biomarkers for predicting treatment response. While further research is deemed necessary for similar scientific breakthroughs to materialize, other unmet medical needs in HCC research have emerged that challenge the community of caregivers, one above all how to scale up patient access to early diagnosis, which stands as the only pragmatic approach to cure HCC and currently relies on hospital-based programs of screening with abdominal ultrasound. Though, in an era of shortened organ donations, a cure from HCC caused by hepatitis B or C can also be attained with non-transplant options like open and laparoscopic hepatic resection and percutaneous local ablation, owing to the possibility of preventing liver decompensation and tumor recurrence with interferon-free antiviral therapy. On the other hand, in the liver transplant setting, direct antiviral agents have gained popularity, having cancelled recurrent hepatitis C that was responsible in one patient every three for shortened graft and patient survival whereas in many patients it was an hurdle for re-transplantation ,too. As we move away from the ages when HCC was considered an inexorably fatal cancer, I am sure that the reading of this textbook will help appreciating the outstanding leaps forward that have been made by liver oncology with the contribution of all the authors listed here.

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Hepatocellular carcinoma (HCC) is one of the most common malignancies. Liver cirrhosis and long-term infection of hepatitis B are associated with the HCC in the majority of Chinese patients. The treatment could be a little different from patients in other country, but the surgical rules are similar. Liver resections remove tumors together while preserving enough liver remnant for normal metabolic function offering the best prognosis for long-term survival. Surgical techniques for HCC have been improved in the recent thirty years with innovations in optics, computer science, material science etc. laparoscopic liver resection emerged in 1990s which decreases the surgical trauma and postoperative pains and CT-based 3D reconstruction improves the accuracy of managing intrahepatic vessels. New dissection instruments and energy devices were developed and facilitated liver resection with meticulous dissection or/and effective coagulation. Liver failure is still a troublesome complication in major liver resections. Normally, the estimated future liver remnant (FLR) less than 40%/30% is the contra-indication for patients with/without liver cirrhosis. In 2012, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) reported. It could trigger fast liver regeneration after the first-stage operation and the indication for liver resection is extended to patients with less FLR. According to recent reports, ALPPS was performed successfully even on patients who had only one segment preserved. However, ALPPS is very traumatic and risky with two raw-surfaces of transected liver left in the abdominal cavity after the first stage-operation, resulting in higher incidence of bile leak and mortality. It would be much better if transection of the liver can be avoided in the first-staged, while the same effect of future liver remnant rapid hypertrophy can be achieved. This concept has been realized in three different ways, namely, Round-the-liver ligation to replace parenchymal transaction (1); Percutaneous Ablation and Liver Partition Planned hepatectomy (PALPP) (2); and Terminal branches portal vein Embolization Liver Partition Planned hepatectomy (TELPP) (3). Furthermore, only one operation is required when PALPP or TELPP is performed.

In addition to the conventional potentially curative treatments, such as liver resection and liver transplantation, some non-surgical treatments have been applied to improve the effect. Image-guided percutaneous radiofrequency ablation, microwave ablation and cryotherapy could improve therapeutic effects in selected patients with or without operations. Transhepatic Arterial chemotherapy and embolization (TACE) have been accepted in HCC treatment for patients who are not amenable for surgery or as a bridging or downstaging method for the future potentially curative treatment. Recently, systemic therapies, including molecular target therapy, systemic chemotherapy and immunotherapy, are adopted as an important palliative method. Progress has been made for the past few decades, Multidisciplinary strategy is required for each patients. Greater progress is expected. International co-operation would be of paramount importance in conquering this drastic disease.

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Hepatocellular carcinoma, the differences that join us

Hepatocellular carcinoma (HCC) is a very complex disease or multiple dimensions. Its particularities include the need for multiple disciplines in the care and management of patients diagnosed with HCC, as well as the global differences that relate to etiology and ethnicity. The effort placed in this volume addresses those two dimensions at length and more importantly bring in ways and approaches that help learn from those differences and solve more pieces to the puzzle of comprehensive understanding of HCC. We aimed at ensuring that different practices and approaches to therapy form all over the world are well illustrated in the second section on “*Current Status of Hepatocellular Carcinoma in Different Countries and Regions*”. We then drew from those observations collective lessons that ranged from different practices and approaches to local therapies, to differing median survival based on etiology and ethnicity. A robust section on the molecular biology and pathology of HCC helped add some explanations to those differences and bridge the gaps of our knowledge of HCC.

This global perspective is also in part an effort to enhance international collaboration with the hope this may also help in streamlining the management of the disease where applicable and hopefully help in more effective accrual to clinical trials and discovery of novel therapies that would help fill the unfortunately still broad unmet needs of patients with HCC for improved outcome and increased curability rate. This comprehensive effort is a special tribute to the solidarity among all investigators of the HCC community from China and worldwide.

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Hepatocellular carcinoma: How could we imagine the future research?

Hepatocellular carcinoma (HCC) and advanced liver disease comprise a major public health burden for which we have only unsatisfactory treatment options. According to the European Association for the Study of the Liver (EASL), the prevalence of liver diseases is about 6% in the Europe (29 million individuals) and the associated mortality rate was estimated at 14.3 per 100,000 (70,000 deaths/year) (1). HCC is the third most common cause of cancer-related death and the leading cause of death among cirrhotic patients (2). According to the EASL, the HCC incidence and mortality rates were of 65,000 and 60,240 cases in Europe, respectively (1). Given the growing incidence of HCC, the economic burden will significantly increase in Western populations during the next decades (3). Treatment options for liver steatosis, fibrosis, cirrhosis and HCC are unsatisfactory. Furthermore, there are no efficient chemopreventive strategies to limit HCC development once cirrhosis is established. Although early-stage tumors can be curatively treated using surgical approaches, they are often undiagnosed and treatment options for advanced HCC are unsatisfactory. Although the multikinase inhibitor sorafenib improves a survival benefit for patients with locally advanced or metastatic HCC, adverse effects and moderate efficacy limit its use in patients with advanced liver disease (4). Thus, a therapy that is well tolerated, cost-effective, and poses an acceptable risk-to-benefit ratio is missing.

Virus-induced chronic hepatitis is a leading cause of HCC in France, Europe, and in Asia. In the developed Western world, only 10-15% of cases can be attributed to hepatitis B virus (HBV) infection, while chronic hepatitis C appears to be the major risk factor for HCC (up to 70% of cases) in Europe (1). Importantly, there are common alterations of pathways that likely account for viral and non-viral pathogenesis regardless of their etiology (5,6). Unsatisfactory therapeutic options are due to several hurdles:

- Mechanisms: pathogenesis only poorly understood
- Targets: limited number, clinical validation pending
- Models: limited small animal model only partially addressing pathogenesis
- Genetics: HCC is highly heterogenous
- Clinical: Advanced liver disease is a key determinant for management and survival

Given these hurdles there is a need for better understanding of pathogenesis of HCC, discovery of novel targets and better animal models for study of hepatocarcinogenesis and preclinical evaluation of therapeutic approaches. Further given the genetic heterogeneity of HCC and their origin in advanced liver disease and cirrhosis, it is of paramount interest to develop individualized treatment approaches and clinical care needs to integrate management of advanced liver disease using surgical and medical approaches

Addressing these unmet medical needs and limited knowledge, four main research axes should be developed in the future:

- Understand pathogenesis and discover targets using HCV-induced HCC as a model
- Develop relevant animal models for pathogenesis and preclinical therapeutic studies
- Develop strategies for individualized treatment using functionalized nanovectors
- Optimize clinical management of HCC using advanced imaging and modeling

In the future, we need to conduct interdisciplinary research projects with high synergistic expertise by using innovative and state-of-the art approaches in molecular and clinical hepatology, surgery, virology, cell biology, chemistry, immunology, functional genomics, genetics, biomaterials, nanovectors, and animal models, to obtain a strong medical relevance with a high likelihood to change the outcome of disease.

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Hepatocellular carcinoma: the way done and what remains to be done

Hepatocellular carcinoma (HCC) is today one of the most common cancers in the world. There is solid evidence that chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse, workplace or environmental exposure to toxic substances, obesity, liver steatosis, non-alcoholic steatohepatitis (NASH) and liver cirrhosis are risk factors for the development of HCC. In particular, the liver cirrhosis represents an independent risk factor for HCC whatever the cause it has been determined (1-6).

Today a lot of knowledge has been acquired on epidemiology, on etiological factors and molecular mechanisms that contribute to the development of HCC, but it will be required that the research community has more ambitious targets in terms of prevention, early diagnosis, molecular typing of various types of HCC. In fact, today it is unthinkable to consider the HCC as one entity; often in a patient with multifocal HCC, single nodule phenotypic features differ from those of the other nodules and it is also possible that the single nodule has some cell groups with cancerous features different from one to another. All this shows that all HCC are not equal and also in the same subject HCC may present different characteristics. Phenotypic diversity is probably a different flaw or molecular aberration that affects its speed of growth, invasiveness and probably response to therapy (7).

Some HCC staging systems have been validated such as the Barcelona Clinic Liver Cancer (BCLC) staging system which predict patient survival and/or define her prognosis and also it helps to identify the best treatment strategy for each patient; and the Milan criteria that select patients with HCC who may undergo a liver transplant. Perfectible in light of new knowledge, such systems have represented a real chance to define as correctly as possible the stage of the tumor disease, and they have permitted the best treatment approach for the patient (8,9).

The study of molecular alterations in HCC has made possible to identify many signaling pathways, but the failure of many molecular therapies in phase II and III of clinical studies shows that many others will have to discover to get the most effective alternative therapist targets and systemic treatment of advanced HCC (C) according to BCLC staging system, probably these treatments will cover the combined use of different drugs target (targeted therapy) (7,8).

The relationship between the immune system and the development of HCC have been recently highlighted and it seems to get more and more important the role of the microenvironment as a factor that encourages tumor growth and its lack of recognition by the immune system (10,11).

It was found that some cancer biomarkers used in the diagnosis of HCC, such as des-gamma carboxy prothrombina (DPC), the glypican-3 (GPC3) play an important role in the growth and invasion ability of HCC, playing the role of growth factors with apocrine and eccrine and capacity factors that promote tumor angiogenesis. In fact, the GPC3 is able to amplify the Wnt/ Yap signaling and the DPC to activate the kinase insert domain receptor-DPC-phospholipaseC- γ -MAPK pathway, and the Ras/Raf/MEK/ERK signaling and Ras/PI3K/Akt/mTOR pathway cascades (12-19). Furthermore, recent researches indicate that DCP antagonizes the inhibitory effects of Sorafenib on HCC by the activation of the Ras/Raf/MEK/ERK and PI3K/Akt/mTOR/Ras signaling pathways (20).

Today these findings allow to classify the tumor based on the biomarker that it produces, and hopefully in the very next future, the antibodies and drugs can be synthesized to block the effects that biomarkers have on growth and on tumor invasion ability and resistance to therapy.

Recently the article of Reig M. and coauthors in Journal of Hepatology 2016 October (21) has generated some worries in the scientific community. The authors show an “unexpected” rate in early recurrence of HCC in subject with HCV infections with HCC history treated with complete respond and absence of HCC nodules from the beginning of anti-HCV treatment with Direct-Acting Antiviral Agents (DAAS). Reig *et al.* report an HCC recurrence rate of 27.6% after a median follow up of 5.7 months (range 0.4 -14.6) from the beginning of treatment with DAAs and conclude by stating that cancer recurrence coincides with the clearance of HCV.

The conclusions by Reig M. and coauthors (21) have been evaluated and commented by Cammà C. *et al.* (22). They

Indicate some problems that we share: the small sample size studied, the wide confidence interval (CI) of 95% which is obviously expected due to the small sample size of the study, having reported the crude rate rather than the entire Kaplan-Meier Curve (K-M), the different clinical features of patients (HCC single *vs.* multinodular), the different treatments of HCC (resection, ablation and TACE), the wide interval of time between the treatment of HCC and the initiation of therapy with DAAs (median 11.2 months; range 1.2-87.7 months). Cammà C. *et al.* (22) correctly consider the start of K-M curve the moment of HCC treatment not the beginning of the therapy, it determines from 6 to 12 months of recurrence rate respectively from 7% and 13% not taking into consideration the crude data of 27,6%.

Moreover, other considerations have been moved by Torres HA *et al.* (23) and especially the fact that some patients have had a HCC recurrence 2 weeks after the start of a therapy with DAAs; it is an inexplicable case with the possible effect that DAAs would have had on the host immune respond, as supposed by Reig M and coauthors.

It is possible, however, that the HCC was already present and not still diagnosable at the beginning of therapy and its development was reasonably foreseeable in subjects already treated for HCC and where HCC little eradication could affect cancer recurrence.

Future studies on large series will give a definitive answer about the effect that the DAAs have on the development of HCC and definitely a real prevention of HCC can be achieved from advocated use of DAAs in mild liver disease patients without cirrhosis (24).

In conclusion, with the evidence we have, we may say that the defeat of HCC consists in the elimination of risk factors, early diagnosis and the inevitable necessity of classification of HCC based on molecular alterations; and therefore, in the near future the possibility of using target drugs for different types of HCC which are probably linked each other. Modulate the immune system and intervene on the microenvironment is the next challenge and it will move probably towards a multidisciplinary approach to the treatment of HCC which will consider surgical treatments of lesions, and in selected cases, liver transplants (25).

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Footnote

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Hepatocellular carcinoma: present and future

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Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in some areas of the world; there is an increasing incidence worldwide, and approximately 500,000 new cases are reported per year. More than 75% of cases occur in the Asia-Pacific region, largely in association with chronic hepatitis B virus (HBV) infection (1). More than 50% of cases of HCC occur in China alone, and an estimated 360,000 patients residing in the Far East countries and regions, including China, Japan, Republic of Korea and Taiwan, die from this disease each year (2,3). The incidence of HCC is increasing in the United States and Europe because of the increased incidence of hepatitis C virus (HCV) infection (4). However, different lines of evidence identify in non-alcoholic fatty liver disease (NAFLD) a possible relevant risk factor for occurrence of HCC. Given the continuing increase in the prevalence of obesity and diabetes, the incidence of non-alcoholic steatohepatitis-related HCC may also be expected to increase (5). In most cases, HCC is diagnosed at a late stage. Therefore, the prognosis of patients with HCC is generally poor and has a less than 5% 5-year survival rate.

The recommended screening strategy for patients with cirrhosis includes the determination of serum alpha-fetoprotein (AFP) levels and an abdominal ultrasound every 6 months to detect HCC at an earlier stage, when it is amenable to effective treatment strategies. AFP, however, is a marker characterized by poor sensitivity and specificity, and abdominal ultrasound is an imaging technology that is highly dependent on the operator's experience. In addition to AFP, Lens culinaris agglutinin-reactive AFP (AFP-L3), des-carboxy prothrombin (DCP), glypican-3 (GPC-3), osteopontin (OPN), and several other biomarkers [such as squamous cell carcinoma antigen-immunoglobulin M complexes, alpha-1-fucosidase (AFU), chromogranin A (CgA), human hepatocyte growth factor, and insulin-like

growth factor (IGF)] have been proposed as markers for the early detection of HCC (6,7). None of them is optimal; however, when used together, their sensitivity in detecting HCC is increased. Recent developments in gene-expressing microarrays and proteomics promise even more potential diagnostic options (8).

More recent research has demonstrated that some of these tumor markers (such as DCP, GPC-3, OPN), in addition to diagnostic and prognostic role in HCC, stimulate HUVEC growth and migration; growth of HCC cells by upregulating autocrine/paracrine canonical Wnt signaling; and Met-Janus kinase 1-signal transducer and activator of transcription 3 (Met-JAK1-STAT3) signaling pathway, which results in HCC cell proliferation (7,9,10). Therefore, these tumor markers have an important role in hepatocarcinogenesis and this could have an important opportunity in the HCC treatment.

DCP increases the expression of angiogenic factors in human HCC cells, as demonstrated by the research of Gao *et al.* (11). The aim of their study was to evaluate the angiogenic activity of DCP in HCC cells. DCP stimulated HCC cell growth in a dose- (5-80 ng/mL) and time-dependent (24-96 h) manner. The increase of cell growth was also observed in nude mice bearing well-established, palpable HepG2 and SMMC-7721 xenografts after a 2-week administration of DCP. HCC cell growth was accompanied by elevated levels of angiogenic factors. The levels of vascular endothelial growth factor (VEGF), transforming growth factor-alpha (TGF-alpha) and basic fibroblast growth factor (b-FGF) in the supernatant of SMMC-7721 cells were increased from 47, 126 and 60 pg/106 cells/24 h to 400, 208 and 298 pg/106 cells/24 h, respectively, after 72 h incubation with 80 ng/mL of DCP. The results of Western blot analysis and immunohistochemical staining of HCC xenografts also showed a significant increase

of VEGF, TGF- α and bFGF in HCC cells. These results suggest that DCP is a type of growth factor and is involved in the progression of HCC. More recent research has demonstrated that DCP stimulates human vascular endothelial cell growth and migration. Wang *et al.* reported the effects of DCP on the growth and migration of human vascular endothelial cells (12). DCP significantly stimulated the proliferation of HUVEC (ECV304) cells in a dose- and time-dependent manner, as measured by the MTT assay. A continuous rapid migration of ECV304 cells was observed in the presence of DCP, as measured by the scratch wound assay. The continuous rapid invasive activity, measured by the transwell chamber assay, also showed that DCP increased endothelial cell migration through the reconstituted extracellular matrix (Matrigel). Furthermore, the tube formation of vascular endothelial cells on a 3-D Matrigel showed an increased number of branch points of ECV304 cells induced by DCP in a dose dependent manner. The levels of vascular endothelial cell growth-related angiogenic factors and matrix metalloproteinase were also examined. DCP significantly stimulated the expression levels of epidermal growth factor receptor (EGFR), VEGF and matrix metalloproteinase (MMP)-2 (latent and active). Together, these data suggest that DCP is a novel type of VEGF that possesses potent mitogenic and migratory activities in the angiogenesis of HCC. Whatever the mechanisms, the levels of DCP production were decreased and the growth and invasion of RCC cells were inhibited in the presence of vitamin K2 (13). Therefore, administration of vitamin K2 should be determined as a promising option for HCC treatment (7).

GPC3 is highly expressed in HCC cells and tissues. It is thought that GPC3 stimulates the growth of HCC cells by up regulating autocrine/paracrine canonical Wnt signaling (14). GPCs have been reported to stimulate both the canonical and non-canonical pathways. GPC3 reportedly regulates migration, adhesion, and actin cytoskeleton organization in tumor cells through Wnt signaling modulation. Matrix metalloproteinases (MMPs) also play an important role in HCC. It has been reported that GPC3 may regulate MMP activity in breast cancer (15). It has also been demonstrated that secreted MMP-9 associates with glypican-like proteoglycans through their heparan sulphate chains, and plays a crucial role in cell motility of murine colon cancer cell line LuM1 cells (14). GPC3 has been shown to bind to fibroblast growth factor (FGF)2 and may function as a coreceptor for FGF2 (15). Two recently identified human heparin-degrading endosulfatases, named sulfatase 1

(SULF1) and SULF2, have been found to be involved in liver carcinogenesis. Interestingly, SULF2 reportedly up-regulates GPC3, promotes FGF signaling, and decreases survival in HCC (15). Moreover, GPC3 reportedly confers oncogenicity through the interaction between insulin-like growth factor (IGF)-II and its receptor, and the subsequent activation of the IGF signaling pathway (15). Specific interactions both between GPC3 and IGF-II and between GPC3 and IGF 1 receptor (IGF1R) have been reported. These results suggest that GPC3 joins a multiprotein complex, which is composed of the ligand, receptor, GPC3, and probably other proteins (16). Since the heparin sulphate chains of GPC3 interacts with heparin-binding growth factors and other growth factors such as HGF and VEGF, can contribute to the development of hepatic cancer.

In the Akutsu N. *et al.* (17) study was analyzed expression of these molecules in HCC cell lines and tissue samples by real-time reverse transcription-polymerase chain reaction (RT-PCR), immunoblotting, and/or immunostaining. Expression of various genes in *GPC3* siRNA-transfected HCC cells was analyzed. In this study, we found overexpression of *GPC3* mRNA in HCC cell lines and tissue samples. The over-expression of GPC3 in HCC was also observed at protein level analyzed by immunohistochemistry. These results further support the notion that GPC3 plays an important role in hepatocarcinogenesis. As a target gene for molecular therapy, its expression in normal adult tissues is important. Considering the expression pattern of GPC3 together with its oncogenic function, GPC3 could be an attractive target for molecular therapy. Antitumor effects of the anti-GPC3 antibody have been reported. Interestingly, we have recently reported the tumor suppressive effect of tyrosine kinase inhibitor of IGF1R, NVP-AEW541, on GPC-3-expressing HCC cell line PLC/PRF/5. Combination of the anti-GPC3 antibody and molecular therapy targeting GPC3-related molecules, such as FGFR, found in this study will be a promising new cancer therapy in the future (7).

The only hope for a cure from HCC rests on early diagnosis as it can be attained through semiannual surveillance with abdominal ultrasound of patients at risk. While the strategy of semiannual screening rests on the growth rate of the tumor that in cirrhotic patients takes 6 months to double its volume, on average, the noninvasive radiological diagnosis of HCC is possible in cirrhotic patients with a de novo HCC and patients with chronic hepatitis B. More recently, metabolic diseases related to insulin resistance, including diabetes and obesity, have

been recognized to be causally related to HCC as well, in most patients bridging HCC to the histopathological diagnosis of non-alcoholic steatohepatitis (NASH). While the endpoint of an early diagnosis is achieved quite easily in most patients with >1 cm HCC by computed tomography (CT) or magnetic resonance imaging (MRI) demonstrating the specific pattern of an intense contrast uptake during the arterial phase (wash-in) and contrast wash-out during the venous/delayed phase, nodules <1 cm in size are more difficult to diagnose, almost invariably requiring an enhanced follow up with three monthly examinations with US until they grow in size or change their echo pattern. Owing to the lack of robust controlled evidence demonstrating a clinical benefit of surveillance, the real support for screening for liver cancer comes from the striking differences in response to therapy between screened populations in whom HCC is diagnosed and treated at early stages and patients with more advanced, incidentally detected tumors (18).

With the recent dramatic advances in diagnostic modalities, the diagnosis of HCC is primarily based on imaging. Ultrasound plays a crucial role in HCC surveillance. Dynamic multiphasic multidetector-row CT (MDCT) and magnetic resonance imaging (MRI) are the standard diagnostic methods for the noninvasive diagnosis of HCC, which can be made based on hemodynamic features (arterial enhancement and delayed washout). The technical development of MDCT and MRI has made possible the fast scanning with better image quality and resolution, which enables an accurate CT hemodynamic evaluation of hepatocellular tumor, as well as the application of perfusion CT and MRI in clinical practice. Perfusion CT and MRI can measure perfusion parameters of tumor quantitatively and can be used for treatment response assessment to anti-vascular agents. Besides assessing the hemodynamic or perfusion features of HCC, new advances in MRI can provide cellular information of HCC. Liver-specific hepatobiliary contrast agents, such as gadoxetic acid, give information regarding hepatocellular function or defect of the lesion, which improves lesion detection and characterization. Diffusion-weighted imaging (DWI) of the liver provides cellular information of HCC and also has broadened its role in lesion detection, lesion characterization, and treatment response assessment to chemotherapeutic agents (19).

HCC is one of the typical tumors with neovascularization, and the alteration in the arterial vascularity may lead to acquisition of the potential for vascular invasiveness

and metastasis. In 2008, phase III clinical trials revealed anti-angiogenic agent “sorafenib” as the first drug that demonstrated a modest improved overall survival in patients with advanced HCC. A new era of HCC treatment had arrived, but there has been limited further improvement in survival benefits.

In the near future, research will have to deal with molecular targeted therapy with a focus on angiogenesis, growth signals, and mitotic abnormalities, as well as the promising concepts of “cancer stemness” and “synthetic lethality” for the strategy of targeted therapy (20).

Improving the overall survival for patients with advanced HCC requires development of effective systemic therapy. Despite the successful approval and extensive application of sorafenib, the prognosis for patients with advanced HCC remains poor and the benefits with sorafenib are modest. In the past few years, there have been renewed and continued interests and active research in developing other molecularly targeted agents in HCC. While the initial efforts are focusing on anti-angiogenic therapy, other agents targeting the epidermal growth factor-receptor, mammalian target of rapamycin (mTOR), hepatocyte growth factor/c-Met among others have entered HCC clinical trials. Combining different molecularly targeted agents or combining targeted agents with chemotherapy represent other strategies under investigation.

Transcatheter arterial chemoembolization (TACE) is the standard of care for patients with preserved liver function and asymptomatic, noninvasive multinodular hepatocellular carcinoma (HCC) confined to the liver. However, the survival benefit of conventional TACE — including the administration of an anticancer agent-in-oil emulsion followed by embolic agents — reported in randomized controlled trials and meta-analyses was described as modest. Various strategies to improve outcomes for this patient group have become the subject of much ongoing clinical research. The introduction of embolic, drug-eluting beads (DEB) for transarterial administration has been shown to significantly reduce liver toxicity and systemic drug exposure compared to conventional regimens. The addition of molecular targeted drugs to the therapeutic armamentarium for HCC has prompted the design of clinical trials aimed at investigating the synergies between TACE and systemic treatments. Combining TACE with agents with anti-angiogenic properties represents a promising strategy, because TACE is thought to cause local hypoxia, resulting in a temporary increase in levels of vascular endothelial growth factor. Recently, a large phase

II randomized, double-blind, placebo-controlled trial (the SPACE study) has shown that the concurrent administration of DEB-TACE and sorafenib has a manageable safety profile and has suggested that time to progression and time to vascular invasion or extrahepatic spread may be improved with respect to DEB-TACE alone. These data support the further evaluation of molecular targeted, systemically active agents in combination with DEB-TACE in a phase III setting (21).

In the HCC setting, liver transplantation (LT) has become one of the best treatments since it removes both the tumor and the underlying liver disease. Due to the improvement of imaging techniques and surveillance programs, HCC are being detected earlier at a stage at which effective treatment is feasible. The prerequisite for long term success of LT for HCC depends on tumor load and strict selection criteria with regard to the size and number of tumor nodules. The need to obtain the optimal benefit from the limited number of organs available has prompted the maintenance of selection criteria in order to list only those patients with early HCC who have a better long-term outcome after LT. The indications for LT and organ allocation system led to many controversies around the use of LT in HCC patients (22).

In conclusion, effective molecularly targeted therapies may also hold promise as adjuvants to primary surgical therapies, currently limited by high rates of disease recurrence. It is hoped that, active research aimed at the elucidation of the molecular pathogenesis of HCC and the identification of new biomarkers will result in further advances in the prevention, diagnosis, and treatment of HCC. Finally, in multi-disciplinary standardized treatment will be needed with Individualized plan for different patients or a single patient at different stages.

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Footnote

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Hepatocellular carcinoma: expanding the horizon

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“Unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity” Santiago Ramón y Cajal, Nobel Prize in Medicine 1906.

Hepatocellular carcinoma (HCC) is a major, increasing, public health problem in Asia. The estimated number of new liver cancer cases and liver cancer deaths in 2015 in China is 486,665 and 450,996, respectively (1). Because of differences in etiology, prognosis, staging systems used and treatment patterns, HCC is managed differently in Western and Asian nations (2). The new guidelines proposed by the expert panel led by Dr Shukui Qin (3), provide a useful specialized multidisciplinary care tool, which may help to improve efficiency when diagnosing and treating HCC patients.

In Eastern Asia the development of HCC is mainly related to chronic infection with the hepatitis B virus (HBV). We should remember that immunization against HBV infection is a cheap strategy to decrease the incidence of HCC (4). Since the strength of the evidence supporting the efficacy of surveillance programs in HBV infected patients in China is controversial (5,6), nomograms based on noninvasive clinical characteristics that may accurately predict the risk of HCC should be validated (7). Future diagnostic tools, such as a plasma microRNA panel (8), might allow the diagnosis of HCC at a very early-stage. In resected HCC patients, an association between survival and a recurrent gene-signature in non-tumorous liver tissue has been reported, opening the possibility of subsequent individualized therapies and a risk-adapted follow-up schedule (9).

The Barcelona Clinic Liver Cancer (BCLC) staging system offers a widely-accepted staging-guided treatment,

requiring only minor regional practice adaptations; notwithstanding, in some studies in both Western and Eastern populations, BCLC is suggested to be less accurate in predicting survival when compared with other currently used staging systems, particularly the Cancer of the Liver Italian Program (CLIP) (10,11). While most of these HCC staging systems take into account tumor biology and liver function, all of them fail to incorporate some major prognostic factors, such as microvascular invasion, for example, which is a fairly more important prognostic factor in surgically-resected HCC than other prognostic factors such as tumor size (12). New molecular prognostic factors, such as plasma levels of vascular endothelial growth factor (VEGF), could be integrated in currently used staging systems (13). Given that HCC is a heterogeneous disease, some molecular classifications of this tumor have been attempted and deserve to be clinically validated (14).

Technical improvements in locoregional therapies have expanded the number of HCC patients that are candidates for surgical resection, radiofrequency ablation and radiation therapy (RT). In patients with chronic liver disease, portal vein embolization before right hepatectomy reduces surgical morbidity and mortality. A novel two-step hepatic resection technique called “associating liver partition and portal vein occlusion for staged hepatectomy” (ALPPS) allows the two operations to be performed only one week apart (15). Recently published phase II clinical trials have shown that RT can be delivered in a safe and effective way, not only for palliative purposes but also for the treatment of early-stage HCC that is not eligible for curative therapies and as a bridge to liver transplantation (16). Several phase III randomized trials comparing RT versus (*vs.*) trans-arterial chemoembolization (TACE), RT plus TACE *vs.* TACE, and

sorafenib *vs.* RT (RTOG1112 trial) in patients with limited multifocal disease are currently ongoing.

Whether the novel and expensive catheter-based therapies using drug eluting beads (DEB) and yttrium-90 (⁹⁰Y)-labeled microspheres are better than the classical TACE is an unresolved issue. Studies to clarify the optimal use of these techniques in terms of patient safety, efficacy, and cost-effectiveness are needed. The SPACE study (17) and the ECOG 1208 (18) are two ongoing randomized trials addressing the question of adding sorafenib to TACE and DEB-TACE, respectively. In the first study, sorafenib is administered continuously throughout the embolization period; in the latter one, sorafenib is temporally interrupted around the time of the embolization. The balance between safety and efficacy will determine which option is the best therapeutic strategy.

Since 2008, sorafenib remains the only systemic treatment that has proved to prolong survival compared with best supportive care in advanced HCC patients with compensated liver function. The cost of sorafenib for such a moderate benefit (less than 3 month improvement in median overall survival and no improvement in time to symptomatic progression), uncertain benefit in patients with Child B cirrhosis, and the lack of validated predictive biomarkers are some drawbacks of this therapy (19). Most of the targeted drugs under development are aimed at the inhibition of the angiogenic pathway; however, single agent anti-angiogenic therapies have reached an efficacy plateau. Many ongoing and planned trials combine molecularly targeted agents that inhibit different pathways or at different steps of the same pathway, usually at the expense of greater toxicities than expected for each drug alone (20). Combining targeted agents with chemotherapy is another rational strategy based on strong preclinical and clinical data (21); an ongoing phase III trial is currently evaluating the combination of sorafenib with doxorubicin *vs.* sorafenib alone.

In unselected advanced HCC populations, sunitinib and lenvatinib in the first-line therapy setting, and brivanib as second-line therapy, have failed to improve survival outcomes in three separate randomized trials that were recently reported (22). When developing new molecular-targeted agents, phase I clinical trials looking for the optimal biologic dose rather than the maximum tolerated dose, and biomarker-based randomized phase II clinical trials with time-to-event endpoints may contribute to maximize the likelihood of success in subsequent phase III trials. As an example, tivantinib, a very promising tyrosine

kinase inhibitor of the mesenchymal-epithelial transition factor (MET) receptor, was tested as a second-line therapy in a randomized phase II trial with a predefined biomarker analysis incorporated into the design, which concluded that this drug was not effective in patients with low expression of MET, but a pronounced benefit was observed in MET-overexpressing patients (23). More affordable drugs against advanced HCC than the current targeted drug therapies are urgently needed. Solid preclinical data support the clinical development of arsenic trioxide and traditional Chinese medicines in this setting.

Hopefully intensive research in this field will bring more accurate diagnosis and staging tools and more efficacious therapeutic options in the near future.

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Footnote

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Guidelines for the management of hepatocellular carcinoma: still in need of standardization

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Guidelines are meant to assist physicians, patients, health-care providers and health-policy makers in the decision-making process according to evidence based data (1), with the understanding that the recommendations are intended to guide clinical practice in circumstances where all possible resources and therapies are available. This implies that recommendations should adapt to local regulations and capacities, not to forget the impact of cost-benefit analysis. Finally, guidelines are essential instrument to update and advance the research and the knowledge, ultimately contributing to improve patient care.

Despite the blossoming of guidelines for HCC, in the West and East, at a global level, the clinical practice of HCC treatment is still far from being standardized even within each country. There are in fact wide discrepancies in the management of the disease among Academic and non Academic Hospitals (2,3) whereas therapeutic approaches of consolidated efficacy like surveillance of at risk population is not widespread even in resources rich countries like US (4). Indeed, population-based studies in the United States indicate that only a minority of patients with an HCC have undergone regular surveillance and consequently received curative treatments, despite most doctors are aware of potentially lethal consequences of a delayed diagnosis and treatment of HCC.

The Chinese guidelines on primary liver cancer reported in this issue (5) of the Journal represent a potentially breakthrough, since they address the most populous country in the world which is also an hyperendemic area for HCC, due to the prevalence of HBV and exposure to aflatoxin contaminated food. While increasing population's awareness of HCC as a relevant health problem represents

the first step for improving management of the disease, further steps are the definition of surveillance, recall policy and treatment standardization. Despite the driving role of the level of evidence and the strength of the data, several aspects of HCC guidelines still remain to define, mainly as a consequence of discordant results by RCTs which hamper common strategies between the various geographic areas. Not surprisingly, therefore, most recommendations are based on expert opinion and local capacity rather than on RCTs. This makes cost-efficacy of surveillance itself to be questioned by many, because of the lack of solid data on the evidence that HCC mortality is decreased by surveillance everywhere, whereas surveillance is a consolidated standard of care in most countries. This notwithstanding, modalities and timing of surveillance are questioned, as the use of serum tumor markers in surveillance programs are endorsed by Japanese and Chinese guidelines (5,6) whereas they are excluded by European and North American guidelines (1-7). The weak sensitivity and specificity of serum markers and the lack of standardized recall policies are the major reasons for their withdrawal. Thus, in our opinion, the endorsement of AFP in screening and recall policies provided by the Chinese guidelines, needs a prospective validation. Once ultrasound detects a de novo liver nodule in at risk population, the investigation are aimed to the detection of the typical vascular pattern of HCC, defined by an increased enhancement of contrast in the arterial phase, followed by a wash-out in the portal/venous phase, by CT or MRI, which allow the radiological diagnosis of HCC worldwide. The Chinese guidelines highlight the use of hepatic artery digital subtraction

angiography (DSA) too, for the radiological diagnosis of HCC in cirrhosis. From a Western perspective, the use of DSA to diagnose HCC in cirrhosis needs prospective validation. One major advance in the Chinese guidelines, is the concept of palliative resection of the tumor in patients with a multinodular HCC and vascular invasion. Again, we think this innovative policy should be validated by a prospective study, being data on increased survival and/or decreased morbidity far from being supported by evidence-based studies.

In conclusion, it seems that to bridge the gap in screening and management of HCC, educational programs should be implemented to target both patients and stakeholders in the field, while waiting for a breakthrough not only in the strategy of the screening but also for tailoring treatment for each patient, with the aim to improve population's access to the surveillance and to standardized treatments.

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New insights in hepatocellular carcinoma: from bench to bedside

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Abstract: Hepatocarcinogenesis is a multistep process involving different genetic alterations that ultimately lead to malignant transformation of the hepatocyte. The liver is one of the main targets for different metastatic foci, but it represents an important and frequent locus of degeneration in the course of chronic disease. In fact, Hepatocellular carcinoma (HCC) represents the outcome of the natural history of chronic liver diseases, from the condition of fibrosis, to cirrhosis and finally to cancer. HCC is the sixth most common cancer in the world, some 630,000 new cases being diagnosed each year. Furthermore, about the 80% of people with HCC, have seen their clinical history developing from fibrosis, to cirrhosis and finally to cancer. The three main causes of HCC development are represented by HBV, HCV infection and alcoholism. Moreover, metabolic disease [starting from Non Alcoholic Fatty Liver Disease (NAFLD), Non Alcoholic Steatohepatitis (NASH)] and, with reduced frequency, some autoimmune disease may lead to HCC development. An additional rare cause of carcinogenetic degeneration of the liver, especially developed in African and Asian Countries, is represented by aflatoxin B1. The mechanisms by which these etiologic factors may induce HCC development involve a wide range of pathway and molecules, currently under investigation. In summary, the hepatocarcinogenesis results from a multifactorial process leading to the common condition of genetic changes in mature hepatocytes mainly characterized by uncontrolled proliferation and cell death.

Advances in understanding the mechanism of action are fundamental for the development of new potential therapies and results primarily from the association of the research activities coming from basic and clinical science.

This review article analyzes the current models used in basic research to investigate HCC activity, and the advances obtained from a basic and clinical point of view.

Keywords: Hepatocellular carcinoma; liver fibrosis; metabolic syndrome; NAFLD; NASH

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Mouse models of HCC

In order to deeply investigate the hepatocarcinogenesis and new potential therapies in humans, there is growing interest to recreate experimental models that could be used in basic research, able to resemble the human characteristics of HCC.

In vitro testing of human HCC cell lines is usually an early step in the process of anticancer drug discovery that requires evaluation of viability, cell proliferation, clonogenicity and apoptosis. Several cell lines are currently used in literature:

Huh7.5, HepG2, Hep3B and SK-Hep1 (1).

While results obtained using cell cultures provide important information regarding drug efficacy and mechanisms of action, *in vitro* systems lack the power to recapitulate the complex relationship between the tumor and its microenvironment.

Based on these data, a key role in the study of HCC is played by the *in vivo* experimental models (2). Concerning experimental models of HCC, genetic models, conditioned knock-out or transgenic models are mainly used to study

the involvement of specific protein in the carcinogenetic process (3,4), while chemotoxic agents-induced HCC [such as N-nitrosodiethylamine (DEN) model] may provide a useful technique to study the interactions of different molecules and drugs. However, chemotoxic-induced HCC models do not completely resemble the human disease.

The DEN (N-nitrosodiethylamine) model of HCC is mainly used in basic research and promotes cancer development both in rats and in mice. DEN may be administered at different age of the mouse, however the results may vary in terms of efficacy and efficiency. To reduce the time of HCC development and limit the administration of the carcinogen, several studies adopted the association of promoting-agents to a single dose of DEN administration, the so called “two stage models” of HCC. Among the promoting agents, phenobarbital (PB) needs to be taken in consideration: the effects of PB promotion on DEN-initiated mice also vary considerably depending upon strain, sex and age of the mice (5-7). These models are largely used in literature and represent a good model to define and study the primitive HCC nodule, independently from the condition of cirrhosis.

Other experimental models of HCC involves AFB administration have been used in literature to specifically investigate the mechanisms involved in AFB-induced hepatocarcinogenesis, yet limited to the specific cases in which the AFB mechanisms need to be elucidated (8,9).

An increasing interest has been recently related to the metabolic conditions leading from simple steatosis to HCC in humans. This issue led to the development of additional mouse-model based on the use of diets, such as the choline deficient diet (CDD). In origin, such a diet has been developed to induce steatohepatitis, fibrosis and cirrhosis in mice and rats (10,11). More recently, it has been observed that mice subjected to CDD diet develop HCC formation after 50-52 weeks (10). The effects of CDD have been also evaluated in association with the administration of chemotoxic compounds (12). Ethionine supplementation to CDD diet is able to enhance the oval cells stimulation increasing the carcinogenetic potential (13,14). Similarly, combination of the CDD and DEN results in the earlier induction of HCC (12). A small variation of the current diet is represented by the choline-deficient and iron-supplemented l-amino acid-defined (CDAA) diet that mimics the same effect of the CDD diet in a shorter time frame (11,15).

An additional method used in basic research for the study of cancer is represented by the xenograft models:

in xenograft models, the tumors are induced by injecting human cancer cells in immune deficient mice, such as athymic (nude) or severe combined immune deficient (SCID) mice (16). Among the xenograft models, the main ones are (I) the ectopic model, in which human cancer cells are directly injected subcutaneously in the flank of mice, and (II) the orthotopic model, in which tumor cells are injected directly into the mouse liver. These models are largely used in literature for the study of the metastatic spread of the tumor (17).

Finally, a considerable part of the basic research has been conducted in the HCC field by the use of genetically modified models. Genetically modified mouse models (GMM) have the purpose to mimic pathophysiological and molecular features of HCC (18). This approach allows to test the effects of oncogenes in the presence or not of carcinogenic agents. GMMs may be further improved by using cDNA constructs containing a promoter able to target a specific cell type (19). Mice with albumin promoter are often used in this field.

Rather than constitutive tissue-specific deleted expression of genes, an alternative model could be represented by the induction of specific genes, obtained generating transgenic mice. Among them, it is important to consider the transgenic mice models expressing viral genes for hepatitis. Most of the HBV-related transgenic animals express the HBx genes, which are associated with altered hepatocellular functions and HCC development (20). Concerning the HCV infection, transgenic mice expressing core, E1 and E2 structural proteins are mainly used in basic research (21).

In line with the *in vitro* study identifying the main signalling pathways potentially involved in HCC, several specific transgenic mice have been created and used in literature (22). The Myc transgenic mice are genetically close to human HCC of good prognosis and may be specifically used to study the entire range of pathways involved at this level (23). β -catenin transgenic mice have been used in the study of HCC: β -catenin is involved in the development and regeneration of the liver and β -catenin mutations are an early event in hepatocarcinogenesis (24). Mutations in growth factor genes, such as Tumor Growth Factor α (TGF α), Epidermal growth factor, Fibroblast growth factor 19, Platelet-derived growth factor (PDGF) and TGF β 1, have been recognized as involved in HCC development (25,26). Thus, specific transgenic mice have been created in basic research.

Moreover, transgenic mice expressing a human form of transport-impaired Alpha-1 antitrypsin [transport-impaired

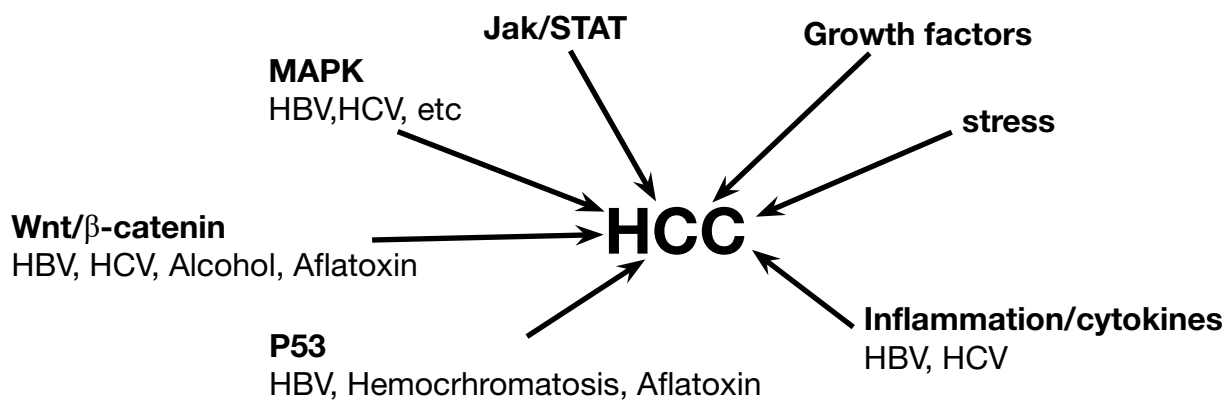


Figure 1 Intracellular pathways involved in the process of hepatocellular carcinoma formation and development

Alpha-1 antitrypsin (AAT) (27)] represents a good model for studying the effects of AAT deficiency on the liver. AAT deficiency is an autosomal recessive disorder in which a mutation causes the production of AAT that is unable to be transported (27). This leads to decreased AAT activity in serum and deposition of excessive AAT in the liver. Both heterozygous and homozygous individuals develop cirrhosis and HCC. AAT-deficient mice develop HCC after 52-90 weeks of age (27).

As demonstrated by *in vitro* studies, PTEN is a tumor suppressor gene that regulates the serine-threonine kinase protein kinase B (PKB/akt) pathway. Thus, PTEN knock out mice also develop HCC *in vivo*, in 66% of male and 30% of female mice by 40-44 weeks of age (28). PTEN deficiency induces cellular hyper-proliferation, anti-apoptosis and oncogenesis (29). Liver-specific PTEN-deficient mice develop hepatic steatosis, inflammation and fibrosis, thus resembling the features of human non-alcoholic steatohepatitis (NASH) (28).

In addition to the pure carcinogenetic mechanism evaluated by the previously described models, recent advances have demonstrated the involvement of inflammation pathways in the process of HCC formation. This issue has been clearly demonstrated by the use of hepatocytes specific NEMO deletion (IKK gamma subunit involved in the regulation of NF κ B pathway). Several studies demonstrated that NEMO-mediated NF-kappaB activation in hepatocytes has an essential physiological function to prevent the spontaneous development of steatohepatitis and hepatocellular carcinoma, identifying NEMO as a tumor suppressor in the liver. NEMO specific hepatocytes-deleted mice spontaneously develop tumor after 10 to 12 months (30-32).

Finally, as a proof of the real existence of a link between fibrosis and cancer in the liver, an additional genetically modified mouse model has been used in basic research: as widely demonstrated in literature hepatocyte-specific deletion of TAK1 in mice results in spontaneous hepatocyte death, inflammation, fibrosis, and consequently in the development of HCC with a success rate represented by clear macroscopic nodules of 80% after 9 months (33).

Signalling pathways

In vivo study and the associated *in vitro* evaluation of specific molecules allow researchers to investigate the main potential mechanisms involved in carcinogenesis, defining several pathways strictly related to the process (Figure 1).

This approach to basic research provided therefore the tools to discover the involvement of several mechanisms in carcinogenesis: among these, a special mention is related to the Wnt signaling pathway that is significantly deregulated in a number of cancers, including HCC (34). Wnt pathway is involved in HCC arising from HBV/HCV infections and alcoholic liver cirrhosis. Up-regulation of one of its component, frizzled-7, and dephosphorylation of β -catenin is frequently observed in HCC (35,36). The use of transgenic mice for β -catenin allowed to directly demonstrate the molecule involvement in the HCC formation, leading researchers to deeply investigate the mechanism. Based on these models, it has been demonstrated that mutations in β -catenin arise in HCC. This issue has been also demonstrated in patients with increased exposure to HCV infection and aflatoxin (37,38).

In the spectrum of genes related to HCC, a key role is played by p53. Several studies have reported that p53

Table 1 Adapted table resuming the BCLC staging system for hepatocellular carcinoma classification and treatment strategy (Bruix, Hepatology 2011)

Features	Definition	Treatment
Single HCC nodule <2 cm	Very early stage	Resection, liver transplantation, RadioFrequency
Single or 3 nodules <3 cm	Early stage	Liver transplantation, radiofrequency
Multinodular	Intermediate	TACE
Vascular portal invasion	Advanced stage	Sorafenib
Critical conditions	End stage	Symptomatic therapy

mutations and inactivation play a critical role in HCC. The studies conducted *in vivo* on experimental models of HCC have been additionally confirmed in humans. Specifically, mutation of p53 correlates with the HCC developments induced by aflatoxin B1 (AFB1), as demonstrated using mouse models and subsequently confirmed in humans. Thus, detection of mutant p53 in plasma serves as a potential biomarker for AFB1 exposure and presence of HCC.

Human ras proteins H-Ras, N-Ras, K-ras4A, and K-Ras4B are small GTP-binding proteins that function as molecular switches to influence cell growth, differentiation and apoptosis (39). Single point mutations in codon 13 of H-ras, codon 12 of N-ras, and codon 61 of K-ras were originally observed in HCC caused by various chemicals such DEN (40-43). By the use of this model it has been demonstrated that Ras interacts with a downstream serine/threonine kinase Raf-1 leading to its activation and downstream signaling, which includes activation of MAPK kinases MEK1 and MEK2, to regulate proliferation and apoptosis (44). Activation of Ras and expression of Ras pathway proteins such as p21 were also reported in solid tumors as well as in cell lines (45,46). The strategies of inhibiting several kinases and suppressing Ras expression using antisense RNA has been successfully applied in cell line and in animal models (47,48).

In vivo mouse models of HCC have been also used to investigate the role of JAK/STAT pathways (49). STAT activation occurs through tyrosine phosphorylation by Janus kinases (JAKs). Activated STATs stimulate the transcription of suppressors of cytokine signaling (SOCS) genes. SOCS proteins, in turn, bind phosphorylated JAKs and their receptors to inhibit this pathway, thereby preventing overactivation of cytokine-stimulated cells (50). Thus, SOCS are part of the negative feedback loop in the JAK/STAT circuitry. Two other families of STAT inhibitors that are described in the literature include the protein inhibitors of activated STATs and the SH2-containing proteins (51). JAK stimulation of STATs activates cell proliferation,

migration, differentiation, and apoptosis, and deregulation of inhibitors leads to human diseases, including cancer (49). Inactivation of SOCS-1 and SSI-1, a JAK-binding protein, in HCC have been reported (49,50) as has the ubiquitous activation of the JAK/STAT pathway (52).

Proteins and cellular factors of other signaling pathways can also influence the molecular dynamics of HCC. For example, vascular endothelial growth factor and fibroblast growth factor play important roles in HCC development (53,54). It was reported recently that inflammation is inherently associated with cancer and a number of cytokines are involved in promoting HCC development and progression, especially during infection with hepatitis viruses (55). In particular, Th2 cytokines are induced and Th1 cytokines decreased in metastases. Therefore, modulating the expression of cytokines and the use of inhibitors of inflammatory cytokines might be critical in alleviating HCC progression. In a recent study, it was shown that the use of inhibitors of epidermal growth factor receptor and transforming growth factor prevented the development of HCC in rat liver, demonstrating the harmful nature of these growth factors if they exist in excessive amounts (56,57).

Clinical relevance and current treatment

Although the enormous amount of data coming from basic research and the interest in developing drugs potentially effective, the clinical and pharmacological treatment of HCC is still limited to the advanced stage of the disease.

As well established in the clinical practice, concerning the HCC development and the best treatment, it is mandatory to refer to the Barcelona Clinic Liver Cancer (BCLC) staging system, that represent not only a useful tool for classifying patients according to their prognosis, but also a method for selecting the appropriate treatment (*Table 1*) (58).

Surgical treatments are the first treatment choice to consider. Resection and Orthotropic liver transplantation

(OLT) achieve excellent results in BCLC 0 and A patients. Resection is the treatment of choice in non-cirrhotic patients where major resections are well tolerated. However, liver function impairment limits the feasibility of resection in cirrhotics if aiming at minimal morbidity and mortality. The best results in liver resection are obtained in solitary HCC. Multinodularity is correlated with recurrence and worse patient survival (59-62). Therefore, in multinodular HCC meeting the Milan criteria, OLT is a preferable option. In fact, the best results in liver transplantation are obtained applying the so-called Milan criteria (solitary ≤ 5 cm or if multiple, a maximum of 3 nodules ≤ 3 cm, without vascular invasion or extrahepatic spread). Meeting these criteria, the 5-year survival exceeds 70%, with recurrence ranging from 5% to 15% (63,64).

If OLT is not available, resection can still be considered in selected cases and optimally within prospective cohort investigations. However, since there are a growing number of publications reporting excellent results for early tumors treated with percutaneous ablation (65,66) or Transarterial chemoembolization (TACE) (65), with a lower rate of complications than with surgical resection, patients with multinodular HCC not suitable for OLT may be equally well served by percutaneous ablation or chemoembolization. To date, the optimal candidates for TACE are patients with preserved liver function (Child-Pugh A), without extrahepatic spread or vascular invasion (BCLC B). These patients have an estimated median survival of 16 months without treatment, while TACE expands this to >24 months (67,68). In contrast, performing TACE in patients with deteriorated liver function may lead to severe complications and death due to liver failure (69).

In very early tumors (≤ 2 cm), whose probability of dissemination is very low, and in which the probability of complete response with a safe margin with radiofrequency ablation (RFA) is high (90-100%), it is likely that resection and RFA are similar in terms of outcome. Thus, as stated recently, resection will not offer better survival than ablation in BCLC 0 patients and RFA would become the first-line option, leaving surgery for those patients with treatment failure.

Differently from the others, patients with advanced HCC fitting into BCLC C (extrahepatic dissemination or vascular invasion, or mild tumor-related symptoms, preserved liver function) have a median survival of about 6-8 months. Until recently there was no effective treatment for these patients. Neither chemotherapy, nor agents such as antiandrogens, antiestrogens or interferon induced any

survival benefit (70). The growing knowledge in the field of molecular pathways involved in hepatocarcinogenesis led to the development of multiple molecules targeted to block those pathways (71). Currently, the multikinase inhibitor Sorafenib represents the drug that is recognized effective for the treatment of advanced HCC in human. Sorafenib has antiangiogenic and antiproliferative effects and has been shown to improve survival patients with advanced HCC compared with placebo (72). As observed in the SHARP trial, median survival for the placebo arm was 7.9 months, whereas it was 10.7 months for the group of patients treated with sorafenib [HR (sorafenib/placebo): 0.69 (95% CI: 0.55-0.88)]. This increase in survival was obtained without a significant radiological response, but with a significant difference in time to progression between the placebo and sorafenib groups that was 2.8 and 5.5 months respectively with a HR (sorafenib/placebo) of 0.58 (95% CI: 0.45-0.74). In the trials where the evidence was provided, treatment was maintained until symptomatic progression and not just until tumor progression as per radiology. Hence, in clinical practice, treatment might be maintained until symptomatic progression unless there are second-line options to be offered.

Future perspectives

Role of stem/progenitor cells in HCC

Over the years, it has been well established that both hepatocytes and cholangiocytes are capable of repopulating liver tissue following injury (73). Therefore, the concept of stem/progenitor cell existence in the liver did not gain much recognition until the past decade. Furthermore, growing evidence also demonstrated that the capacity to sustain tumor formation and growth resides in a small proportion of cancer stem cells (CSCs) (74,75). Subsequent identification of CSCs in a number of tissues including brain (76-78), prostate (79), breast (80), myeloid (81), gastric (82), colon (83,84), and lung (85), has reinforced the notion that stem cells might also exist in the liver. In the early studies, embryonic stem cells from murine embryos were shown to differentiate into functional hepatocytes *in vitro* (86,87). It was later shown that murine as well as human bone marrow-derived mesenchymal stem cells could differentiate into hepatocytes both *in vitro* and *in vivo* (88,89). Studies of bone marrow transplant recipients have shown that these cells could home to liver and differentiate into normal hepatocytes (90). One of the most common liver stem cells is the oval cell (91). Oval cells express

markers common to hepatocytes and cholangiocytes, suggesting that they are bipotential. In fact, they differentiate into hepatocytes and cholangiocytes *in vitro* under the appropriate culture conditions (92). In diseases such as alcoholic liver disease and HCV infection, oval cell numbers increase and correlate with the severity of the disease (93). Several groups have isolated liver progenitor cell lines using oval cells from choline-deficient diet-fed rats (92), c-met transgenic mice (93), p53 null mice (94), and murine embryonic liver cells (95). Successful isolation of oval cells and establishment of liver progenitor cell lines from human liver tumors (96) and isolation of CSCs from human cell lines have been reported (97). The presence of CSCs and successful isolation of oval cells from cancerous tissue suggests that stem/progenitor cells play a key role in tumor formation. Recently, a novel cell type, the liver-derived progenitor cell, was also discovered and was isolated from healthy, uninjured rat livers (98). Further studies with these progenitor cells may provide insight to understand the molecular events that regulate cellular differentiation of the liver and those that lead to tumor progression.

Role of MicroRNAs in HCC

Identification of small, noncoding RNAs in the early 1990s has led to the development of a new research area (99). Several different classes of noncoding RNAs have been discovered in mammalian cells. These include small interfering RNAs (100), small nucleolar RNAs (101), and microRNAs (miRNAs) (102). miRNA complexes bind to imperfect complementary sequences in the 3'untranslated region of target mRNAs and negatively regulate gene expression either through mRNA degradation or translational inhibition (102,103). Recent studies have demonstrated that alterations in miRNA genes lead to tumor formation, and several miRNAs that regulate either the tumor suppression or promote tumor formation have been identified (104). For example, down-regulation of miR-15 and miR-16 results in overexpression of bcl2, cdk6, and cdc27, whereas overexpression of miR-21 causes suppression of PTEN and TPN1 (105). Several miRNAs that regulate the tumor suppressor p53 and p53-responsive genes have also been identified. Among these, miR-34 regulates p53 function in cell cycle arrest, cellular senescence, and apoptosis (106).

Thus miRNA expression profiles serve as signatures to determine not only the stages of a cancer but also a potential therapeutic strategy (107). The most abundant miRNA

currently known in the liver, miR-122, is involved in cellular stress response, hepatocarcinogenesis, and inhibition of HCV replication [reviewed by Girard *et al.* (108)]. Therefore it has been suggested that downregulation of miR-122 could be a potential biomarker for liver cancers (109).

Other studies in literature, by examining microarray profile, found that miR-21 is highly overexpressed in HCC and cell lines. Inhibition of miR-21 in cultured HCC cells is able to increase the expression of the PTEN tumor suppressor and to decrease tumor cell proliferation, migration, and invasion; in contrast, enhanced miR-21 expression shows the opposite effect. These data reveal a correlation among miR-21 and PTEN, suggesting a direct involvement of miR-21 in carcinogenesis (110). Further comparison of miRNA expression profile in the HCC tumors with patient's survival time showed that a set of 19 miRNAs, involved in biological processes such as cell division, mitosis, and G1-S transition, significantly correlated with disease outcome (111). Based on these data, it could be easily stated that miRNAs may be useful to screen patients with cancer and identify those with a high likelihood of developing metastases/reoccurrence.

Conclusions

Animal models represent essential tools in cancer research, since they allow scientists to reproduce genetic, pathological or environmental abnormalities thought to be important for cancer development. Over the last few years, a number of rodent models have been developed allowing to study the different aspects of liver cancer. The cooperation of basic and clinical research has been able to promote an important development in the field of liver cancer, leading to the definition of the best diagnostic and therapeutic approach, as provided and elegantly resumed in the BCLC staging system. In many cases it is difficult to determine to what extent mouse models reproduce features observed in corresponding human conditions, but they could certainly provide a useful and unique approach in understanding novel pathways, unknown mechanisms and potential effective therapies for clinical use. Thus, future research and the use of novel tools and pathways may lead to the development of new drugs able to better interfere with the process of HCC development.

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Footnote

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Hepatocellular carcinoma in the modern era: transplantation, ablation, open surgery or minimally invasive surgery? —A multidisciplinary personalized decision

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Abstract: Hepatocellular carcinoma (HCC) is one of the few gastrointestinal cancers with increasing incidence and mortality worldwide. It arises most frequently in the setting of cirrhosis and presents heterogeneously with varying degrees of preserved liver function. Surgical resection and liver transplantation represent the cornerstones of curative treatment worldwide, whereas tumor ablation is being increasingly used for small tumors. A variety of different treatment algorithms have been developed, taking into consideration both the tumor stage as well as the liver reserve. Currently, many treatment modalities are continuously evolving.

Transplantation criteria are expanding and even higher stage tumors become transplantable with neoadjuvant treatment. Surgical resection is being affected by the introduction of minimally invasive approaches. Ablation techniques are increasingly being used for small tumors. Combinations of different treatments are being introduced such as surgical resection followed by salvage transplantation.

In this continuously changing field, the objectives of this review are to summarize the current curative surgical treatment options for patients with HCC, focusing on the controversial areas that multiple treatments might be applicable for the same patient, highlight the recent advances in minimally invasive surgery for HCC, and emphasize the need for a multidisciplinary approach and treatment plan tailored to the characteristics of each patient.

Keywords: Hepatocellular carcinoma (HCC); surgical resection; liver transplantation; tumor ablation; minimally invasive approaches; multiple treatments; curative treatment

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Introduction-general concepts

The earlier diagnosis, coupled with advances in operative and postoperative management and patient selection have increased survival after hepatectomy for hepatocellular carcinoma (HCC) (1). Survival rates from HCC in the United States have doubled over the past 2 decades (2).

The two most frequently used curative treatments for HCC are surgical resection and orthotopic liver transplantation (OLT) transplantation. In patients with advanced cirrhosis and tumors within transplantation

criteria, in the absence of extrahepatic spread and macrovascular invasion, liver transplantation is the gold standard, as it allows treatment of the tumor and the underlying cirrhosis as well. In patients with well-preserved hepatic function (Child-Pugh grade A and early Child-Pugh grade B) and resectable disease, surgical resection is the most appropriate treatment (3-6).

For years, selection of candidates for resection has been based on the Child-Pugh classification, however even Child-Pugh A patients may already have liver functional impairment with clinically significant portal hypertension (7).

Table 1 The Milan and UCSF Criteria are most frequently used to select patients for transplantation whereas the MELD score to prioritize them in the waiting lists for OLT

Milan Criteria (9) [1996]	Single tumor ≤ 5 cm, or 2-3 tumors ≤ 3 cm, and no vascular invasion and/or extrahepatic spread
UCSF Criteria (10) [2001]	Single tumor ≤ 6.5 cm, or 2-3 lesions, none exceeding 4.5 cm, with total tumor diameter ≤ 8 cm no vascular invasion and/or extrahepatic spread
MELD Score	$0.957 \times \text{Loge}(\text{creatinine mg/dL}) + 0.378 \times \text{Loge}(\text{bilirubin mg/dL}) + 1.120 \times \text{Loge}(\text{INR}) + 0.643$

A normal serum bilirubin level and the absence of clinically significant portal hypertension (i.e., hepatic vein pressure gradient < 10 mmHg) appear to predict a low risk of postoperative liver failure after hepatectomy (8). Other researchers have emphasized that the Model of End-Stage Liver Disease (MELD) score (*Table 1*) can be a useful predictor of postoperative liver failure (11). In Japan, the indocyanine green retention rate is used to identify the best candidates for resection. The hepatocyte clearance of indocyanine green (ICG), an anionic dye, in the bile at 15 minutes is used to evaluate the hepatocyte function (12). A value of 40% retention suggests severe liver dysfunction and prohibits surgical resection (13).

The care of HCC patients was revolutionized after a landmark publication, that established OLT as therapy for HCC patients with cirrhosis, by Mazzaferro *et al.* (9) in 1996. It showed that patients with up to 3 foci of HCC each less than 3 cm in size or one tumor measuring less than 5 cm, without vascular invasion or extrahepatic spread (known as the “Milan criteria”) experienced a 5-year overall survival rate that was comparable to the survival rates of cirrhotics undergoing transplant without cancer (75%) with recurrence-free survival rate of 83%. Before that, it was known that transplantation was associated with a significant disease free survival for 3 or fewer tumors each within 3 cm compared to resection (14).

The Milan criteria have been validated (10,15,16) and are used for selection of patients in the USA and Europe, and accepted by the United Network for Organ Sharing (UNOS).

Subsequently, researchers in the University of California at San Francisco (UCSF), broadened the criteria to include single tumors measuring less than 6.5 cm or 2-3 tumors, none greater than 4.5 cm in size, with total tumor diameter not greater than 8 cm (*Table 1*) (10). The initial study revealed no adverse impact on survival (5-year overall survival rate 75%). However it was criticized as the tumor characteristics were obtained at the time of explantation. Subsequently, prospective validation of the UCSF criteria based on preoperative imaging yielded similar results (17). Patients meeting UCSF criteria had similar 5-year survival as patients

meeting Milan criteria both by preoperative imaging (18,19).

The MELD score (*Table 1*), was implemented in 2002 in an effort to quantify liver insufficiency and prioritize patients in waiting lists for OLT according to their mortality risk. Additional points were allotted to patients with HCC to equilibrate their mortality risk in relation to the mortality of end-stage cirrhosis. Patients with at least a solitary lesion that is greater than 2 cm in size are awarded 22 MELD points (20-22), adjusted every 3 months to reflect a 10% increase in mortality.

The UNOS criteria specify that patients eligible for liver transplantation should not be resection candidates. Only candidates with Stage II HCC are upgraded on the waiting list to a MELD score of 22 (equivalent to a 15% probability of candidate death within 3 months) with the intent to shorten their waiting time. An additional point every 3 months is granted based on the 20-50% dropout rate seen at 1 year due to progression of disease (15). One should always be aware that wait times can vary considerably among regions (23).

Patient eligibility is further being broadened with the use of neo-adjuvant liver-directed therapies. A favorable response to liver-directed therapies prior to transplant resulting in tumor down-staging to within Milan or UCSF criteria coupled with a surveillance period to select individuals that will remain transplantable allows patients with higher stage tumors to receive a transplant and experience similar cancer-specific survival.

In this context, we will examine the controversial areas between surgical resection, transplantation and ablation and give an overview of the recent advances in minimally invasive surgery.

Early hepatocellular carcinoma: surgical resection versus ablation

Ablative techniques destroy tumor via temperature changes [radiofrequency (RFA), microwave (MWA), cryotherapy or laser] while causing minimal damage to adjacent, normal liver, by injection of chemicals (ethanol, acetic acid) or by

Table 2 Comparison of different treatment modalities in selected recent studies, randomized controlled trials or meta-analyses

	Year; Author; Type, (n)	Tumors; (n) Size	RR; SR; (%)	Authors; Conclusions
Resection vs. radiofrequency ablation	2005; Huang GT <i>et al.</i> (29); Res. (n=38) vs. P.E.I. (n=38)	1-2; ≤3 cm	5Y RR: 48 vs. 45; 5Y SR: 82 vs. 46	Similar safety and effectiveness
	2006; Chen <i>et al.</i> (30); Res. (n=90) vs. P.A. (n=90)	Single; ≤5 cm	4Y RR: 46 vs. 52; 4Y SR: 67.9 vs. 64	Similar effectiveness; PA: less invasive
	2006; Lu <i>et al.</i> (31); Res. (n=54) vs. P.A. (n=51)	Within Milan	3Y RR: 18 vs. 49; 3Y SR: 86 vs. 87	Similar survival
	2010; Huang J <i>et al.</i> (32); Res. (n=115) vs. P.A. (n=115)	Within Milan	5Y RR: 51 vs. 29; 5Y SR: 76 vs. 55	Res. better survival lower recurrence
	2012; Feng <i>et al.</i> (33); Res. (n=84) vs. P.A. (n=84)	1-2; ≤4 cm	5Y RR: 61 vs. 50; 5Y SR: 75 vs. 67	Similar therapeutic effects PA might be incomplete in specific sites
	Resection vs. transplantation	2012; Lim <i>et al.</i> (34); Meta-analysis	Within Milan Criteria	5Y RR: 63; 5Y SR: 67
Laparoscopic resection (LLR) vs. Open resection (OLR)	2011; Li <i>et al.</i> (37); Meta-analysis; 244 LLR; 383 OLR			LLR: Less blood loss; fewer transfusions; shorter hospital stay; fewer complications; similar margins and recurrences
	2013; Parks <i>et al.</i> (38); Meta-analysis; 308 LLR; 404 OLR		5Y 62 vs. 57	LLR is acceptable alternative

Res., Resection; P.E.I., percutaneous ethanol injection; P.A., percutaneous ablation; RR, Recurrence rate; SR, Survival rate.

combination of the above. The combination of HCC of a soft tumor surrounded by a fibrotic liver makes HCC an ideal target for ablation (24).

The most commonly used ablation techniques are RFA and MWA with radiofrequency ablation being usually the first line (25). Although most ablations are done percutaneously, open surgery offers some advantages as percutaneous approaches cannot assess the abdomen for extrahepatic disease or additional hepatic disease detectable with intraoperative US (26).

In a review that included 95 studies between 1990-2004 and 5,224 ablated tumors, 2,369 of which being hepatocellular cancer, surgical ablation (open or laparoscopic) was superior to percutaneous. Local recurrences were 14% for tumors ≤3 cm and increased to 25% for tumors 3-5 cm and to 58% for tumors >5 cm (27). In a prospective cohort of 218 patients who underwent RFA for lesions ≤2 cm and were followed for a median of 31 months, overall 5-year survival was 55% and it was 68.5% for 100 patients who were considered potential candidates for resection. However, the overall 5-year risk of recurrence was as high as 80% (28).

Randomized controlled trials have compared the

recurrence and survival rates of ablation *vs.* resection with variable results which are summarized in *Table 2* (29-33).

Huang *et al.* (29) randomized 76 patients with 1 or 2 tumors ≤3 cm to surgical resection and percutaneous ethanol injection and found no statistically different 5-year disease free rates (45% *vs.* 48%, respectively) and survival rates (46% *vs.* 82%, respectively) concluding equal effectiveness. Chen *et al.* (30) randomized 161 tumors ≤5 cm to percutaneous ablation or surgical resection and reported similar 4-year disease free rates (46% *vs.* 52 %, respectively) and survival rates (67.9% *vs.* 64%, respectively). Huang *et al.* (32) randomized 230 patients within Milan criteria to percutaneous ablation for 115 and surgical resection for another 115 and found 5-year disease free rates (29% *vs.* 51%, respectively) and survival rates (55% *vs.* 76%, respectively) concluding that surgical resection was associated with better survival and lower recurrence. A smaller trial of 105 patients with tumors within Milan criteria, randomized them to surgical resection for 54 and percutaneous ablation with RFA or MWA for 51 and reported 3-year disease-free survival were 82% *vs.* 51% and 86% *vs.* 87% respectively which were not statistically significant and concluded similar

results (31). A more recent trial of 1-2 tumors of ≤ 4 cm comparing resection (n=84) and RFA (n=84) found 3-year survival rates of 75% and 67% respectively and recurrence-free survival rates 61% and 50%, respectively, concluding similar therapeutic effects but percutaneous RFA more likely to be incomplete at specific sites (33).

However, these trials have been met with some skepticism as they have power limitations, treatment allocation and consent withdrawal issues whereas patients were not always followed in an intention-to-treat manner. Further evidence is needed before drawing definite conclusions.

A recent meta-analysis of small HCC treated with RFA (n=441) or resection (n=436) found higher 5-year recurrence free and survival rates for the resection group whereas in a subgroup analysis of tumors ≤ 3 cm resection offered improved 3-year survival rates (39).

Another meta-analysis and cost-effectiveness with Markov modeling found that RFA has a similar life expectancy and lower cost for single tumors < 2 cm, resection had better life expectancy and cost-effectiveness for single tumors 3-5 cm whereas for 2-3 tumors ≤ 3 cm similar life expectancy and better cost-effectiveness for RFA (40).

Other studies focusing on long term outcomes for tumors < 3 cm found a superiority of resection compared to ablation (41,42) whereas long term results for single tumors < 7 cm comparing resection to embolization/ablation suggest that their might be a place for a combination of embolization and ablation of larger tumors (43).

Although the heterogeneity of findings necessitates more prospective randomized studies, especially from Western groups, before making definite conclusions many groups consider RFA as an effective alternative to resection for small (≤ 3 cm) HCC. The success of ablation decreases significantly in tumors measuring larger than 3 cm (44) and is not recommended for tumors larger than 5 cm (45).

Localized hepatocellular carcinoma: resection versus transplantation

Not every HCC patient is eligible for both resection and transplantation. Many of the HCC patients who undergo curative surgery harbor tumors beyond any criteria of transplantation. For example, resection is the only curative option for patients with large tumors and preserved liver function. The OS rate for patients with tumors greater than 10 cm is still approximately 40%, which is comparable oftentimes with survival in patients with smaller tumors (46). At the same time for many transplanted patients the degree

of compromise of their liver function does not allow a safe resection. OLT is clearly the choice for patients with significant cirrhosis, although advanced cirrhosis is associated with a worse outcome even after OLT (35). Outcomes of liver resection are poorer for multifocal HCC and some authors argue against resection for multifocal tumors although it can offer good survival rates in some patients. Liver transplantation addresses HCC along with its multifocal potential and underlying cirrhosis.

One of the controversial areas is the choice between surgery and transplantation for cirrhotics with local, early stage lesions and good hepatic reserve (Child-Pugh A). The UNOS transplantation criteria oversimplify this dilemma by stating that resection candidates are excluded from eligibility for transplantation. When HCC is endemic and the number of affected patients is large, guidelines are leaning towards recommending surgical resection as a first-line treatment option for patients with early HCC who have good liver function (47,48). The main benefits of surgery for this patient population are the comparable survival, the avoidance of long waiting periods for an OLT with danger of disease progression as well as the avoidance of lifelong immunosuppression. Patients within Milan criteria appear to have similar survival after resection or transplantation (49). The benefits of transplantation are the lower recurrence rates in stage-matched patients compared to resection (50). The higher recurrence rates associated with resection *vs.* OLT, have made some authors suggesting OLT for tumors within Milan criteria who have good liver function (34,51). True recurrence usually arises within the first 2 years after resection and are related to tumor characteristics such as microvascular invasion, satellites and multifocal disease, whereas late recurrences are related to *de novo* tumors due to the underlying cirrhosis (52-55). However, a recent review of tumors within Milan criteria who underwent curative intent surgical resection concluded that although recurrence rates are high the median overall survival at 5-year was 67% and is improving the recent years (34). When examining results from liver transplant registries such as the Organ Procurement and Transplantation Network and the European Liver Transplant Registry, involving 4,482 and 8,273 patients respectively, the 5-year survival rates of 51% and 60% respectively (35,36) in contrast to the rates of 70 per cent cited by high-volume established centers(9,56).

Salvage transplantation, is a technique which allows some patients to be treated effectively with resection, and offers OLT to patients whose cancer would recur after resection (57-59). Most of the recurrences after resection

occur in the liver and the majority of those are still eligible for a transplantation (49). Some researchers believe that the outcomes after salvage transplantation are similar to using transplantation as the first therapeutic choice i.e., without resection (60,61). This is supported by a recent meta-analysis as well (62). Others have expressed concern that operative mortality and recurrence rates are higher (63). The histopathologic information obtained at resection can also be used as a means to immediate listing for salvage transplantation or not. These represent interesting therapeutic strategies and more data are needed (57).

Another controversial area is the use of neoadjuvant more accurately called conversion treatment to higher stage tumors and subsequent transplantation. The Barcelona Clinic Liver Cancer Group has demonstrated 5-year survival $\geq 50\%$ using expanded criteria, or downstaging to Milan criteria with neoadjuvant therapies (64,65). Recently neoadjuvant TACE was successfully used to downstage 24% stage III/IV tumors to within Milan criteria and, subsequently OLT resulting in 94% survival after limited follow-up of 20 months (66). Yao *et al.* (67) reported that in carefully selected patients effective downstaging can be achieved in the majority followed by an observation period of 3 months minimum, and for the 57% of their patients who received an OLT the 4-year post-transplant survival was 92%. The strategy of adjuvant treatments while waiting for transplantation appears to be cost-effective for patients with anticipated waiting times longer than 1 year (68). Physicians are recommended to treat patients whose wait-list time exceeds 6 months (69,70).

Donor availability is a crucial factor in the decision making as tumors can progress during the waiting period and impede transplantation (71). Anywhere from 18% up to 50% of patients can progress beyond the Milan criteria while waiting for a transplant (15,35,72). In a study by Yao and colleagues, a 6-month waiting period for LT was associated with a 7.2% cumulative dropout probability, increasing to 55.1% at 18 months (73). Policies for transplantation aim to prioritize the sickest patients (74). Intention-to-treat analysis shows that waiting times for liver donors result in decreasing the 2-year survival from 84% to 54% and result in 5-year overall survival rates of 50-60% due to tumor progression (15). Geographic differences in waiting periods can significantly affect the decision to choose transplantation or not for early stage disease (23).

Efforts to address the large waiting list of LT candidates and to decrease the dropout rate have included new transplantation strategies (living donor, domino, split, use of extended criteria donors, and donors after cardiac death). Liver donor grafts

offer shorter waiting times however there are concerns that are associated with much higher recurrence rates compared to patients who receive a cadaveric transplant after being in an observation period for a time period appropriately selective those with a less aggressive tumor biology (75). A recent meta-analysis found decreased disease free survival associated with living donor liver transplantation compared to deceased donor liver transplantation (76). However, most available data are retrospective and heterogeneous; prospective studies are needed in order to delineate under which circumstances different transplant methods should be used.

Minimally invasive surgery for hepatocellular carcinoma

Laparoscopic and robotic surgeries are being increasingly used for hepatic resections. Although the amount of existing data is limited, there is growing evidence that laparoscopic surgery is associated with lower perioperative morbidity and postoperative ascites in patients with cirrhosis and appears to have similar oncologic outcome with adequate surgical margins and long-term survival (77).

The smaller, non-anatomic resections preserve liver parenchyma which might be crucial for patients with marginal hepatic function. Advantages which are met in laparoscopic surgery in general, such as less analgesia, smaller incisions, better cosmetic result, and faster discharges are applicable for HCC patients as well. A recent meta-analysis of the existing experience showed less blood loss, fewer transfusions, shorter hospital stay and fewer complications with no differences in surgical margins and tumor recurrences (37). On the other hand, inability to tolerate pneumoperitoneum and extensive adhesions preclude the use of laparoscopic liver resection (LLR), it entails a learning curve, major bleeding might be difficult to control laparoscopically and there are procedure-specific risks such as gas embolism (78).

There are no prospective randomized clinical data comparing laparoscopic or robotic surgery to open surgery. In a large retrospective study, 116 patients underwent laparoscopic liver resection for HCC reporting a 5-year survival rate of approximately 60% (79). In a matched pair study of 42 LLR with equal open resections laparoscopic surgery appeared oncologic adequate with no differences in surgical margins and disease recurrence at 30 months (80). Adequate surgical margins are important as a RCT comparing wide (2 cm) to narrow (1 cm) resection margins in solitary HCC patients reported decreased disease recurrence and improved survival for the wide margin

Table 3 The treatment of hepatocellular cancer depends on characteristics of the tumor, the underlying liver function, the functional status of the patient and the resources of the health care system

Factor	Surgical resection	Ablation	Transplantation
Tumor	Only curative option for large tumors; Best for small solitary tumors and very well preserved liver function; Limited to normal liver or Child-Pugh A and limited benefit if multiple tumors or major vascular invasion	High recurrence if ≥ 3 cm; Of limit if tumor in perihilar area or close to major vessels	1 tumor < 5 cm or 1-3 each < 3 cm; (Milan Criteria) or 1 tumor < 6.5 cm or 1-3 each < 4.5 cm and all together < 8 cm; ('UCSF criteria'); Best for not good surgical candidates
Liver	Does not address cirrhosis	Does not address cirrhosis	Treats cirrhosis
Patient	Assess comorbidities	Lowest procedural morbidity	Assess comorbidities
Health system	No waiting time	No waiting time	Donor shortage; up to 50% become ineligible while waiting

group (81). A recent review of the international experience with laparoscopic liver resection found 5-year survival rates comparable to open hepatic resections (78). A meta-analysis of studies on laparoscopic versus liver resection focusing on long term outcome and analyzing differently the HCC and the colorectal liver metastases patients found no differences in the 1-, 3- or 5-year survival rates (38). The international consensus conference on laparoscopic liver surgery suggested that laparoscopic surgery does not change the indications for surgery and its primary indication of laparoscopic procedures are single lesions 5 cm or less in peripheral segments recognizing the important of significant experience for extensive operations (82).

It cannot be emphasized enough that these reports of LLR come from high-volume, specialized centers and surgeons with significant experience both in open and laparoscopic surgery and the ability to choose laparoscopic surgery when it can be done safely and effectively.

Even fewer data exist about robotic liver resections (RLR) for HCC. Robotic surgery is associated with some intrinsic benefits which are visual (3-dimensional view, improved depth of perception, magnification capability) and technical (articulating instruments, degrees of freedom, tremor filtration) (83). In the few existing case series in appears to be equally effective with open and laparoscopic surgery with some authors supporting that it allows for better suturing in confined spaces, facilitating demanding procedures such as biliary reconstruction (84). Even though the existing data are limited to small case series it is important to emphasize that the existing series come from experienced surgeons and highly selected patients and tumors and are not generalizable at present. In a recent review of robotic surgery for oncologic surgery it was shown that robotic surgery is widely used

for variety of operations and for several procedures, there is evidence that robotics offer short-term benefits with comparable safety profiles and oncologic outcomes (85). However, long-term oncologic outcomes are generally lacking, and robotic surgeries are more costly than open or laparoscopic surgeries. Prospective, randomized, comparative studies are needed before any statements can be made.

Summary and future perspectives

Curative treatment of hepatocellular carcinoma is particularly challenging because it should incorporate a variety of factors related to the tumor stage (size, number, location, vascular involvement), the underlying hepatic reserve (cirrhosis early *vs.* late), the patient's medical comorbidities as well as the available resources which might be country specific or even hospital specific.

Surgical advances have enabled transplantation for patients with more advanced tumors and underlying liver disease. Pre-transplant therapy coupled with a surveillance period is increasingly being used in order to select the appropriate candidates for such an approach. At the same time surgical resection has entered a minimally invasive era with its inherent advantages and challenges.

Multiple risk stratification schemes exist in an attempt to assess risk and better select patients. One should also be aware that tumor clinical characteristics might be weighed differently by transplant *vs.* non-transplant surgeons (86).

Therefore, a multidisciplinary team, involving surgeons, hepatologists, oncologists, interventional and diagnostic radiologists, and pathologists is the most effective way to tailor the treatment plan to an individual patient's characteristics and to the available resources and experience (Table 3).

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Footnote

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Management of hepatocellular carcinoma should consider both tumor factors and background liver factors

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Abstract: As progression and outcome of relapsed hepatocellular carcinoma (HCC) are distinct from those of a second primary tumor, clonal analyses of initial and recurrent HCCs are thus clinically useful. Although several studies in Japan and Taiwan Area had shown that the multicentric origin (MO) recurrences were more common than intrahepatic metastases (IM), a recent report from China indicated that IM cases outnumber MO recurrences. In managing HCC cases, both tumor malignancy and background liver function are important considerations (and which we characterize as tumor factors and background liver factors, respectively); they indicate both appropriate treatment, and likely post-surgical outcome. In this editorial, we explain why the report had shown such a different conclusion. We also discuss current management of HCC.

Keywords: Tumor factors; background liver factors; hepatocellular carcinoma (HCC); intrahepatic metastases (IM); multicentric origin (MO)

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Introduction

One of the most common tumors worldwide is hepatocellular carcinoma (HCC). Although early HCC may be cured by surgical resection, the central concern of treating this fatal disease is that it is prone to multicentric occurrence. As progression and outcome of truly relapsed HCC are distinct from second primary tumors, clonal analyses of initial and recurrent HCC are clinically significant. Although several studies have shown multicentric origin (MO) recurrences to be more common than intrahepatic metastases (IM) (1-5), an article by a Chinese group concluded that IM-type recurrences were more common and had poorer prognosis than MO-type recurrences (6).

The technique of determining tumor clonality is well-tested from a previous investigation of loss of heterozygosity (LOH) loci using many microsatellites (7). As their figures and tables show, this method of assessing LOH and its frequency at each locus was suitable to their experiments. However, their results differed from those of other researchers, which necessitated consideration of all aspects. Regrettably, the authors did not address this in

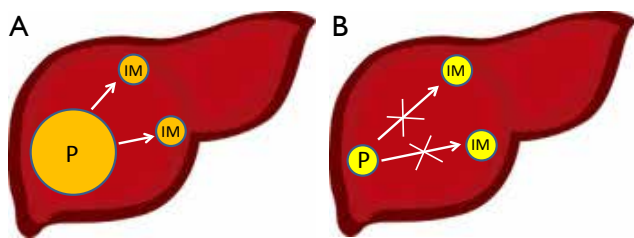
their discussion.

In this editorial, we would like to explain our view of HCC management, and discuss this divergent result.

Tumor factors and background liver factors

When considering appropriate therapy for HCC, we must consider factors of both the tumor itself and the background liver. Tumor factors include tumor size, differentiation, existence of a portal or venous invasion, AFP value etc. and clinical stage (which is determined by tumor factors). Background liver factors include existence of liver cirrhosis, prothrombin time (PT), serum albumin value, Child-Pugh classification, etc. Both tumor factors and background liver factors help determine appropriate treatment, and indicate likely post-surgical outcomes.

A meta-analysis of overall and disease-free survival following resection for HCC found in multivariate analyses that the strongest predictors of adverse prognosis were clinical stage of the tumor and vascular invasion, both of which are tumor factors (8). However, liver background



P: primary lesion (tumor factor ↑) P: primary lesion (tumor factor ↓)

Figure 1 Possibility of intrahepatic metastatic (IM) recurrences with different tumor factors. (A) Tumor factor grade indicates high malignancy; the tumor would tend to make IM recurrences; (B) Primary lesion was resected in early stage; IM recurrences would be less likely to occur.

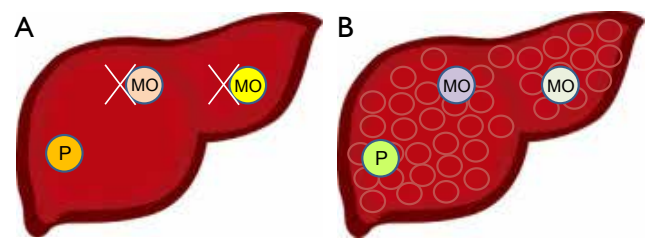
factors, including poor Child-Pugh score and existence of cirrhosis, were also associated with worse prognoses.

Among cancers with apparent recurrences, in cases where tumor factors indicate high malignancy, we can suppose that the original tumor would tend to generate IM recurrences (Figure 1), whereas MO type recurrences would be produced in other portions of the liver, in environments with poor background liver factors (Figure 2); IM recurrences are more common than MO recurrences, but the backgrounds of the examined cases differ greatly.

HCC of HBV or HCV origin

Tables 1 and 2 show background liver factors and tumor factors, respectively, of 320 patients who underwent liver resections in our department. The clinicopathological features of these patients as a group do not seem to differ greatly from other Japanese patients with HCC, and HCC from chronic non-B, non-C hepatitis, such as non-alcoholic steato-hepatitis (NASH), is similarly increasing in Western countries. In examining clonal origins of recurrent tumors (4,5), we examined 19 cases (14 of HCV origin, 3 of HBV origin, and 2 of non-B, non-C hepatitis), whereas the study from China examined 38 cases (37 with HBV infection and 1 non-B, non-C hepatitis).

A report from Japan compared HCC of HBV origin with HCC of HCV origin (9), and found that, although the AFP level of HBV-based tumors was higher, other tumor factors, such as size or TNM stage, were not different from HCV-based tumors. Patients with HCC based on either HBV or HCV were probably periodically screened as candidates for HCC because of these virus infections. Liver functions, such as albumin levels, were worse in patients with HCV



Background liver factor: good Background liver factor: bad

Figure 2 Possibility of secondary [multicentric origin (MO)] recurrences with different background liver factors. (A) As background liver factors were well conserved; the liver is less likely to generate MO-type recurrences; (B) In a liver with poorly conserved background function, MO recurrences in other parts of the liver are more likely to occur.

Table 1 Background liver factors	
Variables	Value
Age (years), mean ± SD (range), (n=320)	63.4±10.1 [21-84]
Sex, (n=320)	
Male	261 (81.6%)
Female	59 (18.4%)
Viral infection, (n=319)	
HBV	78 (24.5%)
HCV	177 (55.5%)
HBV/HCV	4 (1.2%)
Non-HBV/non-HCV	60 (18.8%)
Albumin (mg/dL), mean ± SD, (n=317)	3.84±0.51
Total bilirubin (mg/dL) mean ± SD, (n=317)	0.81±0.50
PT (%) mean ± SD, (n=316)	87.4±15.5
Liver cirrhosis, (n=309)	
(+)	130 (42.1%)
(-)	179 (57.9%)
Child-Pugh classification, (n=315)	
A	293 (93.0%)
B	22 (7.0%)
Liver damage score, (n=308)	
A	237 (77.0%)
B	70 (22.7%)
C	1 (0.3%)
PT, prothrombin time.	

than HBV, and patients with HBV-based HCC had longer overall survival and disease-free survival.

A report from the United States (10) found that patients with HBV were more likely to develop HCC at

Table 2 Tumor factors

Variables	Value
Tumor size (mm), mean \pm SD (range), (n=311)	45.1 \pm 32.0 (0.8-175)
Tumor number, solitary/multiple (n=320)	235 (73.4%)/85 (26.6%)
AFP (ng/mL), <100/ \geq 100 (n=311)	211 (67.8%)/100 (32.2%)
Portal vein or hepatic vein invasion, +/- (n=312)	85 (27.2%)/227 (72.8%)
Differentiation, (n=311)	
Well	66 (21.2%)
Moderate	220 (70.7%)
Poor	25 (8.1%)
Growth form, expansive/infiltrative (n=311)	257 (82.6%)/54 (17.4%)
Formation of capsule, +/- (n=316)	215 (68.0%)/101 (32.0%)
Infiltration to capsule, +/- (n=315)	174 (55.2%)/141 (44.8%)
Septal formation, +/- (n=310)	205 (66.1%)/105 (33.9%)
Serosal infiltration, +/- (n=277)	66 (23.8%)/211 (76.2%)
Surgical margin, +/- (n=288)	59 (20.5%)/229 (79.5%)
Japanese staging	
I	34 (10.8%)
II	163 (51.7%)
III	77 (24.4%)
IVa	38 (12.1%)
IVb	3 (1.0%)
AFP, alpha-fetoprotein.	

young age than patients with HCV, with greater serum AFP production and larger tumors, but without cirrhosis. Conversely, patients with HCV were more likely to develop HCC in association with multiple co-morbidities including cirrhosis, and at older ages. Thus, we supposed that HCC outcomes would vary with these viral causes.

Malignancy of the tumor factors

When we looked more closely at the backgrounds of cases that had more IM-type recurrences, their tumors showed vascular invasion, which is the strongest adverse prognostic factor—as high as 65% in IM type. Moreover, the average tumor diameter was also as large as 65 mm, which indicated that tumor was highly malignant and the TNM stage was advanced. Naturally, cancer in advanced stages shows a poor prognosis.

Frequency of vascular invasion among our cases in Japan

was about 27%; average tumor diameter was 45 mm (Table 1)—almost equivalent to the MO type cases. In our earlier investigations, the average diameter of primary tumors was 41 \pm 27 mm (4, 5).

We predicted the probability of each recurrence of IM and MO. Figure 3A compares a case with malignant tumor factors with a less-malignant case in IM type recurrence, and Figure 2B compares a case with poor background liver factors with a case with healthier background liver factors in MO-type recurrence (Figure 3B). Figure 3C shows the probability of total recurrence, comparing cases with malignant tumors but relatively healthy background livers (blue solid line: MO, blue dotted line: IM), to cases with less malignant tumors but poor background livers (orange solid line, MO; orange dotted line, IM). Although the total recurrence rate is not so different in the first few years after surgery, in the later years, cases with poorer background livers would show higher recurrence rates (Figure 3D).

Thus, we thought that metastatic recurrences increased after surgery because tumor factors of their cases were more malignant. Moreover, in our cases, we considered that background livers were more damaged by HCV, which implied that generating secondary tumors occurred more readily.

Recurrence-free survival rate in HCC cases

Unlike other cancers, the recurrence-free survival rate of HCC must include both IM and MO elements, either of which might recur in any HCC case. A trial to identify which tumor factors and background liver factors were most associated with IM and MO (respectively) might be interesting, and could plausibly allow prediction of recurrence by analyzing a resected tumor. If, for example, the change in percentage of risk for IM and MO recurrence at two years after surgery could be found, we think it will be an epoch-making trial.

Over-all survival rate in HCC cases

The components of overall survival are even more complex. After the initial tumor resection, survival rate changes with the grade of tumor factors of recurrent HCCs, and by their methods of therapy. Moreover, for HCCs, the specific cause of death also varies (e.g., cancer progression, liver failure, etc.), and thus affects overall survival. This would be difficult to predict at initial resection, even if the treatment methods and rule of observation were standardized and causes of death was examined in detail.

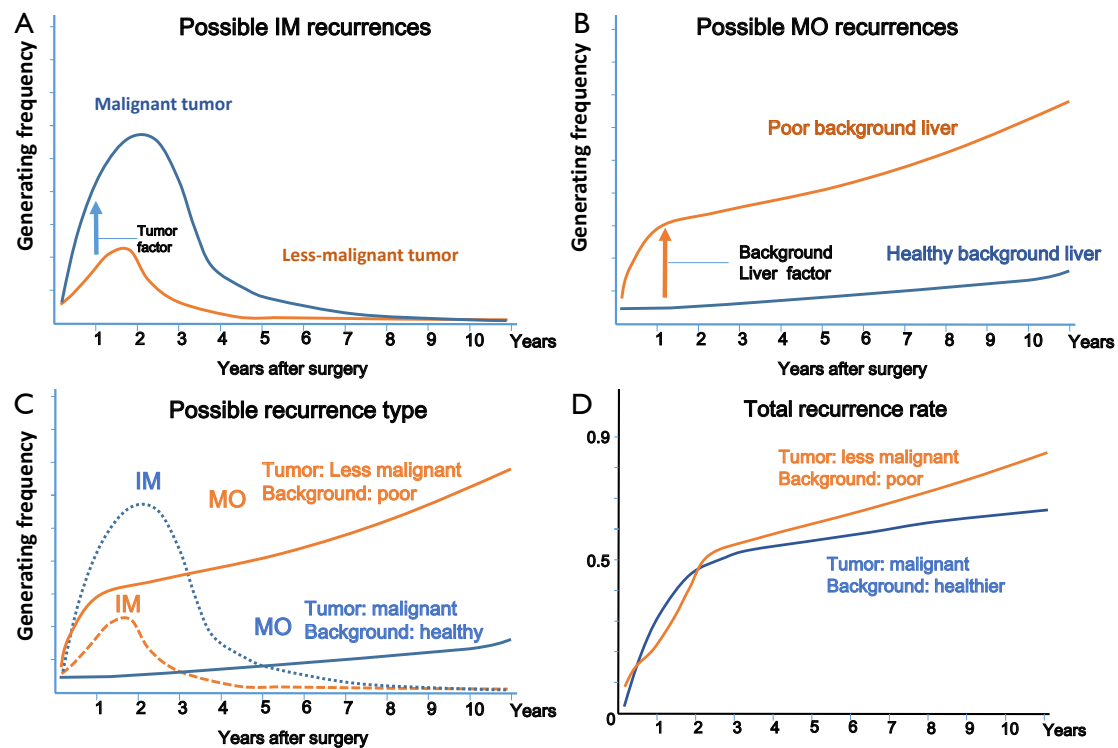


Figure 3 (A) Possible IM recurrences: lines indicate a liver with malignant tumor factors (blue line) and a less malignant case (orange line) with IM type recurrences. IM recurrences happened more in malignant tumors, especially in the first few years after surgery; (B) Possible MO recurrences: a liver with poor background factors would have increased probability of MO-type recurrences, especially in late years after surgery; (C) Probability of total recurrence when a patient had a malignant tumor and a healthy background liver (blue solid line: MO, blue dotted line: IM), or a less malignant tumor and a poor background liver (orange solid line: MO, orange dotted line: IM); (D) Total recurrence rate after liver resection in each case: although the two lines were not so different in early years after operation, in later years, patients with poorer background liver would show a higher recurrence rate. IM, intrahepatic metastases; MO, multicentric origin.

How to manage HCCs for better survival

Physicians who manage HCC cases should be mindful of the following things. IM recurrence risk mainly depends on tumor factor malignancy. To avoid aggravating tumor factors, periodical screening of patients with HCC is important, particularly those with chronic hepatitis.

After the surgery for the primary lesion, recurrences are best discovered at the earliest stage possible to prevent exacerbating tumor factors of the recurrent lesion.

To reduce risk of MO recurrences, anti-viral therapy should be recommended, and should probably be used as a postoperative adjunct therapy.

Surgical managements of HCC

Intraoperative factors that affect prognosis also strongly influence IM recurrence. Surgeons must take care to

leave clean surgical margins, decrease blood loss, etc. In recurrences found after surgery, we should examine both tumor and background liver factors. If the former shows high malignancy, the recurrence is probably due to IM. However, poor background liver factors indicate likely MO; adjuvant anti-viral therapy should therefore be started promptly.

Conclusions

The significance of new information and recognition of clinical patterns in management of HCC should be deeply considered as we strive to improve patient outcomes.

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Footnote

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A bridge between multi-omics data and the management of hepatocellular carcinoma

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Recent technological advancements in comprehensive genome and transcriptome analyses have clarified the molecular pathways underlying the development of human hepatocellular carcinomas (HCCs). However, there is still a gap between the results of multi-omics analyses and their clinical implications. Because of the large quantity of data obtained through these types of analyses, identifying target molecules important for clinical uses is difficult.

Miao *et al.* linked multi-omics results with the management of HCC (1). They performed whole genome sequencing of noncancerous liver samples and multiple HCC nodules of the same patients. They distinguished two types of nodules—metastatic nodules derived from a primary tumor and multicentric nodules that occur synchronously—and successfully clarified the clonality and aggressiveness of multifocal HCCs. For example, metastatic nodules showed a sequential progression of genetic alterations from the primary tumor to the portal vein thrombus and metastatic satellite metastatic lesions. Previously, Tao *et al.* also analyzed mutations in multiple nodules of the same patients using whole genome data; they elucidated cancer growth dynamics and the associated mutations (2). It is possible that comprehensive analyses of genetic alterations should be a powerful tool to distinguish metastatic lesions from the multicentric occurrence of HCCs, and to manage HCCs. For example, the recent development of direct-acting antiviral agents for hepatitis C has enabled the eradication of the virus even in patients with advanced liver cirrhosis and HCC (3). It is also known that a sustained virologic response after treatment of hepatitis can decrease the emergence of HCC and mortality. Therefore, if it could be demonstrated that nodules were not metastatic but instead originated from independent

tumors, such patients would be suitable for antiviral therapies after the curative treatment of HCC, preventing recurrence. Moreover, the indication of liver transplantation for patients with HCC could be expanded by this type of molecular analysis. Typically, the Milan criteria are applied for selecting cases with HCC that are appropriate for liver transplantation. However, it is possible that the risk of recurrence differs for patients with and without metastatic lesions. From this point of view, the clonality of multifocal nodules should be considered for the indication of liver transplantation in HCC patients.

Using a large patient cohort, Miao *et al.* also identified the key mitotic checkpoint regulator *TTK* as a promising overall prognostic marker for HCC (1). Based on the transcriptome analysis, more molecules responsible for cellular function were found to be deregulated to a greater extent in metastatic lesions than in primary tumors. On the other hand, gene expression alterations in non-metastatic nodules resulting from multicentric occurrences were trivial. *TTK* expression was significantly correlated with tumor grade in the expression analysis using a large cohort of HBV-positive HCC cases. Importantly, *TTK* mRNA expression levels were inversely correlated with the recurrence-free survival and overall survival of these patients. The group with high *TTK* expression showed shorter times to HCC recurrence than the group with low *TTK* expression. This finding could also have clinical importance because it affects the HCC management strategy; the selection of HCC cases for invasive treatment including liver transplantation, and the need for antiviral treatment for HCV-positive cases after curative treatment of HCC (4). Further validation using HCV-related and non-viral HCC patients is necessary because the mutational profile might differ between HBV-

positive and -negative HCCs (5,6). Nevertheless, it is possible that “omics” analyses will be a powerful tool for the development of a cure for liver disease including HCC in the near future.

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Footnote

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A review of hepatocellular carcinoma (HCC) staging systems

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Abstract: Accurately staging patients is essential to oncology practice. Cancer staging contributes to prognostication, guides management decisions, and informs clinical, epidemiologic, and health services research. In hepatocellular carcinoma (HCC), staging poses unique challenges due to the geographic and biological heterogeneity of the disease and lack of consensus on how to best classify patients. The features included in various HCC classifications systems have evolved over the last 50 years, but in general, need to account for both tumor characteristics as well as the burden of underlying liver disease.

In this review, we discuss the Child-Turcotte-Pugh and Model for End-Stage Liver Disease, two practical systems that reflect the degree of hepatic dysfunction. We then describe several HCC staging systems, reviewing their development, and applicability to clinical practice, with a critical look at their validation. Finally, we look ahead to novel systems utilizing molecular markers. It is hoped this review will provide context regarding the use of current staging and scoring methods and a glimpse of what we can expect with future systems.

Keywords: Hepatocellular carcinoma (HCC); score; staging systems; stage

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Introduction

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer death worldwide. Despite its enormous global impact, there is much disagreement about how best to stage and characterize this cancer. The differences in approach to HCC are due in part to its inherent clinical and biologic heterogeneity, but are also a function of the prism through which clinicians and clinical researchers observe the cancer. Despite numerous validation and comparative studies, and “consensus” panel recommendations generated by hepatologists, oncologists, surgeons and radiologists, with varying degrees of multidisciplinary collaboration, there is still no single system that could be called the “standard” for classifying HCC.

Like with any cancer, the goals of a tumor staging system in HCC are to estimate a patient’s prognosis, which allows for appropriate therapy to be selected. The identification of that appropriate therapy, in turn, requires a staging

paradigm that standardizes the platform for researchers to exchange data regarding treatments and outcomes (1). Ideally, and most challenging with HCC, staging systems should assure balance of important prognostic factors across treatment arms within a clinical trial population to avoid confounding of outcomes by baseline differences.

The task of accounting for the heterogeneity of HCC is not only a reflection of the different viral or metabolic conditions at the root of the cancer, but also of the extent of impaired liver function. The challenge of measuring the contributions of the cancer and hepatic dysfunction to the overall prognosis was recognized with the first modern-era liver cancer staging system, which was proposed at the Hepatocellular Carcinoma International Symposium in Kampala, Uganda in 1971 (2). Subsequent attempts at HCC staging have continued to employ both tumor and liver-specific variables in the setting where there is often very limited diagnostic tissue, which means that there may be no

Table 1 Comparison of HCC staging systems

System	Tumor factors					Liver factors					PS
	Size	Nodes	Met	PVT	AFP	CTP	Alb	Bili	ALP	Ascites	
TNM	✓	✓	✓								
Okuda	✓						✓	✓		✓	
BCLC	✓		✓	✓		✓		✓			✓
CLIP	✓			✓	✓	✓					
JIS	✓	✓	✓			✓					
CUPI	✓	✓	✓		✓			✓	✓	✓	
French				✓	✓			✓	✓		✓

Met, metastases; PVT, portal vein thrombosis; CTP, Child-Turcotte-Pugh; Alb, albumin; Bili, bilirubin; ALP, alkaline phosphatase; PS, performance status.

information from a pathological examination. This reflects the fact that biopsy may not be a pre-requisite to diagnosis of HCC (3). Serum alpha-fetoprotein (AFP) is a commonly-used screening biomarker in patients at risk for HCC but is not sufficient for surveillance or diagnosis due to lack of sensitivity and specificity (4). Although retrospective data have established high AFP at presentation as a negative prognostic factor, serum AFP level is included in only a subset of HCC staging systems (*Table 1*).

For a staging system to be effective and widely used, it has to be reliable, reproducible and simple, using data elements that can be obtained as part of standard clinical practice across a wide range of treatment sites. Most HCC staging systems have identified prognostic factors through multivariate analyses of large cohorts of patients to weight the different variables according to prognostic impact. Once proposed, a classification system must be validated across the spectrum of HCC cohorts.

We will first review the principal system used to score underlying liver function in cirrhotic patients, the Childs-Turcotte-Pugh score (CTP). Next we consider the Model for End-Stage Liver Disease (MELD), which predicts short-term prognosis and is extensively used in liver transplant evaluation. We then examine seven commonly-utilized HCC staging systems with respect to their development and limitations. Finally, we will look ahead to novel molecular and biomarker-based staging systems which we hope will enable us to refine our understanding and classification of this complex and heterogeneous cancer.

Child-Turcotte-Pugh (CTP)

The prognostic importance of liver function was first

codified in the Child-Turcotte publication in 1964 (5), where patients being considered for surgery for portal venous shunting were risk-stratified into three categories. The initial Child-Turcotte staging included clinical assessments of encephalopathy, ascites, nutritional status and laboratory measurements of serum bilirubin and albumin and then was modified by Pugh in 1973 (6), with the replacement of nutritional status by prothrombin time (*Table 2*).

The CTP score is the simplest and most widely used grading system for liver function. Given that most HCCs arise in the milieu of cirrhosis, and surgical interventions have the highest potential of cure, CTP is ubiquitous in the evaluation of HCC. In addition to routine clinical and research use, the CTP score is referenced routinely by regulatory agencies reviewing new drug applications. However, the drawbacks are many, including inter-laboratory variations, day-to-day fluctuations in the key parameters and the subjective nature of the clinical grading of encephalopathy and ascites (7). Though the CTP score by itself does not include any HCC-specific parameters, it has been incorporated into multiple contemporary scoring systems including Cancer of the Liver Italian Program (CLIP) and Barcelona Clinic Liver Cancer (BCLC).

Model for end stage liver disease (MELD)

The MELD score, initially developed to determine prognosis following a transjugular intra-hepatic shunt (TIPS) procedure for liver failure (8), is now widely used in the liver transplant arena to prioritize donor liver allocation. It is a logarithmic score that is comprised of International Normalized Ratio (INR), serum creatinine, total serum bilirubin and the etiology of cirrhosis. After

Table 2 Child-Turcotte-Pugh score

Measurements	Score		
	1	2	3
Encephalopathy	None	Mild	Moderate
Ascites	None	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (mg/dL)	>3.5	2.8-3.5	<2.8
PT (seconds prolonged)	<4	4-6	>6

Stage A, 5-6 points; Stage B, 7-9 points; Stage C, 10-15 points.

$$\text{MELD Score} = 9.57 * \ln(\text{Serum Creatinine in mg/dL}) + 3.78 * \ln(\text{Serum Bilirubin in mg/dL}) + 11.2 * \ln(\text{INR}) + 6.43$$

Figure 1 Model for end-stage liver disease (MELD) model, UNOS modification.

minor modifications, the resulting MELD model, which has been validated in 4 independent populations (9), can be generalized to all patients with end-stage liver disease.

A modification of the MELD score formula (*Figure 1*), with the variable for etiology of cirrhosis excluded, was adopted by the United Network of Organ Sharing (UNOS) in February 2002 as the standard by which transplant recipients are prioritized. Given that a higher score is associated with shorter survival, priority for receipt of a transplant is logical. The implementation of MELD led to reduction in registration for the waiting list and mortality while on the list (10), as well as reduced median waiting time to liver transplantation (11).

The strength of the MELD score is its prediction of short-term mortality, and is therefore able to identify the “sickest” patients for graft allocation. However, it fails to correctly classify a portion of patients with advanced cirrhosis (12), and several groups have offered refinements to the score (13-15).

Selected patients with HCC may be appropriate candidates for a curative orthotopic liver transplant (16,17). However, patients with early stage HCC but compensated liver disease may suffer cancer progression while waiting for their MELD score to move them up on the graft allocation priority list. This has been “remedied” by awarding extra points to the MELD score for a diagnosis of HCC; while this has been shown to improve the likelihood of timely

transplant in these patients (18), the tilt towards allocating livers to patients who could succumb to the malignancy has been debated (19).

Overview of current staging systems

TNM

No cancer would be complete without a TNM staging algorithm. The criteria are developed jointly by the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) and have been updated regularly since the first edition in 1977; the Seventh Edition took effect in 2010 (1).

The TNM system assesses primary tumor features (T), the, presence or absence of nodal involvement (N) and distant metastasis (M). Additional information which may be included are the histologic grade (G) and fibrosis score (F) based on the Ishak classification (20), but these factors do not affect staging (*Table 3*).

Recent versions of the TNM staging have been influenced largely by data from patients who underwent curative resections. In 2002, Vauthey *et al.* proposed a simplification of the TNM, after stratifying the survival of 557 patients who underwent resections. They recommended that the T-component focus on vascular invasion, tumor number and tumor size (21). In a similar analysis of surgical patients in Hong Kong, with a predominance of hepatitis B, Poon and Fan found the key prognostic factors for 5-year survival are major vascular invasion, microvascular invasion and involvement of surrounding tissues (22).

In essence, the TNM system is based on histopathology and is applicable in prognosticating survival for the distinct minority of patients who have undergone curative surgery. By itself, the TNM T-stage does not offer guidance on resectability and therefore adds very little discriminatory

Table 3 American Joint Committee on Cancer (AJCC) TNM Staging for Liver Tumors (7th ed., 2010) (1)

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors none more than 5 cm		
T3a	Multiple tumors more than 5 cm		
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein		
T4	Tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1
Histologic grade (G)			
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated		
G4	Undifferentiated		
Fibrosis score (F)			
The fibrosis score as defined by Ishak recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale			
F0	Fibrosis score 0-4 (none to moderate fibrosis)		
F1	Fibrosis score 5-6 (severe fibrosis or cirrhosis)		

value to patient assessment. It has little relevance to patients presenting with advanced disease because of the model's inability to reflect the prognosis of underlying liver disease.

Okuda score

The Okuda system is a prognostic score introduced in 1985 (23) and incorporates both tumor features as well as

the degree of underlying cirrhosis. Using a cohort of 850 patients with an unequivocal diagnosis of HCC between 1975-1983, Okuda and colleagues devised a staging system based on four factors representing advanced disease. This includes tumor occupying greater or less than 50% of the liver, the presence or absence of ascites, and serum albumin and bilirubin levels (*Table 4*). In the original cohort, median survival was 11.5 months for Stage I, 3.0 months for Stage

Table 4 Okuda staging

Factors representing advanced disease	
Tumor size >50% of liver	
Ascites	
Albumin <3 g/dL	
Bilirubin >3 mg/dL	
Stage I	No factors present
Stage II	1-2 factors
Stage III	3-4 factors

II and 0.9 months for Stage III.

Because many in the index population (38.5-45%) died of liver failure, the system emphasizes underlying liver dysfunction.

Despite not having been prospectively evaluated, the Okuda system is still in use, but with the evolution of imaging and surveillance, it is the extraordinary patient whose tumor is not discovered well before it occupies more than half the liver. The system's biggest shortcoming is its relatively crude classification of early stage patients and subsequent staging systems have tried to better characterize Okuda Stage I patients. Contemporary models have all adopted the practice of including liver-specific variables and some have even incorporated the Okuda score into newer formulae. Indeed, the Okuda system remains the standard against which newer scoring systems are compared.

BCLC staging classification

The BCLC classification was first published in 1999 (24) and is considered the standard HCC system by the American Association of for the Study of Liver Disease (AASLD) (4) and European Association for the Study of the Liver (25). These endorsements and the substantial contributions to HCC research by the hepatologists who described BCLC sometimes disguise the reality that not every clinician and researcher in the field agrees with the stance of the distinguished liver societies.

Derived from a single institution experience, BCLC takes into account size and extent of the primary tumor, liver function and physiological factors and incorporates the Okuda stage and Child-Pugh score (*Table 5*). There is a corresponding treatment schedule for each stage (*Table 6*), ranging from curative therapies such as resection or transplant for early stage patients to best supportive care

for end-stage patients. Prospective and retrospective studies on Italian cohorts (26-28), in which the majority of patients underwent radical therapies, found BCLC to be a better prognostication system compared to the other commonly used systems. Marrero *et al.* reported in 2005 that, in a cohort of 239 consecutive American patients seen at the University of Michigan Medical Center's Liver Clinics, BCLC had the best prognostic stratification when compared to 6 other commonly used staging systems (29). While other investigators have failed to come to the same conclusion (30-33), BCLC has gained widespread popularity since its introduction.

More controversial than the prognostic scoring system is the treatment algorithm that is a part of the BCLC. It lacks discrimination within the intermediate stage (BCLC-B) patients, a large proportion of the HCC population. The burden of liver disease which falls under BCLC stage B can vary greatly, from four small tumors to near complete replacement of the liver by tumor, provided liver function is preserved and there is no vascular invasion, extrahepatic spread, or compromised performance status, which would upstage to BCLC stage C or D. Consequently, in practice, some BCLC-B patients may no longer be eligible for liver-directed therapies, and are generally treated following BCLC-C algorithms. The heterogeneity within the BCLC-B classification also introduces the potential for prognostic heterogeneity within clinical research protocols employing BCLC stage for eligibility or stratification.

CLIP score

The CLIP score was proposed in 1998 and by incorporating Child-Pugh stage, tumor morphology, AFP level and the presence or absence of portal vein thrombosis, takes into account both liver function and tumor characteristics (34) (*Table 7*). However, what constitutes "massive" is subjective, without specific size criteria.

To derive the score, a retrospective analysis was performed between 1990-1992 of 435 HCC consecutive patients, almost all with cirrhosis, presenting to the 16 CLIP institutions. Univariate analysis identified significant predictors of overall survival, and these were included into a stratified Cox proportional hazards regression model, with loco-regional therapy as the stratification factor. The majority of patients (56.8%) received some form of loco-regional treatment and only a few (2.7%) underwent surgery.

The CLIP score (range from 0-5) was first validated

Table 5 Barcelona Clinic Liver Cancer (BCLC) staging classification

Stage	PST	Tumor status		Liver function studies
		Tumor stage	Okuda stage	
Stage A: early HCC				
A1	0	Single	I	No portal hypertension and normal bilirubin
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumors <3 cm	I-II	Child-Pugh A-B
Stage B: intermediate HCC	0	Large multinodular	I-II	Child-Pugh A-B
Stage C: advanced HCC	1-2*	Vascular invasion or extrahepatic spread	I-II	Child-Pugh A-B
Stage D: end-stage HCC	3-4 [†]	Any	III	Child-Pugh C

PST, Performance Status Test; Stage A and B, All criteria should be fulfilled; *, Stage C, at least one criteria: PST1-2 or vascular invasion/extrahepatic spread; [†], Stage D, at least one criteria: PST3-4 or Okuda Stage III/Child-Pugh C.

Table 6 Treatment schedule proposed for hepatocellular carcinoma (HCC) cirrhotic patients according to the BCLC classification system

Stage	Treatment intention	First/second choice
Stage A: early HCC		
A1	Radical	Surgical resection
A2		Surgical resection → OLT/percutaneous treatment
A3		OLT/percutaneous treatment
A4		OLT/percutaneous treatment
Stage B: intermediate HCC	Palliative*	Transarterial embolization (associated or not to percutaneous treatment) chemoembolization
Stage C: advanced HCC	Palliative*	New agents
Stage D: end-stage HCC	Symptomatic	Supportive treatment

*In the setting of phase II investigations or randomized control trials.

Table 7 Cancer of Liver Italian Program (CLIP) scoring system

Variables	Scores		
	0	1	2
Child-Pugh stage	A	B	C
Tumor morphology	uninodular and extension ≤50%	multinodular and extension ≤50%	massive or extension >50%
AFP (ng/dL)	<400	≥400	
Portal vein thrombosis	No	Yes	

by the original investigators on a prospective cohort of 196 HCC patients with cirrhosis being enrolled in a clinical trial (35) and has subsequently been validated on Japanese, Canadian and German cohorts of patients (36-38). CLIP was found to be a good predictor of recurrence in a retrospective analysis of a Chinese cohort of

174 predominantly Hepatitis B positive patients with HCC who underwent curative resection (39). The CLIP score also performed better than other prognostication systems when used to retrospectively analyze 131 Korean patients, with unresectable HCC, who were undergoing transarterial chemoembolization (TACE) (40).

Table 8 Japan integrated staging (JIS) scoring system

Variables	Scores			
	0	1	2	3
Child-Pugh stage	A	B	C	
TNM stage by LCSGJ	I	II	III	IV

LCSGJ, Liver Cancer Study Group of Japan.

The CLIP score is not flawless. The paucity of patients undergoing curative surgery in the original cohort may limit its ability to prognosticate early stage patients. Although a retrospective analysis of patients in Canada (37), 28% of whom underwent surgery, CLIP was found to be superior to Okuda in identifying early stage patients with a good prognosis, it is not as accurate at the JIS (see below). However, other investigators have suggested the CLIP is comparatively superior to contemporary systems (41,42) and may be further improved by the inclusion of performance status (42).

Japan integrated staging (JIS)

In 2003, the The Liver Cancer Study Group of Japan (LCSGJ) proposed the JIS score (43). Arguing that the CLIP score, previously validated in a Japanese population (36), did not provide sufficiently accurate prognostication for the early stage patients commonly diagnosed in Japanese centers due to screening programs and increased awareness of HCC, these investigators directed their efforts towards emphasizing the very favorable group from other early-stage patients.

The JIS score was developed from a cohort 722 consecutive Japanese patients and appears superior at prognosticating survival compared to CLIP, particularly in patients with early stage disease. The JIS system incorporates the LCSGJ's modification of the TNM system and the Child-Pugh score (*Table 8*). Patients with a JIS score of 0 had a 10-year survival rate of 65% while patients with a CLIP score of 0 had 10-year survival rates of only 23%.

While it has been validated in Japan (44,45) and in other Asian populations, the JIS has not been prospectively validated in a Western population. There have been attempts to modify the JIS (46), as well as to incorporate biomarkers like AFP into the system (47,48); these versions have also not been validated and have not gained traction outside of Japan.

Table 9 Weight of six prognostic factors in Chinese University Prognostic Index (CUPI)

Variable	Weight
TNM Stage	
I and II	-3
IIIa and IIIb	-1
IVa and IVb (reference)	0
Asymptomatic disease on presentation	-4
Ascites	3
AFP ≥ 500 ng/mL	2
Total bilirubin ($\mu\text{mol/L}$)	
<34 (reference)	0
34-51	3
≥ 52	4
Alkaline phosphatase ≥ 200 IU/L	3
CUPI Stages: score ≤ 1 (Low risk); 2-7 (Intermediate risk); ≥ 8 (High risk).	

Chinese University Prognostic Index (CUPI)

The CUPI was developed at a single center in Hong Kong based on a retrospective analysis of 926 ethnic Chinese patients (49). As expected, based on the population's demographics, the cohort had a high proportion with hepatitis B (79%). The cohort was also predominantly male (83%) and the majority (58.4%) of patients were too advanced to receive any surgery or interventional therapy. A Cox regression model was constructed containing TNM staging followed by forward stepwise addition of 18 other relevant clinical variables. The outcome measurement was death within 3 months of diagnosis. In addition to confirming TNM staging as a highly significant predictor of 3-month survival, the model identified presentation with asymptomatic disease, AFP level, total bilirubin, serum alkaline phosphatase and clinical detection of ascites as significant prognostic factors (*Table 9*).

The original investigators were able to prospectively validate CUPI in a group of 595 largely hepatitis-B positive Asians (50). The CUPI is well-designed and easy to use. The weighted scoring system in CUPI is more refined than the rather blunt assignment of points in CLIP and JIS. CUPI is derived from a cohort which is predominantly hepatitis B and performs well in similar Asian populations. Of note, 2 recent studies have found that CUPI, as well as the CLIP score, are the best models to predict survival

Table 10 French classification

Weight	0	1	2	3
Karnofsky index (%)	≥80			<80
Serum bilirubin (μmol/L)	<50			≥50
Serum alkaline phosphatase (ULN)	<2		≥2	
Serum alpha-fetoprotein (μg/L)	<35		≥35	
Portal obstruction (ultrasonography)	no	yes		
ULN, upper limit of normal.				

in patients with advanced HCC enrolling in clinical trials for systemic therapy at Asian centers (33,51). However, it has not performed well in comparative studies in Western populations, which are characterized by a greater proportion of patients with hepatitis C.

Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH)

The French scoring system, proposed by GRETCH in 1999 (52), uses objective measures and an estimate of performance status to predict survival. A cohort of 761 consecutive patients across 24 institutions in Europe and Canada were randomly assigned to a training sample (506 patients) or a validation sample (255 patients.) Predictors of survival were identified using univariate analysis with Kaplan-Meier estimates and then included in a Cox proportional hazards model. Using a forward stepwise selection, five factors were found to affect 1-year survival from the time of diagnosis. These are performance status by Karnofsky score, serum bilirubin, serum alkaline phosphatase, AFP, and presence or absence of portal obstruction by ultrasonography (*Table 10*).

An advantage of the French classification is that its variables are generally available at the time of initial diagnosis and do not require invasive procedures or sophisticated imaging. The increasing use of cross-sectional imaging as a diagnostic modality could impact the prognostic value of this scoring system by altering the sensitivity for diagnosis of portal obstruction. To date, however, this classification system has not improved prognostic discrimination in comparison to other systems when tested on various cohorts (26,42,53).

Limitations of current staging systems

The heterogeneous nature of HCC has made it difficult

to implement a universally accepted staging system. While the various systems emphasize to a different degree the importance of tumor characteristics and liver function (*Table 1*), none of the classification algorithms account for location of the tumor or its proximity to major vessels. In turn, the tempo of the deterioration of the underlying liver disease is also difficult to calculate, both because of the risk of worsening cirrhosis if it exists or the proclivity for central HCC tumors to invade the portal vein. Frequently, patients can be clinically stable for an extended period of time before experiencing decompensated liver failure. With serial liver function tests and imaging, clinicians hope to recognize impending signs of liver failure.

Finally, the underlying risk factors and the complex tumor biology of HCC are not accounted for by any of these systems. Many studies describe differences in cancer outcomes based on the etiology of cirrhosis. For example, hepatitis C patients and patients with alcoholic liver disease generally experience poorer outcomes than HBV-positive patients undergoing resection (54,55), which is generally attributed to the propensity of some HBV-associated HCCs to bypass the premalignant state of cirrhosis. Conversely, post-hoc subset analyses suggest that HCV and alcoholic liver disease HCC subgroups experience better outcomes with sorafenib therapy (56). An increasing number of patients now develop HCC secondary to underlying non-alcoholic fatty liver disease (NAFLD), which also may impact prognosis (57). These examples highlight the challenges of discriminating the prognostic impact of the extent and etiology of underlying liver disease from that of tumor factors such as stage and tumor biology.

Novel staging systems

With emerging understanding of HCC genomics, it is now apparent that common molecular subclasses exist which are associated with prognosis, may be enriched in certain subsets according to etiology of liver disease, and which could impact response to targeted therapies (58,59). In this clinically- and genomically-complex disease, it is likely that tumor biology will play an important role in future staging. Several recently proposed staging systems, which incorporate molecular biomarkers—of both tumor and cirrhosis—are discussed below.

Genomic signatures

Over the past decade, numerous molecular signatures have

been proposed to predict recurrence and cancer outcomes in surgically resected HCC (58,60). In 2011, Villanueva *et al.* evaluated 22 different molecular signatures and identified 2—the G3 signature from tumor and the poor-survival signature from adjacent nontumoral cirrhotic tissue—which, together with clinico-pathological features, were associated with recurrence (61).

5-gene score

Recently, a gene expression score has been proposed to predict disease-specific survival and early tumor recurrence of resected HCC (62). Five genes (*TAF9*, *RAMP3*, *HN1*, *KRT19* and *RAN*) were selected for their prognostic value in a French cohort. Patients were stratified into good and poor risk groups and the authors applied the gene score to several independent cohorts.

IGF-modified CTP staging

Serum insulin-like growth factor-1 (IGF-1) has been proposed as a surrogate for hepatic function because its production is reduced in cirrhosis (63).

Conclusions

The perfect unifying HCC staging system does not exist, nor is one necessary. Striving to better characterize and classify this disease remains a worthy endeavor, particularly if we are able to identify subsets of patients who garner substantial benefit from interventions. Depending upon the direction in which the field moves, we may be discussing entirely different systems a few years from now.

Accurately staging a disease and stratifying patients in clinical trials is not the same as correctly managing it. Because of its widespread presence in contemporary HCC research, BCLC is used by many practitioners to guide clinical decision-making. While this is certainly reasonable, and lays the framework for investigators and treating physicians alike to make best use of current data in treating a difficult cancer, it should not be taken as evidence that BCLC is the most accurate or refined system.

On the horizon, our growing understanding of the complex tumor biology in HCC along with novel imaging techniques and advances in the management of viral hepatitis and cirrhosis herald a new era of staging and scoring systems. As a complement to clinical staging, it is certainly to be hoped that these emerging systems will

allow us to improve our prognostic ability and deliver more effective care to patients with HCC.

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Footnote

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Features and treatment options of Chinese hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. More than 53% of the total HCC patients in the world come from China. The absolute number of new Chinese HCC cases still keeps increasing and it remains a most dominant cancer burden in the next several decades. Compared to the HCC occurred in Europe and North America, Chinese HCC patients have their own special features in etiology, demographic features (risk factors, age of onset, gender distribution time trend of incidence), biological behavior, clinical manifestation, treatment strategy and prognosis. The success or failure of a series of clinical trials related with systemic therapy for advanced HCC can be partly attributed to those features of Chinese HCC. Thus it is suggested that new trials should be performed respectively for Chinese HCC patients from the Western population, like the success of sorafenib SHARP and ORIENTAL studies. The protocol design, organization and practice of trials in HCC of China should be made individually to avoid or reduce the possible heterogeneity of HCC populations and facilitate the personalized therapy of HCC. The present review discussed the features and treatment options of HCC in China that maybe help to understand the clinical course for Chinese patients with HCC. More importantly, the future strategies for clinical trials of Chinese HCC were emphasized.

Keywords: Hepatocellular carcinoma (HCC); incidence; etiology; personalized therapy; China

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Features of Chinese hepatocellular carcinoma (HCC)

Primary liver cancer (PLC), mainly consisted of HCC, is the fifth most common cancer and the third most common cause of death from cancer worldwide. It has been estimated that there are above 749,000 new cases of liver cancer (523,000 in men and 226,000 in women) and 695,000 deaths (478,000 in men and 217,000 in women) per year around the world in 2008. In China, HCC is also one of the most popular cancers. More than 401,000 new patients (53.5% of the world) are diagnosed with liver cancer and more than 371,000 patients (53.4% of the world) are killed by the terrible disease annually (1).

Based on the national cancer sample survey data during 1998-2007, the PLC incidence was 25.84/100,000 in China, with an age-standardized rate (ASR) of 18.82/100,000. The annual percent change (APC) of urban male and female liver cancer incidence rates were 1.1% and -0.5%, with ASR at -0.5% and -1.9% individually; While the APC of rural male and female liver cancer incidence rates were 3.7% and 3.1%, with ASR at 1.9% and 1.3% respectively (2). The Chinese PLC incidence is expected to increase in the following decades but its ASR will decrease slightly. The PLC absolute number will keep increasing and remain a most dominant cancer burden in China in the next several decades.

From the data released above, the fatality ratio of

mortality to incidence can be calculated to be 0.93 for both the total world and Chinese population. It is very close to 1.00, indicating that most patients who were diagnosed with PLC will die within one year. The poor outcome of HCC is mainly due to it rarely presents with specific or obvious symptoms at early stage. Actually, nearly 80% of patients have progressed to the advanced stage and lose the chance of curative hepatectomy when the diagnosis of HCC was made (3). The median survival for HCC after diagnosis with supportive care ranges from approximately 6 to 9 months in Western countries and only 3 to 4 months in East Asian countries (4). HCC is always deemed as one of the most aggressive tumors in East Asian countries as well as China.

The possible etiology for HCC is manifold, including hepatitis virus infection, exposure to aflatoxins, water pollution (blue-green algae toxins), excessive alcohol consumption, tobacco smoking, and non-alcoholic fatty liver diseases (NAFLD) plus obesity, plus other less common etiologies (5). However, there is a wide variation in the predominant risk factors for different populations. Chronic infection with hepatitis B virus (HBV) remains the overwhelming cause of HCC in China, where the prevalence of hepatitis B is nearly 10% in the general population (6,7). Whereas in Western countries, such as the United States, Europe and Japan, where hepatitis B is rare but hepatitis C is the major cause of HCC. In addition, the alcohol-related cirrhosis usually due to alcohol abuse also play a non-neglectable role in the carcinogenesis of HCC in Western developed countries (8). That is the most important difference in the etiology of HCC between Chinese patients and those in developed countries.

Besides the etiology and risk factors for Chinese HCC patients is unique, some other demographic features, e.g., age of onset, gender distribution and change of incidence rate over time for HCC between China and Western developed countries are also greatly distinct.

From the statistics between year 2000 and 2005 presented by Professor Jin-Lin Hou, Nanfang Hospital, Guangzhou, China, the incidence of HCC in Chinese population increases with age. For every age stratum, males have a higher incidence of HCC compared to females. The ASR are 58/100,000 persons for men and 22/100,000 persons for women, and male-to-female ratio is nearly 3:1 (9).

The common age of HCC at onset is 40–60 years. Although the incidence of HCC is relatively low for women below the age of 40 years (<3/100,000), it is already at 21/100,000 for men between the ages of 35 and 40 years.

This incidence increases proportionally with age in both sexes from the age of 40 onward, reaching >160/100,000 for males and 94/100,000 for females after the age of 70 years (9).

With national vaccination program against hepatitis B since 1990s, the incidence of HBV-associated HCC is estimated to be decreased in China after several decades later. However, the HCC might still be a severe disease burden for Chinese people because the seemingly rising prevalence of hepatitis C infection and alcohol abuse in recent years in China (10). HCC is still the dominant cancer to be prevented and controlled in China in the following several decades.

Current treatment options of Chinese HCC

Current treatment options for HCC in China are multi-disciplinary, and the use of available treatment depends on liver function and tumor stage. Generally speaking, the treatment strategies could be divided into two main fields: surgical and non-surgical approaches. Surgical techniques for HCC usually include radical lesion resection, liver transplantation, and palliative surgery; Non-surgical techniques include trans-catheter arterial chemoembolization (TACE), radiotherapy, immunotherapy, systemic chemotherapy, molecularly targeted therapy, and traditional Chinese herbal medicine (e.g., Pishuang, mainly consisted of arsenic acid). In addition, several types of local-regional ablation therapy, including anhydrous alcohol injection and radiofrequency, are also used in clinical setting of China.

HCC can be treated curatively with surgical resection, liver transplantation, or radiofrequency ablation, but only 15% of patients are diagnosed at a stage where curative treatment is possible. In China, the early stage of HCC is referred to as “small HCC” (carcinoma with a maximum diameter ≤ 3 cm). For those patients with early disease who present with solitary tumors and good liver function, 5-year survival rates of greater than 50% are observed after surgical resection. However, as most HCC patients in China have progressed to the advanced stages at the time of diagnosis, they are unfortunately ineligible for surgical resection and other potentially curative treatments.

When patients are diagnosed at an advanced stage of HCC, as are 80% of all cases, median survival times are less than a half-year. In such a case, embolisation or chemoembolisation, often are regarded as the important options in China and survival advantages have been identified in well-selected candidates. However, for the

patients not suitable for chemoembolisation, a significant effective medical strategy is greatly needed to treat advanced HCC in China.

In the past several decades, systemic chemotherapy is also commonly used in China, despite the lack of evidence of a survival benefit (11). For example, the PIAF regimen (cisplatin, IFN α , doxorubicin, and infusional 5-FU) was one of the best-studied regimen for Chinese patients with advanced HCC (12-14). Particularly, in a randomized phase III study, PIAF (cisplatin 20 mg/m² on days 1 through 4, IFN α 5 MU/m² subcutaneously on days 1 through 4, doxorubicin 40 mg/m² on day 1, and 5-FU 400 mg/m² on days 1 through 4) was compared to single doxorubicin (60 mg/m² every three weeks) in 188 unselected patients with chemotherapy-naïve unresectable HCC. While objective response rates were higher with PIAF (21% *vs.* 11%), this difference was not statistically significant, nor was the difference in median survival duration (8.7 versus 6.8 months, *P*=0.83). Treatment-related toxicity was more pronounced with PIAF (neutropenia 82% *vs.* 63% grade 3 or 4, thrombocytopenia 57% *vs.* 24% grade 3 or 4, hypokalemia 7% *vs.* 0% grade 3 or 4) (15).

The failure to show a survival benefit in this trial may be attributed to the lack of patient selection. The importance of liver function to the response with the PIAF regimen was demonstrated in a series of 149 patients with unresectable HCC who were treated with PIAF (13). The objective response rate was significantly higher in patients with a normal bilirubin and a non-cirrhotic liver compared to those with cirrhosis and a serum bilirubin >0.6 mg/dL (50% versus 6%).

Recently, FOLFOX, serial regimens containing oxaliplatin plus short-term infusional 5-FU and leucovorin which are most commonly used in the treatment of advanced colorectal cancer, has been reported to be active in Chinese HCC. In a recent published phase III trial (EACH study), 371 patients with advanced or metastatic HCC were randomly assigned to FOLFOX4 versus single doxorubicin (50 mg/m² intravenously every 3 weeks) across 38 centers in four Asian countries (16). Approximately 90% of patients in both arms were positive for HBV infection and approximately 80% in both arms had Barcelona Clinic Liver Cancer (BCLC) stage C disease. At the pre-specified final analysis, median OS was 6.40 months with FOLFOX4 and 4.97 months with doxorubicin (*P*=0.07). Median PFS was 2.93 months with FOLFOX4, and 1.77 months with doxorubicin (*P*<0.001). ORR was 8.15% with FOLFOX4 and 2.67% with doxorubicin (*P*=0.02). On continued

follow-up, the trend toward increased mOS with FOLFOX4 was maintained (6.47 months with FOLFOX4 *vs.* 4.90 months with doxorubicin, *P*=0.04). Toxicity was consistent with previous experiences with FOLFOX4; Proportions of grade 3-4 adverse events were similar between treatments.

Clearly, FOLFOX4 showed a lower OS and PFS benefit in Asian HCC (6.40 and 2.93 months) than that brought by GEMOX (11 and 4.5 months) or XELOX regimen (9.3 and 4.1 months) in European HCC patients (17-20). Systemic chemotherapy may be less effective overall in HCC patients with severe liver cirrhosis. This was illustrated in an evaluation of predictive factors among 147 patients receiving chemotherapy for HCC. There were no objective responses among patients with a poor performance status, ascites, portal vein tumor thrombus, or serum total bilirubin >2.0 mg/dL (21). The great difference as to the underlying cause of cirrhosis for Asian HCC, HBV rather than alcohol or HCV, and therefore a possible worsen hepatic reserve may accounted for the survival difference.

Approval of sorafenib as the first molecularly targeted therapy for treatment of advanced HCC represents a milestone in the treatment of the disease. The results from the phase III trial (SHARP study) have shown a survival benefit compared to best supportive care alone (22). The multicenter SHARP trial in European and America randomly assigned 602 patients with inoperable HCC and Child-Pugh A cirrhosis to sorafenib (400 mg twice daily) or placebo. The primary endpoint OS was significantly longer in the sorafenib-treated patients (10.7 *vs.* 7.9 months), as was time to radiologic progression (5.5 *vs.* 2.8 months). Treatment was well tolerated with manageable side effects. These results established sorafenib monotherapy as the new reference standard systemic treatment for advanced HCC.

The efficacy and safety of sorafenib in Asian patients was demonstrated by a second placebo-controlled phase III trial (Oriental study) in the same time. A total of 226 patients with Child-Pugh A cirrhosis and no prior systemic therapy for HCC received sorafenib 400 mg twice daily or placebo. Patients receiving sorafenib had significantly better mOS (6.5 *vs.* 4.2 months) and mTTP (2.8 *vs.* 1.4 months) (23).

The survival benefit was markedly less in this trial than that achieved in the SHARP study. Factually, the treated group in the Asian trial had shorter survival duration than the control group in the SHARP trial (6.5 *vs.* 7.9 months), despite the both trials used the same entry criteria. The possible reason might lie in the fact that patients enrolled in the Asian trial were more ill at the start of therapy

than those in the SHARP study, with a generally worse performance status and more advanced stage of disease (24).

The difference in response to sorafenib between different populations might be explained partly in terms of the etiology of the HCC. Asian patients have a higher prevalence of infection with HBV as compared to Western populations; 73% of the patients enrolled to the Asian trial had HBV infection versus 18% of those enrolled to SHARP (21,22). At least some exploratory analyses suggest that patients with HCV infection as the etiology of their cirrhosis may have a better response to sorafenib as compared to those with other underlying causes of cirrhosis (25). As an example, in an exploratory analysis of the phase III SHARP trial, although a survival benefit was seen in all subgroups treated with sorafenib, the difference in median overall survival between sorafenib and placebo-treated patients was highest in those with HCV-related cirrhosis (6.6 months, 14 versus 7.4 months); It was 3.6 months (9.7 versus 6.1 months) in patients with HBV-related cirrhosis, and 2.3 months (10.3 versus 8 months) in those with underlying alcohol-related liver disease (25). These differences in outcome according to hepatitis virus type could potentially explain some of the survival differences between the SHARP and Asian trials of sorafenib.

Future strategies for clinical trials of Chinese HCC

There have been many clinical trials since the success of sorafenib to look for further targeted therapies to offer patients with advanced HCC. Randomized phase III trials of other novel targeted agents including sunitinib, lenvatinib, brivanib, and the combination of sorafenib plus erlotinib have failed to improve overall survival compared with sorafenib as a single agent in the first line setting, as well as compared with placebo in the second-line setting, in the case of brivanib. These negative studies are a sobering reminder of the challenges to clinical study in HCC, including the competing comorbidity of liver dysfunction, marked clinical and biologic heterogeneity, and the unreliability of surrogate endpoints to accurately predict survival (26).

More detailed speaking, the main reasons for the failure of these systemic therapies might be lied in the following four important factors. (I) Firstly, ignoring the great heterogeneity in etiology and clinical features of HCC between Asian and Western patients and pooling them into the same one study; (II) Secondly, underrating of particularity of HCC, which frequently occurs in the setting

of chronic hepatitis and cirrhosis. The diagnosis of HCC factually implies three types of diseases including chronic hepatitis, cirrhosis, and liver cancer simultaneously. This factor must be made into consideration when clinical practice executed and the anticancer therapy must be accompanied with antiviral and hepatoprotective agents. The lack of the latter two in the treatment of HCC would inevitably discount the anticancer effect of new drugs; (III) Thirdly, there still is no well-recognized molecular typing (gene type) available for HCC and the biomarker-driven personalized therapy of HCC is faraway until now. In the future, the participants enrolled into trials should be chosen under the guide of genotype. The candidate novel agent or regimen for systemic therapy of HCC should be designed to fit a specific population, not fit all population with great heterogeneity; (IV) Lastly, the stratifying strategy on subgroup analysis was not desired. When subgroup analysis conducted, the difference in region, hepatic function, TNM stage, and vascular invasion should be considered independently as the possible stratifying factors. Virtually, the aim of the stratification is to reduce the impact of population heterogeneity as great as possible and screen the predominant population for a specific therapy.

Conclusions

HCC is a more aggressive tumor that frequently occurs in the setting of chronic liver disease and cirrhosis. Hepatic reserve often decides the therapeutic options. Systemic therapy for HCC is an evolving field in recent years. The response to systemic treatment depends on ethnicity and cause of cirrhosis to some extent. Systemic therapy for HCC needs to be intensively investigated in the future.

In the design of following new trials for HCC, a key point must be specially considered is that Chinese HCC largely differed from HCC patients in Western developed countries in etiology, biological characteristics, treatment strategies and prognosis. Based on these unique features of Chinese HCC, new trials should be performed independently from the Western population, like the success of SHARP and ORIENTAL studies. The protocol design, organization, conduct and practice of trials for Chinese HCC patients should be made individually to avoid or reduce the possible heterogeneity of HCC populations and facilitate the personalized therapy of HCC. It comes personalized or individualized medicine time now. Thus even clinical trial should be personalized or individualized, namely one should fit one, not one fits all.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Status of hepatocellular carcinoma in Republic of Korea

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Abstract: In Republic of Korea, liver cancer is the 4th most common cancer in men and 6th most common cancer in women. However, the incidences of liver cancer among Korean men and women have been declining from 1999 to 2010. The reason for the declining incidence appears secondary to decreased hepatitis B virus (HBV) infection, which is the leading risk factor for hepatocellular carcinoma (HCC), with successful implementation of HBV vaccination since 1983. Despite recent advances in the treatment of HCC, including liver transplantation (LT), radiofrequency ablation (RFA), transarterial embolization, and the use of molecularly targeted agents, many patients cannot be cured due to the advanced stage of HCC at the time of diagnosis in Republic of Korea. While the 5-year survival rate of HCC patients in Korea is relatively lower than other cancers, it has been gradually increased from the early 1990s to the late 2000s. The reason for the improvement in 5-year survival rates is attributed that early detection of HCC becomes possible by well-established surveillance program in high-risk populations for HCC in Korea. In Korea, national surveillance program for HCC was established in 2003, in which repeated applications of screening tests [serum α -fetoprotein (AFP) and liver ultrasound] at 6-month intervals have been recommended in patients at high risk for developing HCC, such as men and women older than 40 years of age with positive hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) or underlying liver cirrhosis. It is essential that the nationwide surveillance program for HCC should be effectively executed in high-risk patients for developing HCC. Optimal application of multidisciplinary team approach and active involvement in clinical studies with new agents in HCC patients are critically important not only for the management of advanced HCC patients but also for the improvement in natural history and therapeutic outcomes of HCC patients in the future.

Keywords: Hepatocellular carcinoma (HCC); Republic of Korea, epidemiology; surveillance

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Incidence and mortality of hepatocellular carcinoma (HCC) in Republic of Korea

According to National Cancer Information Center (NCIC, www.cancer.go.kr) in Korea, 15,921 cases (22.9 cases per 100,000 population) were estimated to be diagnosed with liver cancer, accounting for 7.9% of all cancers diagnosed in 2010. Liver cancer ranks the 5th most common cancer after thyroid cancer, stomach cancer, colon cancer and lung cancer in Republic of Korea. It is the 4th most common cancer in Korean men and 6th most common cancer in Korean women. However, the incidences of liver cancer among

Korean men and women have been declining from 1999 (48.5/100,000 and 12.6/100,000) to 2010 (37.1/100,000 and 10.4/100,000) (*Figure 1*). The reason for the declining incidence appears secondary to decreased hepatitis B virus (HBV) infection, which is the leading risk factor for HCC. With the implementation of national HBV vaccination program for infants since 1983 in Republic of Korea, HBV infection has become preventable, the incidence of HCC has been dramatically decreased. In contrast, the incidences of HCC in recent decades have increased in Western countries due to the rise in hepatitis C virus (HCV) infection through continued transmission by drug abusers (1). In addition,

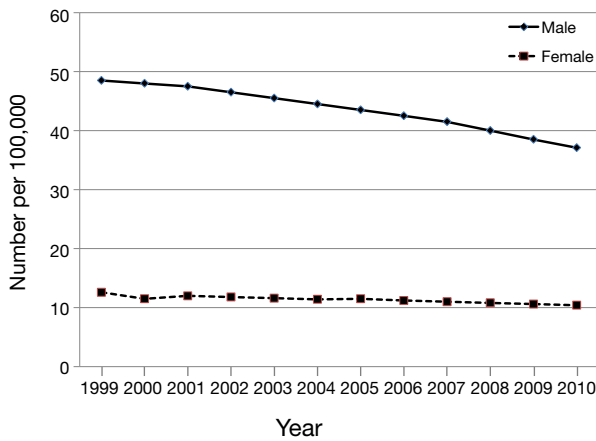


Figure 1 Trends in liver cancer incidence for men and women over time in Korea (expressed as the numbers per 100,000 population).

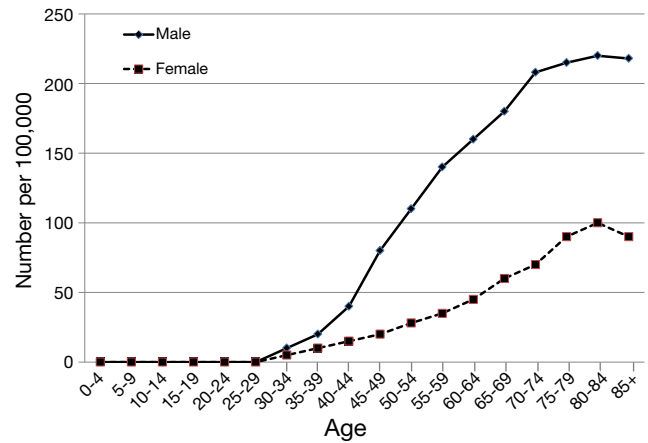


Figure 2 Age-adjusted incidence of liver cancer for men and women in 2010 in Korea (expressed as the numbers per 100,000 population).

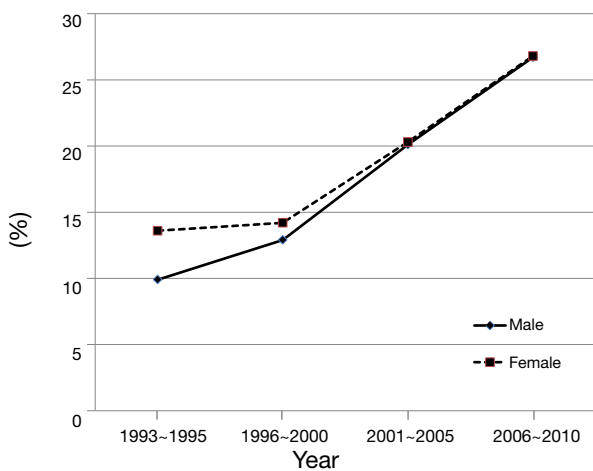


Figure 3 Trends in 5-year survival rates for liver cancer for men and women in Korea.

recent report showed that obesity is positively linked with the developing HCC paradigm in Western countries (2,3). Accordingly, the geographic variations for the incidence of HCC can be explained by the regional differences in the prevalence of risk factors for HCC.

The HCC incidence rates in Korea are more than twice higher for males than females. The age-standardized (or adjusted) incidence rate per 100,000 population for liver cancer in 2010 is shown in *Figure 2*. The incidence rate continues to increase with age and is highest between the age of 80 to 85 both in man and women. However, along with the recent trend towards increased incidence of oral cancer among young adults, HCC appears to be the most

common cancer in their forties.

According to mortality data from Korean Statistical Information Service (KOSIS, <http://kosis.kr>) in 2011, the liver cancer death rate was reported as high as 32.8/100,000 for men and 10.9/100,000 for women. The number of death from liver cancer in Korea increased gradually from 2003 (9,500/100,000) to 2011 (10,946/100,000). Despite recent advances in the treatment of HCC, many patients cannot be cured due to the advanced stage of disease at the time of diagnosis in Korea. Accordingly, the 5-year survival rate in Korea is relatively lower than other cancers. Nonetheless, it has been gradually improved from the early 1990s (10.7%) to the late 2000s (26.7%) (*Figure 3*). The reason for the improvement in 5-year survival rates can be attributed that early detection of HCC becomes possible by well-established surveillance program in high-risk population for HCC in Korea.

Risk factors

Hepatocarcinogenesis has been proposed as a progressive multistep process evolving from chronic inflammation and cirrhosis to HCC. In general, the risk factors for developing HCC are well known in comparison with other cancers. In Korea, among the major risk factors, chronic HBV infection has been reported as the most common risk factor for developing HCC and approximately 65% to 75% of HCC cases were positive for hepatitis B surface antigen (HBsAg) (4,5). Next, chronic HCV infection was the 2nd common cause for developing HCC, estimated to be accountable for 11.2% to 13.2% of all HCC cases (4,5). Other, probably compound, risk factors included heavy alcohol

consumption, cigarette smoking and family history of HCC (5,6). Specifically, Aflatoxin B1, a mycotoxin produced by the *Aspergillus* fungus, can cause HCC in non-cirrhotic livers (7). In addition, other less common or very rare risk factors observed in Korea include primary biliary cirrhosis, hereditary hemochromatosis, α 1-1 anti-trypsin deficiency, Wilson's disease, echinococcosis, and schistosomiasis (8).

The reason for high incidence of HCC in Korea results from a large number of HBV carrier among general population, approximately accounting for 5% of the general Korean population (9). Moreover, a previous study by Jee *et al.* in Korea reported that, while cigarette smoking, heavy alcohol consumption, and HBsAg were independently associated with increased risk of mortality from HCC, they appeared not interact synergistically (6). Regarding the association between the incidence of HCC and family history of HCC, Park *et al.* reported a retrospective analysis in a large group of HCC patients (5). Of the 2,242 patients diagnosed with HCC, 165 (7.4%) had a positive family history of HCC. Among 1,713 HCC patients with HBV infection, 136 patients had a positive family history. The number of patients under 45 years of age with HBV infection and positive family history was 26 (19.1%), whereas those out of 1,577 patients with negative family history was 197 (12.5%), suggesting that a positive family history may be associated with earlier development of HCC in the Korean population.

Diagnosis and staging of HCC

Diagnostic investigations for HCC comprise three processes including blood tests (serum tumor markers), imaging procedures and the histologic confirmation. In principle, the diagnosis of HCC should be based on histologic confirmation. However, percutaneous liver biopsy has several drawbacks, such as incorrect tumor targeting for the small lesion and the potential for tumor seeding through the needle track. Accordingly, non-invasive methods like tumor markers or imaging studies are commonly used for the clinical diagnosis of HCC. However, a histologic confirmation of HCC is mandated for most of prospective clinical studies especially with investigational new drugs or target agents.

Currently used tumor markers for the diagnosis of HCC have included α -fetoprotein (AFP), des- γ -carboxy prothrombin (DCP) or protein induced by vitamin K absence or antagonist (PIVKA-II) and a fucosylated variant of the AFP glycoprotein which has a high affinity to the sugar chain of *Lens culinaris* (AFP-L3) (10). Previous studies have shown

that the sensitivity and specificity of AFP for the diagnosis of HCC are 41-65% and 80-94%, respectively, with a cutoff value of 20 ng/mL (11). This variability in the sensitivity among different studies is thought to be due to several factors including study design (retrospective *vs.* prospective study), insufficient sample size, etiologic factors of HCC, race and the different cutoff values used for AFP (10). DCP as a new diagnostic marker for HCC was initially reported by Liebman *et al.* (12). Recent reports have described the sensitivities and specificities of DCP for the diagnosis of HCC ranging from 44.3-92% and 93-97%, respectively (13-15). The comparative study of AFP, DCP and AFP-L3 for diagnostic value showed that DCP was significantly better than total AFP or AFP-L3 in differentiating HCC from cirrhosis, with a sensitivity of 86% and specificity of 93% (15). Although AFP-L3 was approved as a diagnostic tumor marker for HCC, it is not widely used in the clinical practice because of its difficulties in procedure and interpretation. In Korea, AFP and PIVKA-II are commonly used as a diagnostic marker at the present time and the use of additional DCP has been continuously increasing.

Meanwhile, with the advancement in the imaging techniques, such as multiphase spiral computed tomography (CT), dynamic magnetic resonance imaging (MRI) showing higher sensitivity and specificity, the diagnostic value of currently used serum tumor markers has been enfeebled and their diagnostic values have recently been with a significant controversy worldwide. The current practice guidelines established by the American Association for the Study of Liver Diseases (AASLD) (16) and the Asia-Pacific Association for the Study of the Liver (APASL) (17) as well as by the European Association for the Study of the Liver (EASL) (18) do not recommend AFP test for the surveillance or diagnosis of HCC. While the AASLD guidelines recommended that the diagnosis of HCC should be based on imaging techniques and/or biopsy, the APASL guidelines recommended dynamic imaging techniques regardless of the tumor size and AFP (17). However, Korean Liver Cancer Study Group (KLCSG) guidelines established in 2009 (19) included AFP level for the diagnosis of HCC. If the serum AFP level is ≥ 200 ng/mL in a high-risk patient, typical characteristics of HCC in either dynamic contrast enhancement CT or dynamic contrast enhancement MRI may satisfy the diagnosis of HCC. If the serum AFP level is < 200 ng/mL, two or more positive findings of (I) dynamic contrast enhancement CT; (II) dynamic contrast enhancement MRI; or (III) hepatic arterial angiography are necessary to make the diagnosis of HCC. A histologic

confirmation is not necessary to establish the diagnosis of HCC in Korea if certain imaging criteria are met. When the diagnosis of HCC by a radiologic or histologic examination for the liver nodule less than 1 cm in diameter cannot be verified, repeated periodical examinations of serum tumor markers and ultrasonography at 3- to 6-month interval have been recommended.

In general, the treatment options and prognosis of HCC have been mainly determined according to the tumor stage, liver dysfunction and performance status. To date, several staging systems in different countries have been proposed for HCC, including Barcelona Clinic Liver Cancer (BCLC) (20), TNM (21), Cancer of the Liver Italian Program (CLIP) (22), Chinese University Prognostic Index (CUPI) (23), Japan Integrated Staging Score (JIS score) (24), the Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire Prognostic Classification (GETCH) (25). However, there is no universally accepted consensus among different staging systems for HCC at the present time. In Korea, modified International Union Against Cancer (UICC) staging system (26) and the BCLC staging system have been commonly used as a staging system for HCC. Nonetheless, greater portions of HCC patients are diagnosed at advanced stage. For example, we analyzed the tumor stage at the time of diagnosis in 2,241 HCC patients who were treated at a single tertiary academic hospital in Korea over 18-year period (5). By the modified UICC staging classification, only 185 patients (8.3%) were diagnosed at stage I, followed by 655 (29.2%) patients at stage II, 648 (28.9%) patients at stage III, and 753 (33.6%) patients at stage IV. More than half of the HCC patients (62.5%) were diagnosed at advanced stages, including stages III and IV, in this retrospective analysis. Meanwhile, according to the registry data from the Korean Liver Cancer Study Group (www.klcsq.or.kr), the stage distributions at initial diagnoses were 10.7%, 43.4%, 27.7%, and 18.2% for stages I, II, III, and IV (Modified TNM Stage by LCSGJ), respectively, for 4,521 patients from 32 Korean hospitals randomly sampled from 31,521 patients registered with the liver cancer during a 3-year period [2003-2005]. Accordingly, only a small proportion of the HCC patients can receive curative treatments including surgical resection and liver transplantation (LT) in Republic of Korea.

Screening and surveillance program for early detection for HCC

Screening refers to the use of simple and inexpensive test across healthy population in order to identify

individuals who are likely or unlikely to have a cancer whereas surveillance defines continuous monitoring of disease occurrence using the screening test until a cancer appears. Because the surveillance program in the high-risk patients of HCC allows for the detection of HCC at early stage, a greater portion of patients are suitable for potentially curative treatments including liver resection or LT. AFP, most commonly used tumor marker, and liver ultrasonography have been employed for the surveillance test of HCC in Korea. The national surveillance program for HCC was established in 2003, in which repeated applications of these screening tests at 6-month intervals have been recommended in patients at high risk for developing HCC, such as men and women older than 40 years of age with positive HBsAg, anti-HCV Ab or underlying liver cirrhosis in Korea. A 15-year prospective study in Korea indicated an improved survival of HCC patients with surveillance interval ≤ 6 months compared with >6 months (27).

Treatment and management of HCC

Similar to rest of the world, treatment of HCC in Republic of Korea has been remarkably advanced over the last 20 years. The treatment of HCC can be classified into two categories: curative treatment and palliative treatment. Curative treatments include LT, surgical resection and radiofrequency ablation (RFA) while palliative treatments include transarterial chemoembolization (TACE), radioembolization using radionuclide Yttrium-90, systemic therapy, radiation therapy and molecular target therapy. The treatment option for HCC depends on the tumor stage and liver dysfunction.

LT, in theory, is the most ideal therapeutic modality because it can cure underlying liver cirrhosis as well as removing the tumor in HCC patients with liver cirrhosis. However, only a small proportion of HCC patients can undergo LT because of the donor shortage, high cost and advanced tumor stage at the time of diagnosis. In general, a precise tumor assessment in HCC patients according to Milan criteria, including single tumor less than 5 cm or two to three tumors with the largest being less than 3 cm in the absence of portal vein invasion and extrahepatic metastasis (28), is required prior to LT. Although the first case of LT was performed in a 14-year old boy with Wilson's disease in 1988, cumulative experience on LTs performed in Korea before 2000 is not available. According to the Annual Report of the Transplantation published by

the Ministry of Health and Welfare, ROK [2013], there were a total of 9,380 cases of LT in Korea during a period of 2000–2012 (29). The majority (79.6%; 7,468 cases) of LT had been performed with living donors, while 1,912 cases (20.4%) were by donors with brain death. During the year of 2012, there were a total of 1,260 patients underwent LT in Korea; 897 with living donors and 363 with brain death donors. The 1-year and 5-year survival rates were 88.5% and 80.0% respectively after living donor LTs, and 77.3% and 69.5% respectively for LTs with brain death donors.

Although surgical resection has been accepted as a treatment modality of choice for HCC, it has a limited role since the tumors in most patients are unresectable due to variety of factors including poor hepatic reserve, multifocality of HCC or inability to obtain an optimal tumor-free margin. Furthermore, recurrent HCCs are frequently found in the residual liver within a short period of time after surgical resection. Nevertheless, the possibility of surgical resection should be considered as a therapeutic option when the initial clinical diagnosis of HCC is made in a patient in Korea. In addition, surgical resection is also considered for HCC patients beyond Milan criteria. A retrospective review of a single Korean institution experience on LT *vs.* surgical resection reported a statistically insignificant overall survival but a significant ($P=0.002$) recurrence-free survival for LT (30). However, after recurrence, surgical resection had a better survival than LT. Depending upon the location and size of the HCC, surgical resection of HCC lesion has been performed via laparoscopic approach in selected patients.

Loco-regional treatments for HCC are important alternatives to curative LT or surgical resection. Among them, RFA is accepted as the most popular technique showing excellent local tumor control and acceptable morbidity as adopted in practice guidelines in North America, Europe and Japan (31). The overall survival after RFA is comparable to after surgical resection in a selected group of patients with smaller (<3 cm) tumors. RFA has been frequently used in Korea as well. Choi *et al.* reported single institution experience of percutaneous RFA in 570 patients with 674 early-stage HCCs as a first-line treatment option (32). The primary technique effectiveness rate was 96.7% (652 of 674). The cumulative rates of local tumor progression at one, two, and three years were 8.1%, 10.9%, and 11.8%, respectively. The cumulative survival rates at one, two, three, four, and five years were 95.2%, 82.9%, 69.5%, 60.8%, and 58.0%, respectively. Patients with Child-Pugh class A cirrhosis, of younger age (≤ 58 years), or

having lower AFP level (≤ 100 $\mu\text{g/L}$) demonstrated better survival results ($P<0.05$).

Although TACE is considered a palliative therapeutic modality for HCC patients, >50% improvement in the 5-year survival rates has been reported (33). While it is recommended that TACE should be used for intermediate stage according to BCLC staging system, many cases with various stages under specific condition have been treated with TACE in real-life clinical practice in Korea. TACE was introduced as a palliative therapy of HCC in mid-1980s and has been adopted as the most commonly used loco-regional therapeutic modality for HCC in Korea. Earlier 6-year experience on 1,067 HCC patients at a single Korean institution reported 1-, 2-, 3-, 4-, and 5-year survival rates of 60.6%, 42.3%, 29.1%, 23.7%, and 14.7%, respectively (34). For 432 patients with tumors ≤ 5 cm in diameter, 1-year survival rate and median survival were 77.7% and 33 months, respectively. Significant prognostic factors included size and type of the tumor, portal vein invasion, and Child-Pugh classification. A prospective single institution cohort study comparing TACE to surgical resection on 182 patients with operable HCC (Child-Pugh class A and UICC stage T1–3N0M0) reported that survival rate of surgical resection group was comparable to that of TACE group ($P=0.0596$) (35). Recently, in order to maximize the therapeutic efficacy of TACE, doxorubicin-loaded drug-eluting beads (DC beads) have been developed to deliver higher doses of the chemotherapeutic agent and to prolong contact time with the tumor. We recently reported the comparative study in the efficacy and safety between DC bead TACE and conventional TACE (cTACE) (36). The time to progression was significantly better in the DC bead[®] group than in the cTACE group (11.7 and 7.6 months, respectively). Subgroup analysis showed that DC bead[®] treatment resulted in a significantly better treatment response and longer time to progression than cTACE ($P<0.001$ and 0.038, respectively) in intermediate-stage HCC.

There are limited options for the systemic treatment of patients with advanced or metastatic HCC. Although systemic anti-cancer chemotherapeutic drugs have been applied for these patients, data demonstrating their efficacy in patients are limited. Therefore, novel molecularly targeted therapy directing key signaling pathway has been explored based on the molecular mechanism underlying various HCC. Sorafenib is a multikinase inhibitor targeting Raf, vascular endothelial growth factor receptor (VEGFR) linked in angiogenesis signaling pathways (37). The results

from two independent (one in Europe and US and another in Asia-Pacific region) phase III studies with sorafenib in chemotherapy-naïve unresectable advanced HCC demonstrated advantages in OS compared to placebo (10.7 *vs.* 7.9 months in Europe/US study and 6.5 *vs.* 4.2 months in Asia-Pacific study) (37,38). Subsequently, sorafenib has been approved by regulatory authorities and used worldwide as a standard agent for the systemic therapy of advanced HCC. While sorafenib was approved by the Korean Food and Drug Administration for the treatment of advanced/metastatic HCC in March 18, 2008, the agent became fully reimbursable by the national insurance system only early this year.

Future perspectives

In order to overcome the poor prognosis of HCC patients, it is absolutely imperative to recognize the risk factors for developing HCC. Chronic HBV and HCV infections account for 54.4% and 31.1% of all HCC cases occurred globally, and thus both HBV and HCV infection should be prevented or eradicated using effective immunization or anti-viral agents, respectively. Therefore, the main goal for the treatment of chronic HBV infection should be the eradication of HBV or at least suppression of viral replication. Among several viral markers for chronic HBV infection, both HBV DNA and HBsAg levels were shown to be associated with HCC development (39). Since the introduction of nationwide HBV vaccination program in 1983 in Korea, the incidence of HBV in neonates is now estimated less than 0.5%, which is predicted to be nil by 2030. With adoption of successful HBV vaccination program, it is anticipated that HBV related HCC incidence will be proportionally decreasing and Non-B (HCV or NBNC) related HCC will be proportionally increasing in Korea. Therefore, new strategy to screen and control of non-B related chronic liver diseases will be necessary to control HCC in Korea and continued education and training for health-care providers for screening and surveillance as well as management for HCC are indicated. The consensus-based treatment algorithm (e.g., BCLC algorithms) may not always be optimal for Korean HCC patients in clinical practice. Therefore, the development of a consensus HCC management algorithm optimal for Korean HCC patients based on the updated data is desirable. In the future, evidence-lacking parts of the algorithm should be improved through prospective studies.

Besides having a liver disease, patients with HCC

require different management strategies for their illness, delivered by various specialists. Furthermore, the presence of confounding factors means that no single treatment strategy can be applied to all patients, and therefore therapy may be tailored to each patient's needs. In particular, since no specific guidelines exist to ensure the best care for HCC patients with cirrhosis, it is crucial to establish a close cooperation between these specialists, together with a cautious approach to decision making for these patients. Of note, specialists in pathology, gastroenterology, hepatology, hepatobiliary surgery, transplant surgery, interventional and diagnostic radiology, medical oncology, radiation oncology and nuclear medicine are involved in the management of HCC patients. In Korea, liver resection has been performed by a liver surgeon and regional intrahepatic therapeutic modalities (TACE, RFA, etc.) have been achieved by either diagnostic or interventional radiologists. Until recently, medical therapy of HCC using anti-cancer agents in Korea, including TACE, intrahepatic/regional and/or systemic chemotherapies, has been predominantly managed by gastroenterologists (hepatologists) and interventional radiologists. Similar to other malignant diseases, with rapid advances in medical and oncologic sciences, integrated multidisciplinary team approach should be implemented for optimal management of HCC patients with improved clinical outcomes.

The development of selective targeted drugs, especially Sorafenib (Nexavar[®]), represented a major progress in the treatment of advanced HCC with well-preserved liver function. However, since the therapeutic benefit of sorafenib monotherapy is rather limited, continued exploration of new novel agents for HCC is obviously indicated. There are a number of clinical studies with new agents currently ongoing or planned in Korea. The patient accrual has been completed for a phase 2b randomized trial of JX-594 (Vaccinia GM-CSF/TK-deactivated virus) in patients with advanced HCC who have failed sorafenib conducted at a limited number of Korean institutes. Several Korean institutions are actively participating in a randomized, double-blind, multicenter, phase 3 international study evaluating ADI-PEG 20 (Arginine deprivation agent) as a second-line therapy of metastatic HCC. Another phase 3 randomized, double-blind, international trial to evaluate Cabozantinib (XL184; oral tyrosine kinase inhibitor with potent activity against MET and VEGFR2 signaling) is ready to be started in Korea. A phase I/II study of a combination of Sorafenib and Resminostat [a hydroxamic acid with an inhibitory effect

on histone deacetylases (HDACs)] in patients with systemic therapy naïve metastatic HCC has been designed and plans to be conducted at limited Korean and Japan institutions. Proposals for clinical trials with Enzalutamide (Androgen Receptor inhibitor) as well as other agents (e.g., ASP5878) are currently under discussion.

In conclusion, chronic HBV infection remains to be the most important risk factor responsible for the development of HCC in Korea. It is essential that the nationwide surveillance program for HCC should be effectively executed in high-risk patients (e.g., HBV cirrhosis or carrier) for developing HCC. In addition, extensive research should be explored in order to understand molecular pathways of HCC, and to identify new biomarkers and candidate target molecules. Optimal application of multidisciplinary team approach and active involvement in clinical studies with new agents in HCC patients are critically important not only for the management of HCC patients but also for the improvement in natural history and therapeutic outcomes of HCC patients in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Current status of hepatocellular carcinoma in Japan

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Abstract: Approximately 32,000 patients die of primary liver cancer each year in Japan. The annual number of deaths from primary liver cancer in Japan ranks second only to that in China in the world. In recent years, there has been a gradual trend towards decrease in the number of liver cancer patients from its peak in Japan, and this trend is expected to also continue in the future. The main reason for this decreasing trend was the establishment of screening of transfusion products for hepatitis B and hepatitis C viruses, which prevents transfusion-related transmission of the viral infection. Most patients with hepatocellular carcinoma (HCC) in Japan have underlying viral hepatitis, with hepatitis C accounting for about two-third of all the patients and hepatitis B accounting for about 15%. Regular screening of patients with viral hepatitis infection makes it possible to diagnose HCC early, and also enables effective loco-regional treatment, such as surgical resection, local ablative therapy and transcatheter arterial chemoembolization (TACE). However, HCC recurrence is encountered frequently even after these potentially effective treatments. After numerous loco-regional treatments for recurrent HCC, chemotherapy is administered for patients with highly advanced HCC. Among the modalities of chemotherapy, hepatic arterial infusion chemotherapy (HAIC) is employed more commonly than systemic chemotherapy, although no survival advantage has ever been demonstrated. Randomized controlled studies are currently under way to clarify the survival benefit of HAIC. Also, various novel systemic chemotherapeutic agents are currently under development in Japan, and further improvements in the treatment outcomes are expected.

Keywords: Hepatocellular carcinoma (HCC); surgical resection; liver transplantation; local ablative therapy; transcatheter arterial chemoembolization (TACE); hepatic arterial infusion chemotherapy (HAIC); systemic chemotherapy; Lenvatinib; Orantinib; S-1; Peretinoin

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Trends in liver cancer patients in Japan

The number of deaths from primary liver cancer in Japan in the year 2011 stood at 31,875, and primary liver cancer ranked fourth among the causes of death from cancer, after lung cancer, stomach cancer and colorectal cancer (1). According to the 182-country database of the World Health Organization in 2008, the number of deaths from liver cancer in Japan ranked second in the world, after only China (2) (*Figure 1*). Examination of the male-female ratio of the deaths from liver cancer

revealed that there were 20,972 males to 10,903 females, indicating approximately twice as many deaths among males than among females with liver cancer (1). It appears that after reaching a peak, the number of deaths has tended to slowly decline in recent years (*Figure 2*). The main reason for this decline is considered to be the decrease in the number of patients newly infected with hepatitis viruses because of implementation of screening of blood products for hepatitis B viral (HBV) and hepatitis C viral (HCV) infection (3,4). Another reason is the

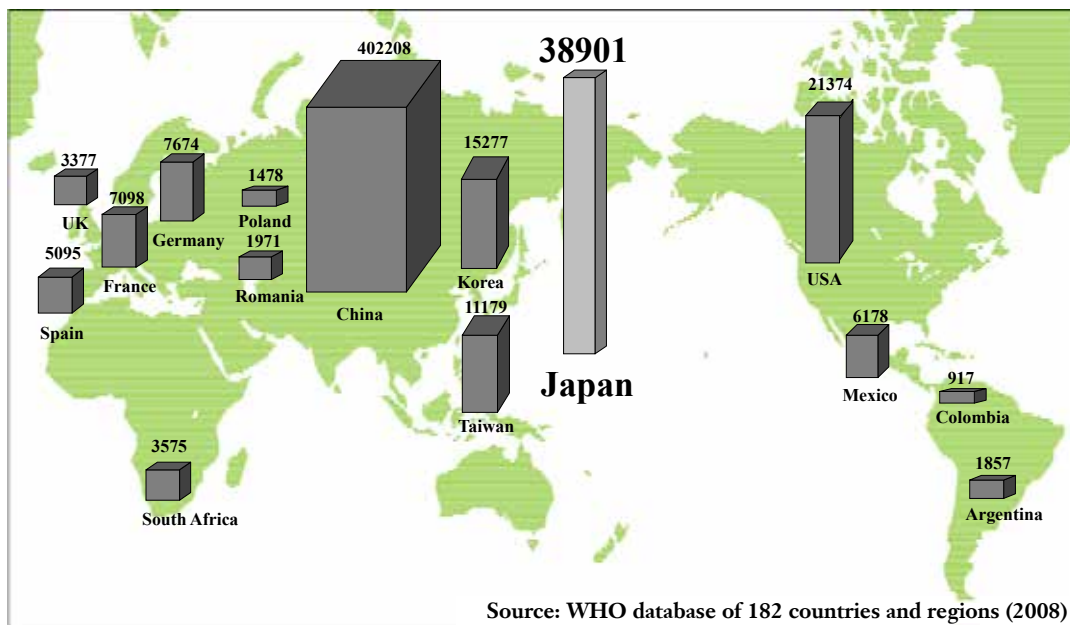


Figure 1 Numbers of deaths due to primary liver cancer in various countries and regions around the world based on the World Health Organization database 2008.

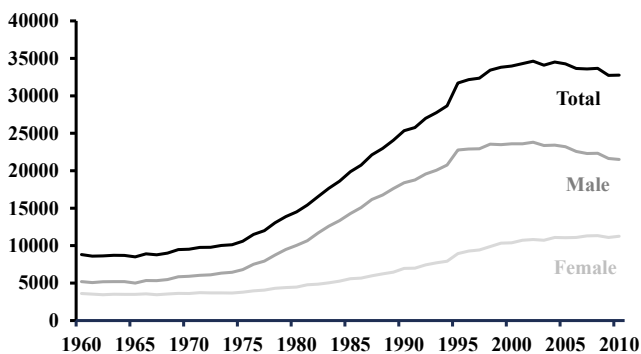


Figure 2 Trends in deaths from primary liver cancer in Japan.

development of improved therapies for viral eradication of HCV and HBV, such as peg-interferon plus ribavirin, or entecavir therapy (5,6). Against this backdrop of decrease in the number of deaths from primary liver cancer in Japan, it is predicted that the total number of deaths will have decreased to 24,600 in the year 2025.

In 2011, the number of deaths from primary liver cancer of patients who were 80 years of age or older accounted for 35.1%, approximately one out of every 3, of all deaths from primary liver cancer. Stratification according to the gender showed that 28.0% of all male deaths and 48.7% of all female deaths involved patients who were 80 years of age or over.

Thus, the female hepatocellular carcinoma (HCC) patients were older, and approximately half of the female patients were 80 years of age or older at the time of death. This tendency appears to be increasing year by year (1) (Figure 3).

HCC accounts for 94.0% of all primary liver cancers. In Japan, HCC is characterized by the development of the disease against a background of chronic hepatitis or liver cirrhosis caused by persistent HCV or HBV infection in a majority of the patients. According to the survey of the 20,753 patients in the Report of the 18th follow-up survey of primary liver cancer 2004–2005 of the Liver Cancer Study Group of Japan (7), 67.7% of the patients were HCV antibody-positive, and 15.0% were hepatitis B surface antigen-positive.

Screening for HCC in Japan

As described above, HCC often develops in patients with viral hepatitis, such as HBV or HCV. Therefore, periodic screening by ultrasonography or computed tomography with serum α -fetoprotein measurement has been recommended in patients with HBV or HCV who are at a high risk of development of HCC, for early detection of HCC. Owing to the implementation of periodic screening of patients at high risk in Japan, HCC tumors were 2 cm or less in diameter at diagnosis in 33.5% of cases and 2.1–5.0 cm

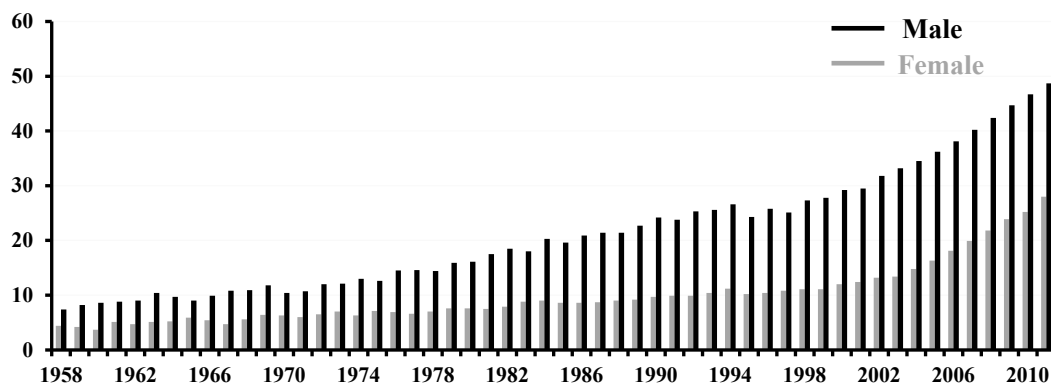


Figure 3 Proportions of patients aged 80 years or over among primary liver cancer deaths in Japan.

in diameter in 45.5% of the cases. Moreover, in 57.7% of the cases, the tumors were solitary at diagnosis, and the HCCs were often diagnosed at a relatively early stage (7). According to the Japanese Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma (8,9), tumor marker measurements and an ultrasound examination once every 3-4 months as a regular screening method, and if necessary, dynamic CT/MRI every 6-12 months, is recommended for patients with liver cirrhosis B or C. For patients with chronic hepatitis B, chronic hepatitis C, and liver cirrhosis caused without HBV or HCV, the Guidelines recommend tumor marker measurements and an ultrasound examination once every 6 months, and dynamic CT/MRI as needed. α -Fetoprotein (AFP), protein induced by vitamin K absence or antagonists-II (PIVKA-II), and the lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) are mainly used as the tumor markers. Ultrasound contrast agents are also often used to make a definitive diagnosis of HCC or for easy screening of liver tumors by ultrasonography. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI, which allows evaluation of the blood flow in liver tumors and hepatocyte function, is used to make a more accurate diagnosis and for differential diagnosis. Thus, the advances in diagnostic imaging techniques enable the diagnosis of HCC to be confirmed in many patients even without a tumor biopsy. The Japanese Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma (8,9) state that tumor biopsy is indicated only when it is impossible to make a definitive diagnosis by dynamic CT/MRI. Therefore, the indications of tumor biopsy should be decided cautiously, and the procedure should be avoided as far as possible.

Treatment policy for HCC in Japan

The main treatment modalities for HCC include surgical resection, liver transplantation, local ablative therapies, including radiofrequency ablation (RFA) and ethanol injection, and transcatheter arterial chemoembolization (TACE). According to the Report of the 18th follow-up survey of primary liver cancer in Japan 2004-2005 (7), the initial therapy was surgical resection in 31.7% of all treated patients, local ablative therapy in 30.6%, and TACE in 31.7%. For highly advanced HCC, such as that with vascular invasion, hepatic arterial infusion chemotherapy (HAIC) is often employed. After the introduction of sorafenib, systemic chemotherapy has also often been employed in recent years. Radiotherapy, including proton therapy and heavy-ion therapy, is sometimes employed as a treatment option. While determining the most appropriate treatment strategy for HCC, it is important to take the hepatic reserve into consideration, not just the condition of the HCC such as the number and size(s) of the tumors. The HCC treatment algorithm based on the consensus proposed by the Japan Society of Hepatology (JSH) in 2010 (10) is helpful for selecting the appropriate treatment for patients with HCC (Figure 4).

The cumulative overall survival times according to each treatment in the reports of the follow-up surveys of primary liver cancer in Japan from 1994 to 2005 are shown in Table 1 (7). The overall survival times were favorable in patients treated by surgical resection, local ablative therapy, and TACE, in that order. Also, the reported 5-year survival rates in Japan, Republic of Korea and the United States in 2005 were 42.7%, 18.2%, and 13%, respectively, and the 5-year survival rate in Japan might be best in the world (11).

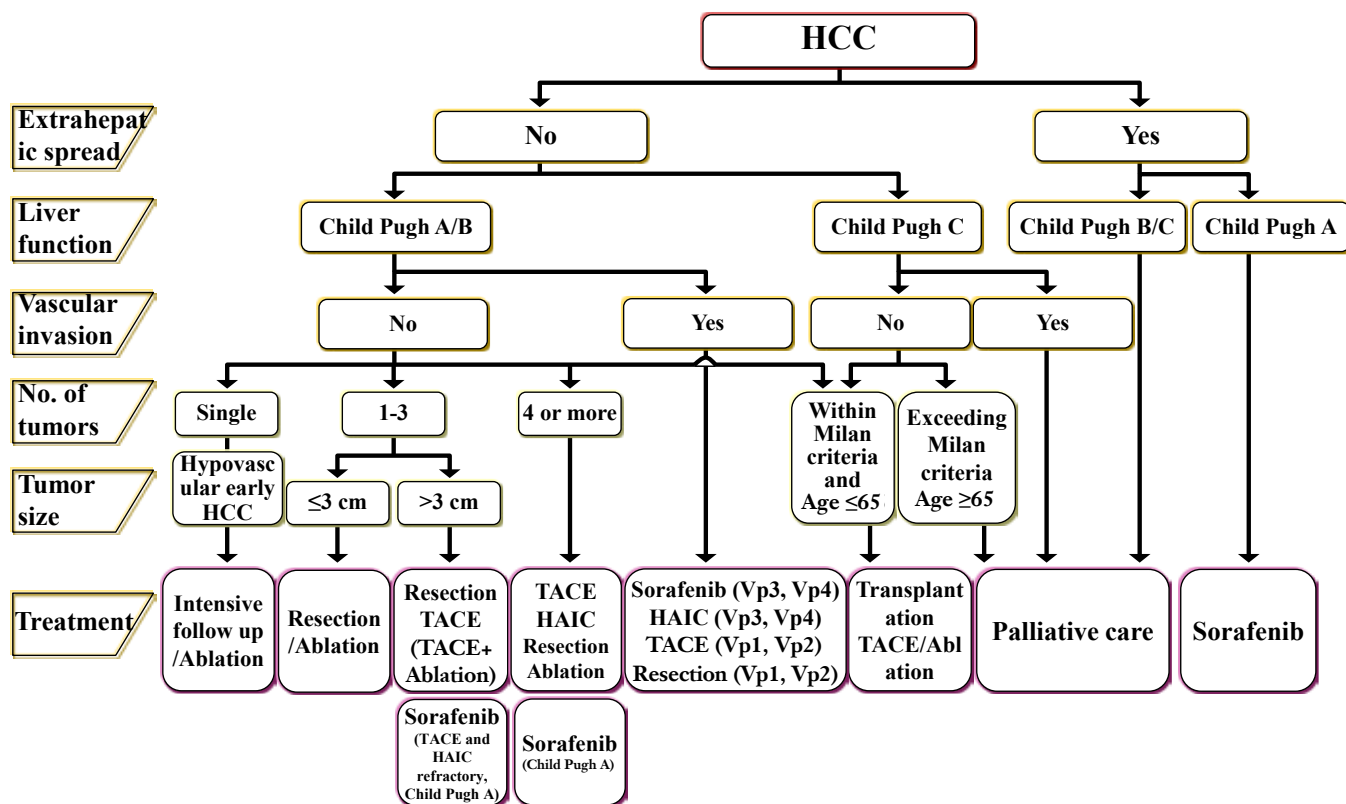


Figure 4 Treatment algorithm for hepatocellular carcinoma based on the consensus of the Japanese Society of Hepatology (2010 revised version).

Table 1 Cumulative survival times for each treatment according to the reports of the follow-up survey of primary liver cancer in Japan 1994-2005

	No. of patients	Survival proportion (%)					
		1-year	2-year	3-year	5-year	7-year	10-year
All patients	101,977	79.1	66.1	55.0	37.9	26.7	16.5
Surgical resection	25,066	88.2	78.4	69.5	54.2	42.0	29.0
Liver transplantation	183	74.2	69.3	63.4	56.7	NA	NA
Local ablative therapy	27,150	92.8	81.4	68.6	45.6	29.8	15.7
Transcatheter arterial chemoembolization	19,569	77.8	59.0	44.2	24.2	14.0	6.5

NA, not available.

Loco-regional treatments: surgical resection, liver transplantation, local ablative therapy, and TACE

Surgical resection

Surgical resection is generally recommended for HCC patients with Child-Pugh A or B liver disease with a solitary tumor, or two or three tumors no greater than 3 cm in

diameter each. However, even in patients with four or more tumors, surgical resection is sometimes performed if the tumors are considered resectable. According to the Report of the 18th follow-up survey of primary liver cancer in Japan 2004-2005 (7), the tumor diameter was under 2 cm in 17.7% of the patients, 2-5 cm in 54.9%, and 5-10 cm in 20.2%, and the tumor was solitary in 74.3% of the patients.

In addition, there was portal vein invasion in 16.2% and hepatic vein invasion in 7.3% of patients.

Liver transplantation

Liver transplantation for HCC is an ideally best treatment modality, because it provides the potential for cure of HCC and underlying liver diseases. In Japan, living donor liver transplantation is predominantly applied for the treatment of HCC because of a crucial shortage of deceased donor. According to a large survey of 1,225 patients who underwent living donor liver transplantation conducted by 65 centers in Japan (12), and HCV infection was a leading cause of liver cirrhosis (60%). The survival proportions at 1, 3 and 5 years were 84.5%, 74.4% and 69.3%, respectively. Because the opportunities for liver transplantation are limited under the current circumstance of shortage of donors, the other treatment modalities were mainly considered as initial treatment in Japanese HCC patients.

Local ablative therapy

RFA is the predominant treatment among local ablative therapies. According to the Report of the 18th follow-up survey of primary liver cancer in Japan 2004-2005 (7), RFA had been performed in 72.1% of the patients, ethanol injection therapy in 18.6%, and microwave coagulation therapy in 8.5% of patients. The general indication for local ablative therapy was a tumor no greater than diameter of 3 cm and no more than 3 tumors. Patients with a single nodule accounted for 71.2%, those with a tumor diameter of 2 cm or less for 59.3%, and those with a tumor diameter of 2-3 cm for 28.5%. The therapeutic efficacy after 6 months was complete response (CR) in 80.3% and partial response (PR) in 9.9% of the patients.

TACE

Because the local control rate and long-term prognosis of patients treated by TACE are generally unfavorable as compared to those of patients treated by surgical resection or local ablative therapy, TACE is usually employed for patients who would be unsuitable candidates for surgical resection or local ablative therapy, for example, those with multiple nodules. According to the Report of the 18th follow-up survey of primary liver cancer in Japan 2004-2005 (7), anticancer drugs and lipiodol were used in combination with TACE in 93.2% and 99.8% of these patients, respectively.

The therapeutic response after 6 months of treatment was CR in 40.5% and PR in 27.6% of the patients.

Chemotherapy: intra-arterial chemotherapy and systemic chemotherapy

Chemotherapy is employed to treat patients who are unsuitable candidates for surgical resection, local ablative therapy or TACE, that is, patients with extrahepatic metastasis, vascular invasion or resistance to TACE. Chemotherapy consists of systemic chemotherapy and HAIC. In Japan, HAIC is mainly employed for patients with localized advanced HCC, e.g., those with vascular invasion, while systemic chemotherapy is employed for HCC patients with extrahepatic metastasis. According to the Report of the 18th follow-up survey of primary liver cancer in Japan 2004-2005 (7), HAIC accounted for the higher proportion of the patients, i.e., 85.8%.

Systemic chemotherapy

The results of two pivotal randomized controlled trials have demonstrated the evident survival benefit over placebo of the orally administered molecular-targeted agent sorafenib [a multikinase inhibitor of RAF, vascular endothelial growth factor receptor (VEGFR), platelets deprived growth factor receptor (PDGFR), etc.], and this drug has come to be regarded as a standard treatment agent for advanced HCC (13,14). In May 2009, use of sorafenib for treatment of HCC was approved for coverage by the national health insurance in Japan, and over 20,000 HCC patients have already been treated with sorafenib.

Sorafenib has some troublesome adverse effects, such as the hand-foot syndrome, hypertension, liver dysfunction, etc. Higher incidences of these adverse events have been reported in HCC patients from Asia, including Japan, than in those from Western countries (13-19) (*Table 2*). The reason for this difference remains unknown, although it may be related to racial differences. Therefore, it is important in clinical practice to devise methods to properly manage such adverse events so as to avoid suspension/discontinuation of treatment due to serious adverse events and enable treatment continuation for long periods of time.

A global international prospective, non-interventional study (GIDEON trial) was performed to elucidate the safety and efficacy data of sorafenib in clinical practice worldwide (20) (*Table 3*). According to the interim analysis of the GIDEON trial, the background of Japanese patients

Table 2 Comparison of the incidences of adverse events during treatment with sorafenib between Asia and other countries

Authors	Year	Countries	n	Hand-foot syndrome (%)		Hypertension (%)		AST (%)		ALT (%)		Comments
				All	Grade	All	Grade	All	Grade	All	Grade	
				grade	3	grade	3	grade	3	grade	3	
Abou-Alfa GK (14)	2006	US/EU	137	30.7	5.1	NA	NA	NA	NA	NA	NA	Phase II
Iavarone M (15)	2011	Italy	296	28.0	9.0	18.0	7.0	NA	NA	NA	NA	Prospective study
Llovet JM (12)	2008	US/EU	297	21	8	5	2	1.7	1.7	0.7	0.7	Phase III
Cheng AL (13)	2009	Asia	149	45.0	10.7	18.8	2.0	NA	NA	NA	NA	Phase III
Chiu J (16)	2012	Korea	172	40.4	13.5	24.4	3.5	NA	NA	67.7	12.4	Retrospective
Furuse J (17)	2008	Japan	27	44.4	7.4	18.5	18.5	3.7	3.7	7.4	7.4	Phase I
Kudo M (18)	2010	Japan/Korea	229	82.0	35.0	31.0	15.0	25.0	12.0	21.0	8.0	Phase III
Our hospital		Japan	127	69.0	7.0	35.0	12.0	57.0	48.0	49.0	24.0	Retrospective

NA, not available.

treated with sorafenib was characterized by a larger number of patients who were elderly and had PS-0 as compared to the patients from other countries. The percentages of patients that had undergone surgical resection, RFA or TACE prior to the start of sorafenib treatment were also higher among patients from Japan than among patients from the other countries. Furthermore, another characteristic of the HCC patients from Japan was the longer interval between the diagnosis of HCC and commencement of sorafenib treatment (30 months), suggesting that HCC is diagnosed earlier in Japan, and that sorafenib therapy is initiated after first employing potentially effective loco-regional treatments. Regarding sorafenib therapy, the duration of administration (median) of 13 weeks in Japan was similar to that in the other countries. However, the incidence rate of serious adverse events and the proportion of patients requiring discontinuation of sorafenib due to the appearance of adverse events were higher in the HCC patients from Japan than in those from the other countries. Thus, HCC patients from Japan treated with sorafenib have often been treated heavily before the introduction of sorafenib and show a higher incidence of serious adverse events during sorafenib treatment, although their treatment outcome were almost equivalent to those in the patients from other countries.

HAIC

Because the anticancer agents are directly injected into the hepatic arteries, HAIC is associated with increased local

concentrations of the anticancer agents in the tumor and reduced systemic distribution of the drugs. Therefore, HAIC may be expected to have a stronger antitumor effect and lower incidence of systemic adverse reactions, as compared to systemic chemotherapy. Among the numerous chemotherapeutic regimens employed for HAIC, cisplatin (21-24), 5-fluorouracil (5-FU) plus cisplatin (25-28), and 5-FU plus interferon (29-33) are the most frequently used in Japan, and high response rates and favorable long-term outcomes have been reported (*Table 4*). Thus, HAIC is an effective treatment, however, no large-scale prospective randomized controlled trials have been conducted until date. Because no randomized controlled trials have demonstrated any survival advantage of HAIC, no consensus has been reached as to the standard treatment for advanced HCC. Sorafenib has been approved as a treatment for similar subjects with advanced HCC in Japan. Nonetheless, HAIC is still often performed in Japan, because a favorable tumor-shrinking effect and long-term survival of the patients are often observed in patients with highly advanced HCC in response to HAIC. To elucidate the usefulness of HAIC, several studies of sorafenib and HAIC, including randomized controlled trials of sorafenib plus intra-arterial cisplatin and sorafenib alone (UMIN00005703), of sorafenib plus intra-arterial 5-FU + cisplatin and sorafenib alone (NCT01214343), and of intra-arterial 5-FU + interferon therapy and sorafenib alone (UMIN00000240) are currently underway. In the future, demonstration of the survival advantage of HAIC and recognition of HAIC as one of the standard treatments for patients with advanced

Table 3 Differences between Japan and other countries in the results of interim analysis in the GIDEON trial conducted to determine the efficacy/safety of sorafenib

	Total (n=1,571)	USA (n=313)	EU (n=588)	Latin America (n=59)	Asia (n=450)	Japan (n=161)
Baseline characteristics						
Age (Median)	62	60	67	65	53	69
Performance status 0	40	28	46	25	30	73
Performance status 1	43	42	39	63	51	26
BCLC stage A	7	12	9	20	2	3
BCLC stage B	19	12	24	36	10	30
BCLC stage C	54	39	53	31	68	57
Child Pugh A	61	38	66	34	65	84
Child Pugh B	23	32	22	47	20	12
Prior surgery	19	11	14	7	24	40
Prior locoregional treatment	55	49	44	29	69	84
Transcatheter arterial chemoembolization	46	37	32	15	64	76
Radiofrequency ablation	15	10	15	15	12	38
Median time from initial diagnosis to start of sorafenib (months)	4	3	3	1	3	30
Sorafenib administration						
Treatment duration (median: weeks)	12	12	14	25	9	13
Daily dose (median: mg)	693	575	746	800	763	489
Initial dose level: 800 mg	74	57	81	98	78	62
Initial dose level: 400 mg	22	34	15	2	20	36
Discontinuation rate because of adverse events	19	22	20	3	15	32
Adverse events of all grades of severity	64	71	66	44	51	89
Adverse events of grade 3-4 severity	25	26	28	8	14	44
Serious adverse events	9	9	10	8	4	17
Overall survival (median: months)	-	8.4	9.4	12.5	7.9	9.3
GIDEON, Global investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib; BCLC, Barcelona Clinic Liver Cancer Group; USA, United states of America; EU, European union.						

HCC are expected.

Agents against HCC under development in Japan

Various chemotherapeutic agents such as sunitinib, brivanib, linifanib, tivantinib, bevacizumab, cabozantinib, etc., are under development worldwide for the treatment of advanced HCC. In Japan, phase III trials of lenvatinib (34), orantinib (35), S-1 (36) and peretinoin (37), all originally developed in Japan and expected to be effective against HCC, are currently underway.

Lenvatinib

Lenvatinib (34) is a tyrosine kinase inhibitor of VEGFR2,

RET, etc., and a phase II trial of the drug as first-line treatment and second-line treatment was conducted in 46 patients with advanced HCC. Favorable treatment outcomes were reported, with a response rate [assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria] of 23.9%, median time to progression of 9.4 months, and median survival time of 18.3 months. A global phase III trial comparing lenvatinib and sorafenib in the first-line setting is currently ongoing (NCT01761266).

Orantinib

Orantinib is a tyrosine kinase inhibitor of PDGFR, VEGFR-2, etc (35). A randomized controlled phase II

Table 4 Treatment efficacy of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma

Chemotherapeutic regimens	No. of patients	Response rate (%)	Time to progression/ progression-free survival (median: months)	Overall survival (median: months)	Comments	Authors	Year
CDDP	84	4	1.7	7.1	retrospective	Iwasa S (20)	2011
CDDP	80	34	NA	67.5% (1 year)	Phase II	Yoshikawa M (21)	2008
CDDP	67	37	NA	10.7	retrospective	Court WS (22)	2002
CDDP*	25	28	3.6	7.1	Phase II	Furuse J (23)	2008
5-FU/CDDP	41	22	7.0	12.0	Phase II	Park JY (24)	2007
5-FU/CDDP*	52	39	4.1	15.9	Phase II	Ueshima K (25)	2010
5-FU/CDDP	97	28	7.0	12.0	retrospective	Kim BK (26)	2011
5-FU/CDDP	114	36	NA	10.2	retrospective	Yamasaki T (27)	2012
5-FU/IFN α *	55	44	5.2	11.8	retrospective	Ota H (28)	2005
5-FU/IFN α *	116	52	NA	34% (1 year)	retrospective	Obi S (29)	2006
5-FU/IFN α *	55	29	7.5	9.0	retrospective	Uka K (30)	2007
5-FU/IFN α *	102	39	2.0	9.0	retrospective	Nagano H (31)	2011
5-FU/IFN α *	30	27	3.5	8.4	Randomized phase II	Monden M (32)	2012

*The study subjects were patients with Hepatocellular carcinoma with tumor thrombosis in the main portal vein; 5FU, 5-Fluorouracil; CDDP, Cisplatin; IFN, Interferon; NA, not available.

trial comparing orantinib with observation in the adjuvant setting was conducted in 101 patients who had undergone TACE. The median time to progression was 5.2 months in the orantinib arm as compared to 4.0 months in the observation arm, and a favorable trend with a hazard ratio of 0.699 [95% confidence interval (CI): 0.450-1.088, $P=0.054$] was reported in the orantinib group. A placebo-controlled phase III trial of orantinib is currently underway in Japan, Republic of Korea and Taiwan Area, to elucidate its usefulness in combination with TACE (NCT01465464).

S-1

S-1 is an oral anticancer agent composed of a mixture of tegafur and two modulators, gimeracil and oteracil, that was developed with the aim of intensifying the antitumor effect of 5-FU by increasing the serum concentration of the drug and mitigating its gastrointestinal toxicity (36). A phase II trial of the drug was conducted in 23 patients with advanced HCC against a background of Child-Pugh A or B liver disease, and favorable treatment outcomes were reported, with a response rate of 21.7% (5/23), median time to progression of 3.7 months, and median survival time of 16.6 months. A placebo-controlled phase III trial of S-1 (JapicCTI-090920) is currently ongoing in Japan in patients

with advanced HCC refractory to sorafenib.

Peretinoin

Peretinoin is an oral acyclic retinoid vitamin-A derivative targeted at the retinoid nuclear receptor. A placebo-controlled phase II/III trial of peretinoin 300 mg and peretinoin 600 mg was conducted on 401 HCC patients who had undergone surgical resection or RFA (37). The trial demonstrated a significant difference in the 2-year recurrence-free survival rate between the peretinoin 600 mg group, but not peretinoin 300 mg group, and the placebo group (hazard ratio 0.27, 95% CI: 0.07-0.96), and a new placebo-controlled phase III trial of peretinoin 600 mg is underway in Japan (NCT01640808).

Thus, phase III trials of several anticancer agents originally developed in Japan are underway at present, and positive results are expected in the near future.

Conclusions

Before the introduction of sorafenib, the three major treatments used for the treatment of HCC in Japan were surgical resection, local ablative therapy and TACE. HAIC was used for patients in whom these potentially effective

treatments were not indicated. However, the situation has changed greatly after the advent of sorafenib. It is now necessary to clarify the role of HAIC for the treatment of advanced HCC, especially from the standpoint of the availability of sorafenib. In addition, it is also necessary to aggressively address the development of other effective chemotherapeutic agents after sorafenib. Japan is the country with the second largest number of HCC patients in the world, and it will be important to strive to further improve the treatment outcome of HCC in collaboration with Western and other Asian countries.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Hepatocellular carcinoma in India

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Abstract: Cancers of the liver are one of the commonest cancers that occur in the world, the commonest of which is the hepatocellular carcinoma (HCC). It is considered to be the 5th commonest cancer in the world. In the areas that are endemic for hepatitis B and C, it is extremely common. Unfortunately, India which is an endemic zone for hepatitis B, there has been no comprehensive analyzed data for HCC.

Incidence of HCC in India occurs at two peaks, one at a young age between 40 to 55 years and another above 60 years. Eighty per cent of all HCCs occurring in India occur with cirrhosis of liver in the background and 60% of all these cases are hepatitis B positive carriers. Symptoms are reflective of late presentation with advanced disease.

Surgery, the only curative modulus available, unfortunately is not possible in 95% of HCC patients. Majority of the patients are treated with palliative and supportive care and life spans are limited. Sorafenib is used in a small section of patients. Characterization of HCC with molecular sub-typing is the need of the hour.

Keywords: Liver cancer; hepatoma; epidemiology; characterisation; management; India

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Background

Cancers of the liver are one of the commonest cancers that occur in the world, the commonest of which is the hepatocellular carcinoma (HCC). It is considered to be the 5th commonest cancer in the world. In the areas that are endemic for hepatitis B and C, it is extremely common. Unfortunately, India which is an endemic zone for hepatitis B, there has been no comprehensive analyzed data for HCC. HCC in India occurs in two peaks, one at a young age between 40 to 55 years and another above 60 years. The two peaks occur because of acquiring hepatitis B either in utero or in childhood, or exposure in adulthood (1,2). Eighty per cent of all HCCs occurring in India occur with cirrhosis of liver in the background and 60% of all these cases are hepatitis B positive carriers (3-5). The estimated number of cases per year in India is approximately close to 22,000 with a similar mortality (3).

Etiology

In India, 70% to 80% of all HCCs are related to the hepatitis B virus (HBV), approximately 15% are related to hepatitis C virus (HCV), and 5% to both HBV and HCV (3). Alcohol alone accounts for approximately 8% of all HCCs. In about 10%, no direct etiology is seen. Iron overload and Aflatoxin may have a role to play in some geographical areas in India (3,6).

The prevalence of hepatitis B in India varies between 0.2 to 1.6 per 100,000; 2.77 for males and 1.38 for females. This relative low prevalence is due to an under-reporting of the disease, thus India erroneously falls in the low incidence zone (3,7). The under-reporting of HCC is possibly due to non-surveillance of chronic hepatitis B patients and carriers, and cirrhotic patients (3,7). This also attributes to majority of cases being diagnosed at a late stage of the disease.

The majority of patients with a viral etiology have a silent course, picked up by foeto-maternal transfusion.

Blood transfusion related hepatitis occurs in approximately 3 in 100,000 in India. There is a long gestation period before the cancer develops (8-11).

Clinical features

The common age of presentation (median) is around 52 years; ranging between below 14 years in children and above 60 years in adults, increasing in incidence with age and peaking around 45 to 55 years (2,12). All HCCs occurring in the age group below 14 years are hepatitis B positive (13). Ninety percent of patients are symptomatic at diagnosis. The duration of symptoms is usually from five months to almost a year. About 15% of these patients are diagnosed after one year of symptoms. The clinical presentations commonly seen are anorexia in 60%, fever in odd 25% (14).

Males predominate in this disease in the ratio of 5:1 similar to distributions worldwide (3).

At diagnosis, approximately 10% to 15% are found to have cirrhosis, while on working up it is seen that a further 60% are cirrhotic that is around 70% of the total patient population is cirrhotic. Hepatic decompensation is seen in 50%, with 5% of patients presenting with encephalopathy. Hematemesis and melena occur in 25% (3,13,15) of patients.

Weakness, anorexia, abdominal pain, weight loss, ascites with jaundice, fever and gastro-intestinal bleeding are common symptoms. Patients present commonly with hepatomegaly, pallor, edema, and clubbing (in about 20%). Massive hepatomegaly is seen in about 50% of patients. The enlarged liver is usually firm to hard. Approximately 15% of patients do not have an enlarged liver. About 60% of patients present with ascites while worsening of ascites occurs in about 20%. Sometimes fever, leukocytosis and recurrent hypoglycemia occur as a para-neoplastic syndrome (16,17).

Biochemical and laboratory investigations

The majority of patients are anemic with a mean hemoglobin of 10.8 gm/dL (5.1 to 15.2 gm/dL), and serum bilirubin of 2.5 (0.1 to 30.8). Serum albumin is normal in 1/3rd of patients and mild to be moderately depressed in 50% of patients. Hepatic enzyme disturbances in the form of raised AST, ALT and SAP are seen in 55%, 39% and 33%, respectively (3,13,17).

Serum alpha-fetoprotein (AFP) has a sensitivity of 39% to 65%, specificity of 76% to 94% and a positive predictive value of 9% to 50%. The normal value of AFP in India is

around 10 to 20 ng/mL. A level greater than 400 ng/mL (14) which is accepted by European Association for Study of Liver (EASL) as diagnostic, is seen only in 46% of patients, approximately 20% of patients have normal values. Serum AFP values are higher in patients with cirrhotic changes as compared to those without cirrhosis. Fifty-three percent of cirrhotic patients have values greater than 400 ng/mL compared to 26% of non-cirrhotic patients (14,18-23).

Etiological studies

HBV accounts for 73% of all cases of HCC diagnosed using HBV markers as (HBsAg positive-81.3%, HBe antibody positive-7.48%, HB Core positive-9.35%, HBV DNA positive-0.94%). Data on, HBV genotypes is not available. Fifteen per cent are HCV related (of which Anti HCV antibody positive is 95.5%, HCV RNA positive is 4.55%). About 5% patients are co-infected with HBV and HCV. Alcohol accounts for about 8% of cases and, approximately, 9% to 10% have both an alcohol and viral etiology. No etiological cause is seen in 10% of patients (3,6-9,14).

Radiologic studies

Ultrasound is the most common surveillance and diagnostic imaging technique used in India, owing to its low cost, ease of use and low risk. CT scan is also used and may have more definitions than ultrasound.

Forty-eight per cent of all HCCs involve the right lobe, 1/3rd occur in both lobes, while the left lobe is involved in 1/5th of cases. 2/3rd of the tumors are single, large lesions with an average size of 6.8 cm × 6.1 cm. Very large tumors that are greater than 5 cm occur in 75% of patients (3,14).

Small HCCs are seen in only 8%. Three or more lesions are seen in approximately 20% of cases (3,6,14).

Ultrasound appearances are either heterogeneous or hypo-echoic. In CT Scans 23% occur to be hyper-dense.

Vascular invasion of either the major branch or spleno-portal axis or of hepatic veins is seen in more than 50% of patients. The main trunk of the portal vein is involved in about 45%.

Extra-hepatic spread occurs in 15% of which the commonest sites are the peri-portal lymph node or retroperitoneal node in about 60% of these patients and the lung in 15% (3,6,14).

Histopathologic studies

There is a tendency in India to do a fine needle aspiration

(FNA), rather than a core biopsy (3,16). This is often due to fear of bleeding. In fact FNA is done in more than 80% of patients, (the exact number of patients not receiving even this procedure is not known) (3). This leads to an equivocal diagnosis of HCC in approximately 20%. This trend seems to be changing more so in teaching centers and corporate hospitals, with more biopsies being done, helping in the characterization of this disease.

Staging

In India staging is usually done by the TNM and Okuda staging system. This is because of the simplicity of the staging system (3). Based on clinical and radiological data, 73% of patients are seen in Stage III and Stage IV of the disease. In the Okuda Staging, the majority are in Stage II [70] and Stage III [20], hence HCCs are large and very advanced in most cases. The Okuda Staging and TNM Staging are not related to AFP. Advanced Liver Cancer Prognostic System (ALCPS) scoring system, although available is not commonly applied (3,12,13). Majority of the patients have an intermediate ALCPS score (12), in whom it was done. Because of the advanced nature of the disease, the outcomes are poor.

Management

Management and treatment of patients with HCC varies according to various factors which include; patient factors, socioeconomic factors, etiological, as well as the disease status. In urban areas, mainly in tertiary hospitals, all modern facilities for HCC are available, but in rural areas such facilities are scarce and scanty.

Surgical therapy in the form of resection and hepatic transplants are available for early stage disease, in a few centers, and occur possibly in less than 1 in 10,000 patients. Liver transplants done in India are approximately five to six cases in a year. The deterrent factors are cost, availability and patients' ability to withstand (3). Radio frequency ablation (RFA) is available in very few centers but limited experience suggests that RFA may have similar results as hepatic resection in properly selected cases (3,6,17).

Use of trans-arterial chemoembolization (TACE) or RFA is available in some centers, but these are extremely small in number. No organized data is available. Discussion with experts suggests that encouraging results are available for these procedures, even in some advanced cases (1,3).

For advanced liver cancer, there exists no standard

chemotherapy for HCC, although sporadic use of doxorubicin, interferon and thalidomide is available, for which there is no organized data. Options of targeted therapy are available. The drug commonly used is Sorafenib. Results suggest that the time to progression is around six months with overall survival of seven months, suggesting an improvement of 40% over Best Supportive Care in these patients. Most patients who were treated on the drug Sorafenib are in Performance Status WHO 0, 1 and 2 and Child Score A and B, and the benefit of this drug seems to be around four months more than the Best Supportive Care. (Unpublished data of 118 patients in India, Bhattacharyya & Datta).

All patients are usually offered Best Supportive Care, which includes management of ascites, nutritional manipulation, treatment of co-morbidities and prevention of deterioration of hepatic functions which includes the anti-virals for hepatitis B and hepatitis C. Most commonly for hepatitis C, pegylated interferon alfa and the anti-viral drug ribavirin, depending on the type of HCV genotype, is used. Most often single drug pegylated interferon is used and viral control is seen in 80%. For hepatitis B lamivudine is usually used as a single drug. Sixty-five per cent of the patients have control of hepatitis B proliferation (9,17).

Prevention of hepatitis B and hepatitis C, which are predominant causes of HCC, is the primary prevention for HCC. Neonatal vaccination of HBV has decreased not only the prevalence of HBV carriers (24) but also the incidence of HBV related HCC.

Increasing awareness of blood borne infection control can also bring down the incidence of hepatitis B and hepatitis C. Therapeutic use of interferon and antiviral in chronic infections of hepatitis can bring down the incidence of viral hepatitis induced HCC (25,26).

Status of clinical trials in India

The number of registered clinical trials in India for HCC is 12 of which epidemiological trials are five and interventional trials for advanced disease is six, of which three are targeted therapy related trials sponsored by multinationals (27).

Conclusions

Treatment and management of HCC remains a challenge. Advanced HCC is not uncommon at diagnosis in developing countries like India, where routine tests for screening are not performed. It is therefore imperative to develop

effective and affordable therapeutic treatment strategies for advanced disease. So far no systemic chemotherapeutic agent other than Sorafenib has shown survival benefit. Multimodality approach is the need of the hour and has shown much better survival benefit, in single modality, in developed countries.

Researchers need to unravel the underlying hepatocarcinogenesis and key molecular targets for development of more effective chemotherapeutic agents to improve survival in advanced HCC.

Vaccination against hepatitis B and antivirals for hepatitis B and hepatitis C in chronic state, screening program for early diagnosis are the challenging task in hepatology for developing countries.

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Footnote

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Status of hepatocellular carcinoma in Gulf region

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Abstract: Hepatocellular carcinoma (HCC) has a unique geographic distribution that is likely to be determined by specific etiologic factors. There is a distinctive difference in sex and age related occurrence of disease. In the Gulf region, there are contradicting data on the prevalence and death rates due to HCC. In this review we highlight some aspects of HCC specific to the Gulf region. A retrospective analysis of 150 patient's data is presented, including demographic, epidemiological, aetiological disease status assessment with child Pugh criteria, modes of treatment and treatment related outcome. Hepatitis C virus (HCV) infection was the most common (45%) documented etiology, similar to Western European countries, followed by hepatitis B virus (HBV) infection in 27% of cases, alcoholic liver disease only in six patients (4%). Child-Pugh assessment was A in 33%, B in 37% and C in 30% of observed patients. Surgery (liver resection or transplantation) was performed in 12% and local ablation in 5% of cases. The others were treated by chemo-embolization in 17% and by systemic therapy with sorafenib in 13% of patients. Nearly half of the patients (53%) were in advanced stages and received palliative treatment. To improve the outcome of treatment in HCC patients in the Gulf region, an effective and strategic screening program must be implemented for early diagnosis and treatment to improve the outcome of this mostly fatal disease.

Keywords: Hepatocellular carcinoma (HCC); hepatitis C; hepatitis B; chemoembolization; radiofrequency; sorafenib

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Background

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world with an increasing incidence in some areas like Europe, USA and the Gulf region (1). The unique geographic distribution is likely to be determined by specific etiologic factors. There is a distinctive difference in sex and age related occurrence of disease. HCC results in about one million deaths per year. There is no clear data about the prevalence and death rate due to HCC in the Gulf region. The Arabian Peninsula (the Gulf) is a unique geographical area. Thirty five percent of the Arab World comprises Saudi Arabia, Oman, Qatar, Bahrain, United Arab Emirate (UAE), and Kuwait with population of nearly 40 million. Depending on the individual nation, the ratio of nationals

and expatriates living in the area is in the range of 30-70% being expatriates (*Figure 1*). The information in this review is based on PubMed literature, national cancer registries and cancer incidence data from various sources (2,3).

Patients with HCC continue to have a dismal prognosis, with 1- and 3-year survival rates of 36% and 17%, respectively (4). This is in part related to more than two-thirds of tumors being diagnosed at advanced stages (5,6), as well as a substantial portion of patients with early HCC failing to receive potentially curative treatments (7). As more therapies are available for patients with HCC, treatment decisions become increasingly complex. HCC generally develops secondary to chronic liver disease and cirrhosis (8). In the Gulf region the incidence varies in males between 3.4-8.1 and in females between 1.8-3.1 cases



Figure 1 The Gulf States, Bahrain, Kuwait, Qatar, Saudi Arabia, Oman, United Arab Emirates (UAE).

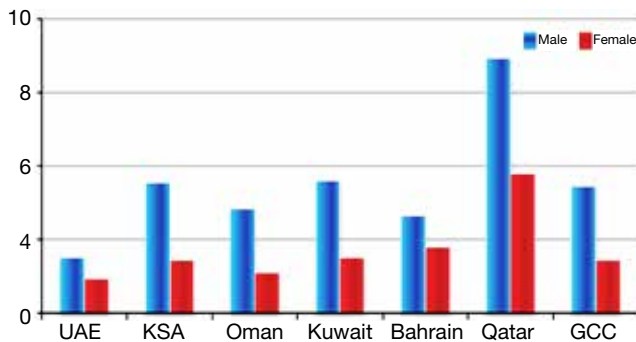


Figure 2 Age-standardised rate (ASR) of liver cancer in the Gulf region 1999-2007.

per 100,000 per year (9,10).

Recent data on the epidemiology of HCC shows that the incidence of this liver malignancy continues to increase rapidly in most parts of the world including the Gulf Region. In contrast to the West, where HCC is less common and mainly secondary to alcoholic hepatitis and hepatitis B virus (HBV) (11,12), in many Middle Eastern countries including the Gulf Region, HCC is one of the most common cancers and usually develops secondary to hepatitis C virus (HCV) (13,14). Chronic HBV infection still is one of the main risk factor beside the HCV.

Table 1 Prevalence of HCV among population and among haemodialysis patients

Region/country	Prevalence of HCV among	
	Population in M (prevalence*, %)	Haemodialysis patients (%)
Arabian Gulf region		
Saudi Arabia [Sa]	23.513 (1.7)	4.0
Oman [Om]	3.2 (1.2)	26.5
Bahrain [Bh]	0.656397 (1.7)	29.2
Qatar [Qr]	0.793341 (6.3)	44.6
UAE	4.496 (2.3)	37.0
Kuwait [Kt]	3.442 (0.8)	71.0

Abbreviations: HCV, hepatitis C virus; UAE, United Arab Emirate; M, million; *, prevalence per 100,000 population.

Table 2 Nationality and gender distribution (Grand total =150)

	Qatari (N)	Non-Qatari (N)
Male	27	87
Female	21	15
Total	48	102

Table 3 Risk factors for primary liver cancer in Qatar

HBV	40 (26%)
HCV	68 (46%)
Alcohol	6 (4%)
Other	37 (24%)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

Another report from Gulf region indicates that liver cancer is the sixth most common cancer in the Gulf Cooperation Council (GCC) states. A total of 4,965 liver cancer cases (5.2% of all cancers) were reported from all GCC States in 1998-2007. The overall Age Standardized Rate (ASR) for all GCC States was 6.9 and 2.9 per 100,000 populations for males and females respectively. The liver cancer incidence was significantly higher among men compared to women in all GCC States. Qatar reported the highest incidence among men and women with ASR of 13.9 and 7.6 for males and females respectively. Kuwaiti men ranked second and Saudi men ranked third. UAE reported the lowest ASR in both genders (ASR of 3.0 and 1.9 for males and females respectively) (Figure 2) (Tables 1-3) (15,16).

Type of adverse effect	Number of patients, n=27 [%]
Elevated liver enzyme	5 [17]
Contrast media reaction	2 [6]
Renal impairment	2 [6]
Fever	3 [9]
Variceal bleeding	1 [3]
Hand-foot syndrome	1 [3]

Methods

Qatar has a population structure not very different from other Gulf Countries. As an example for the Gulf Region we present a retrospective analysis of all Qatari cases of HCC diagnosed in Hamad Medical Corporation as collected from patient files, Medicom data (the corporation electronic system for patient's data) and the Qatar National Cancer Registry during the period March 2004-December 2010. One hundred fifty patients were included in the study. This study was approved by the research and ethical committee (IRB) of Hamad Medical Corporation, Doha, Qatar.

Statistical data analysis methods and quantitative variables were expressed as means. Standard deviations and frequencies (percentages) were calculated to summarize quantitative data. Medians and ranges have been reported for skewed (non-normal) data. Univariate Kaplan-Meier survival analysis was performed to estimate overall and group wise survival. Furthermore, the log-rank test was applied to determine any statistical difference in survival among various subgroups. In addition, the multivariate Cox regression method was used to assess the significant effect of various prognostic factors on outcome survival time. Statistical significant values were reported with their corresponding 95% CI values. $P < 0.05$ was considered to indicate a statistical significant difference. All the statistical analyses were performed using statistical software package Statistical Package of Social Sciences (SPSS, version 18.0, Chicago, IL).

Results

Epidemiology

One hundred fifty HCC patients diagnosed during the period March 2004 to December 2010 at HMC were included in the study. The mean age was 58.8 [31-87] years with male: female ratio 3:1 (76% male; 24% female). There were 48 (32%) Qatari and 102 (68%) non-Qatari patients.

The non-Qatari patients were of different nationalities from all over the world and those presenting with HCC mostly from Egypt and South Asia. HCV related disease was the most common cause of HCC in 68 patients (45%), HBV in 40 patients (27%) alcoholic liver disease only in 6 (4%) and the remaining 36 (24%) no underlying risk factors identified.

Diagnosis

Diagnosis was confirmed by histopathology in 56 patients (37%) and by AASLD criteria for the remaining 94 (63%). The criteria were typical radiological features of HCC with arterial enhancement and venous wash from lesions more than 2 cm in diameter in cirrhotic liver or other radiologically evident lesion with high alpha-fetoprotein (AFP) levels (more than 400 ng/mL).

Liver function and stage

Child-Pugh assessment was A in (33%), B in (37%) and C in (30%), using Barcelona Clinic for Liver Cancer (BCLC) which depend on the liver functions status, patients performance and the TNM stage of the tumor. One quarter of the patients were in early stages, another quarter intermediate stage and nearly half of them were in advanced stages of disease.

Treatment

Surgery

Surgery, whether resection or liver transplantation, was the treatment option in a small group of patients 18 (12%). Most of them were done abroad but have follow up at our center. Recently a center for liver transplantation was established in Qatar as another treatment option for HCC patients in our country. Up until now two patients had successful cadaveric liver transplants. There is a liver transplant center established in Saudi Arabia with more extensive experience in liver transplantation, a close collaboration partner for Qatar.

Local therapy

Ablation with radiofrequency or percutaneous ethanol injection was the treatment of choice in a smaller group of 6 (5%) patients and chemoembolization was possible in 27 (17%) patients. The treatment was generally well tolerated with some side effects as summarized in *Table 4*.

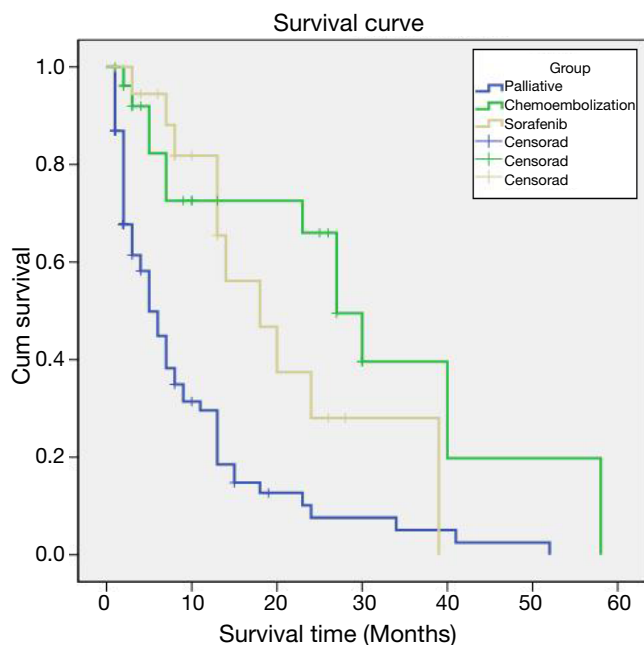


Figure 3 Survival curve of the three treatment groups, local, systemic, and palliative.

Median survival time for patients who received local therapy was 27 months (*Figure 3*).

Systemic therapy

Systemic targeted therapy with sorafenib was offered in 19 (13%) patients and palliative care in 80 (53%). The most common toxicity observed with sorafenib therapy was fatigue. Others were skin rash (*Figure 4*) and hand foot syndrome, one patient developed grade 3 hand-foot syndrome reaction (*Figure 5*). The survival for group received sorafenib was 18 months (*Figure 3*). There was no statistically significant effect detected on survival time for factors like age, gender, or bilirubin level. Though not statistically significant, it was observed that patients who had AFP level higher than 150 ng/mL are likely to have less survival than those having AFP level less than 150 ng/mL [hazard ratio, 1.34; 95% CI (0.86-2.11); $P=0.2$]. The only statistical significance was observed with Child Pugh staging and survival time. Patients having a Child Pugh score of C were likely to have significantly less survival than those patients with Child Pugh score as A [hazard ratio, 3.35; 95% CI (1.7-6.6); $P<0.0001$]. As expected, though having not statistically significant, patients with a Child Pugh score B were likely to have a survival disadvantage over patients with Child Pugh A [hazard ratio, 1.49; 95% CI (0.79-2.1); $P=0.22$]. It is clear that Child Pugh A has the best survival time as they have best liver function.



Figure 4 Hand-foot syndrome after chemoembolization with Doxorubicin.



Figure 5 Adverse effect of Sorafenib, mucosal and some of the skin reactions.

Palliative therapy

The median survival for the patients who received palliative treatment was five months (*Figure 3*). Eighty patients (53%) received only palliative care, pain and other symptom control, at a newly established unit of palliative care at the national center for care and research in Qatar.

Discussion

The Gulf region is a unique geographical area, it includes six countries; Bahrain, Qatar, Saudi Arabia, Oman and United Arab Emirates (UAE). There are heterogeneous

patterns for the prevalence of HCC in the Gulf region. The main predisposing factor is viral hepatitis, both HCV and HBV. It is more common in males (ratio M:F, 3:1). Diagnosis is usually in advanced stage, and the treatment outcome meets international standards when compared to other parts of the world (15,17-21).

From the data presented herein, it is deduced that a 3-fold increase in the age-adjusted rates for HCC, up to seven cases per 100,000 people, is possibly correlated to the increasing incidence of HCV infections in the last three decades. Moving forward, the reduction of the incidence of HCV infections, which has currently plateaued, would ultimately contribute to a reduced incidence of HCC due to HCV (22). This could be accomplished through preventive and educational strategies. However, a liver injury and repair model characterized by HCV damaged liver cells, developing dysplasia and ultimately HCC, is estimated to occur only over 10-30 years (23). As there are more people infected with HCV coming to Qatar we may expect a rising incidence.

All therapies are readily available in the Gulf, with few limitations though. Recently a center for liver transplantation was established in Qatar as another treatment option for HCC patients in our country. There is a liver transplant center established in Saudi Arabia with more extensive experience in liver transplantation, a close collaboration partner for Qatar. This is an excellent example for the critical need for collaboration in the region that will help better use available resources and optimize medical care.

So far, only few hospitals in the Gulf Region have established multidisciplinary hepatobiliary teams for the management of HCC patients. In Qatar a well established hepatobiliary multidisciplinary team has been up and running since 2011. Same applies for several centers in Saudi Arabia.

This study have it is limitation, it is a small sample size only 150 patients with HCC included, different modalities of treatment were applied, local, systemic and palliative measures. The survival outcomes were similar to what were reported internationally in the literature.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Risk factors for developing hepatocellular carcinoma in Egypt

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Abstract: Hepatocellular carcinoma (HCC) is a common disorder worldwide and ranks 2nd and 6th most common cancer among men and women in Egypt. HCC has a rising incidence in Egypt mostly due to high prevalence of viral hepatitis and its complications. Proper management requires the interaction of multidisciplinary HCC clinic to choose the most appropriate plan. The different modalities of treatment include resection (surgery or transplantation), local ablation, chemoembolization, radioembolization and molecular targeted therapies. This paper summarizes both the environmental and host related risk factors of HCC in Egypt including well-established risk factors such as hepatitis virus infection, aflatoxin, as well as possible risk factors.

Keywords: Hepatocellular carcinoma (HCC); Egypt; risk factors; epidemiology

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Incidence

In Egypt, hepatocellular carcinoma (HCC) is the second most common cancer in men and the 6th most common cancers in women (*Figures 1,2*) (1). Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers in Egypt, from approximately 4% in 1993 to 7.3% in 2003 (2). This rising incidence (3) may be due to high prevalence of hepatitis C virus (HCV) and its complications (4) and the fact that people born 20 years ago or earlier in Egypt has not been vaccinated against hepatitis B virus (HBV) (5). Investigations in Egypt have shown the increasing importance of HCV infection in the etiology of liver cancer, estimated to account for 40-50% of cases, and the declining influence of HBV and HBV/HCV infection (25% and 15%, respectively) (2,6). The rising incidence of HCC in Egypt could be also explained through improvements in screening programs and diagnostic tools (7), as well as the increased survival rate among patients with cirrhosis allowing time for some of them to develop HCC. The higher HCC incidence among urban residents could represent better access to medical facilities, resulting in an underestimate of HCC in rural populations.

Environmental risk factors

Cirrhosis

It has been recognized that the most important clinical risk factor for the development of HCC is cirrhosis. Approximately 80% of HCCs develop in cirrhotic livers (8). The high rate of co-existing cirrhosis in HCC patients and the emergence of HCC in prospectively followed cirrhosis patients have led to the assumption that pre-existing cirrhosis is an important prerequisite for hepatocarcinogenesis, although some HCCs do arise in the absence of cirrhosis (9).

Viral hepatitis and HCC (Table 1)

Although HBV is considered worldwide as a major risk factor for liver cirrhosis and HCC, the prevalence of HBV infection in Egypt has been declining over the last two decades (16). It was found that occult HBV infection and the HBV genotype B or D may influence the outcome of HBV infection leading to the development of HCC and may be strongly associated with HCV in liver carcinogenesis. A decrease in the immune status may

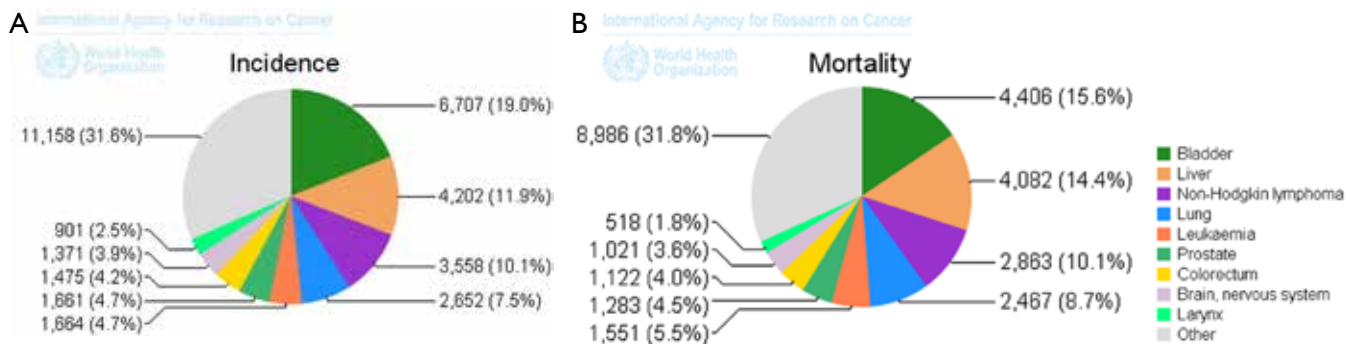


Figure 1 Incidence and mortality of HCC in Egyptian men (Globocan, 2008) (1).

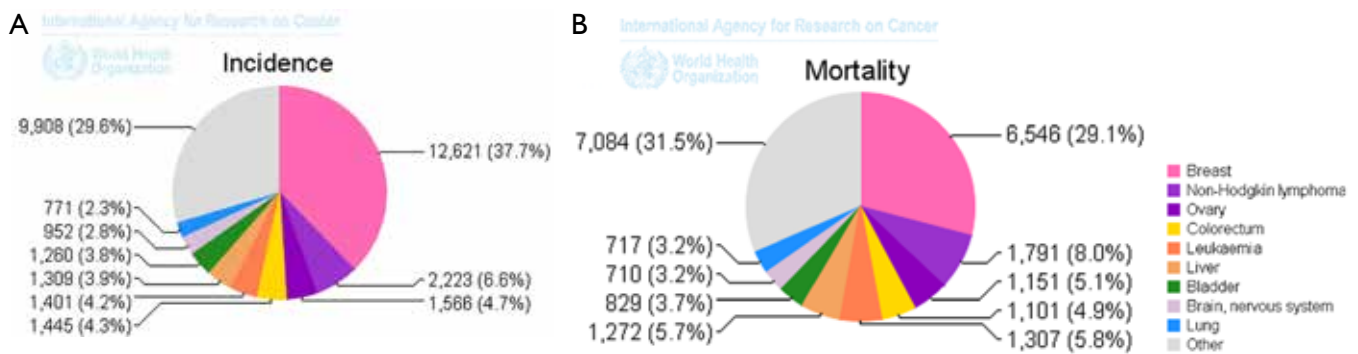


Figure 2 Incidence and mortality of HCC in Egyptian women (Globocan, 2008) (1).

Table 1 Frequencies of HBV and HCV in HCC Egyptian patients						
First Author, year (ref.)	Study period	Patient source	Patient N	HBsAg	HCV Ab	HCV/HBV co-infection
Shaker <i>et al.</i> 2013 (10)		Tropical Medicine Department, Ain Shams University, Cairo, Egypt. 75% rural	1,313	2.51%	91.32%	
Schiefelbein <i>et al.</i> 2012 (11)		Tanta Cancer Center and the Gharbiah Cancer Society in the Nile delta region. Mainly rural	148		89.2%	
El Azm <i>et al.</i> 2013 (12)	March 2009 to February 2012	Tanta University Hospitals. Mainly rural	281	26 (9.25%)	186 (66.19%)	29 (10.32%)
Montaser <i>et al.</i> 2007 (13)		HCC clinic of the National Liver Institute, Menofeya University	32	15	22	12
Abd El-Moneim <i>et al.</i> (14)		National Liver Institute, Menoufiya University	60	19	31	
Hassan <i>et al.</i> 2001 (6)		National Cancer Institute, Cairo University	33	15.2%	75.8%	
Darwish <i>et al.</i> 1993 (15)		National Cancer Institute, Cairo University	70	43	48	28
Yates <i>et al.</i> 1999 (5)		National Cancer Institute, Cairo University	131	95/129 (74%)	99/131 (76%)	

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

result in HBV reactivation in anti-HBs positive patients undergoing chemotherapy (17).

Egypt has possibly the highest HCV prevalence worldwide (18), estimated among the general population to be around 14% (19). Studies of the HCV genome confirmed a uniquely high proportion of genotype 4 (over 90%) in Egypt (20,21). Yet, much of the HCV prevalence data are limited by variability in and selectivity of the populations studied, inconsistent HCV testing methods, and a lack of data regarding mode of transmission. A strong correlation between HCV infection and intravenous treatment for schistosomiasis was frequently reported (22). Schistosomiasis, trematode blood flukes, is endemic in tropical areas of Africa, South America, Asia and the Caribbean. Only *S. japonicum* which is not present in Egypt has been classified as possibly carcinogenic in humans (23). Since chronic HCV does not typically lead to carcinogenesis for 10-30 years following infection, the rates of liver cancer can be expected to continue increasing until the cohort of intravenous antischistosomal treatment related infected individuals has worked its way through (2,24). This suggests that the true burden of liver cancer in Egypt has yet to be realized.

Chronic HCV infection mostly leads to hepatic cirrhosis before developing HCC (25). HCV is a RNA virus and hence cannot integrate into the host genome. The carcinogenesis of HCV-associated HCC is proposed to be a multistep process involving upregulation of inflammatory cytokines and induction of oxidative stress from chronic hepatitis, fibrosis, liver regeneration, and, ultimately, the development of cirrhosis (26). Moreover, HCV may play a direct role in hepatic carcinogenesis through involvement of viral gene products in inducing liver cell proliferation (27).

Aflatoxins and HCC

There is suggestive evidence for an additional etiologic role of aflatoxin in hepatocarcinogenesis in Egypt. Aflatoxins are toxic and carcinogenic metabolites of moulds, mainly *Aspergillus flavus* and *parasiticum* that contaminate a variety of agricultural commodities, particularly peanuts, maize and cottonseed, in countries with hot and humid climates. Aflatoxin B1 (AFB1) is the major metabolite produced by these moulds. Aflatoxins are classified as human carcinogens based on sufficient evidence of carcinogenicity (28).

Dilber *et al.* detected a significant higher percent of aflatoxins in the serum of Egyptian patients with HCC compared to their controls; with a two-fold increased

risk (29). Also, Rahman El-Zayadi *et al.* examined 200 HCC cases and 120 healthy controls and detected AFB1 in 17% of the HCC cases compared to 9.4% of the healthy controls (risk ratio =2) (30). The level of AFB1 was significantly higher in patients having multiple lesions and also in patients presenting with tumor size more than 5 cm. This may be related to the effect of AFB1 as predisposing factor affecting all the liver homogeneously (31). El-Kafrawy *et al.* documented the presence of *p53* codon 249 mutations associated with aflatoxin exposure in a sample of HCC tumor tissues analyzed by gene chip analysis in Egypt (32). Generally, in human cancer, in more than 50% of tumors, *p53* is mutated and these mutations occur at the third position of codon 249 with the GC-TA transversion (33,34). Both aflatoxin exposure and HCV were strongly correlated with liver disease progression to stage G3S3, that was indicative of HCC (35).

Role of pesticides in the etiology of HCC

Occupational exposure pesticides may have a contributory role in the etiology or progression of HCC. A major segment of the Egyptian population (i.e., around 26%) is employed in agriculture (36) and uses pesticides routinely to control insects, weeds, rodents, and fungal infections of crops and livestock. Studies suggested that exposures to organophosphorus and carbamate pesticides, as a result of increasing discharge of untreated industrial wastes and agricultural irrigation waste water, are additive risk factors to current HCV and HBV infection among rural males (37,38). Future investigation should address the possible hepatocarcinogenicity of pesticides using biomarkers of exposure and other techniques to better estimate dose-response relationships (35).

Alcohol, coffee, smoking, OCs

Alcohol consumption increases the risk of HCC primarily through the development of cirrhosis. It has been suggested that heavy alcohol consumption of >80 g/d ethanol for at least five years increases the risk of HCC by nearly 5-fold (39). Epidemiological studies suggested a strong synergistic effect of alcohol on both HBV and HCV infections in developing HCC (40). Egyptian surveys have found a gradual increase in the consumption of alcohol, leading to the prediction that this will be the most common form of substance misuse in the coming years (41).

Coffee consumption may have a potentially favorable

effect on the prevention of liver diseases, including liver cirrhosis and HCC (42,43). Some components in coffee, including diterpenes, cafestol, and kahweol, may act as blocking agents via modulation of multiple enzymes involved in carcinogenic detoxification as demonstrated in animal models and cell culture systems (44-46). Moreover, coffee constituents modify the xenotoxic metabolism thorough induction of glutathione-S-transferase and inhibition of N-acetyltransferase (47,48).

The effect of tobacco in the development of HCC is biologically plausible, due to the carcinogenic potential of several of the ingredients in tobacco that are metabolized in the liver (49). A Korean study has found a 50% increase in the risk of primary liver cancer for current male smokers compared to never smokers (50). However, a population based case-control study from the United States did not observe a significantly increased risk of primary liver cancer among current male smokers (51). A prospective study of 12,008 men observed that smoking significantly increased the risk of HCC only in anti-HCV-positive patients but not in those who were anti-HCV-negative when compared to anti-HCV-negative nonsmoking individuals (52). In Egypt, a preliminary case-control study showed significantly higher percentage of HCC patients used to smoke for more than 20 years, more than 20 cigarettes/day and heavier than those in the controls (53). Bakir *et al.* reported that smoking was found in 64% of Egyptian patients with HCC compared to 38% in patients with liver cirrhosis and 39% in controls (54). Another study revealed that tobacco smoking was a common risk factor of HCC among both cirrhotic and noncirrhotic patients (55). According to WHO statistics 2009, an estimated 40% of Egyptian males above the age of 15 years are smokers.

Oral contraceptives (OCs) appear to be associated with the development of benign liver tumors such as hepatic hemangioma, hepatocellular adenoma or focal nodular hyperplasia (56). Malignant transformation can occur within the context of hepatic adenomas after 11 years mean duration of OCs use (57). The frequency of HCC among hepatic adenomas appears to vary from 5% to 18% (58,59). In Egypt, 10.8% of married women aged 15-49 years were relying on OCs (60).

Host-related risk factors

Obesity

The prevalence of obesity has increased to epidemic proportions over the last three decades. According to

WHO statistics 2008, an estimated 46.3% of females in this age group are said to be obese, in comparison with approximately 22.5% of Egyptian males. Excess body mass is classified as overweight if the body mass index (BMI) is >25 and <30 kg/m^2 , or obese if the BMI is ≥ 30 kg/m^2 . Both are associated with a higher risk of developing all cancers, including liver cancer (61). Those patients who were overweight had a 17% increase in risk of developing HCC, whereas obese patients had an 89% increase in risk (62). Thus, surveillance is important for diagnosis of asymptomatic HCC among this population.

Diabetes mellitus (DM)

A positive correlation between the history of diabetes mellitus and HCC was observed (63). Some possible mechanisms explained this association. Most non-insulin dependent diabetics show hyperinsulinemia. Thus, insulin or its precursors may interact with liver cells to stimulate mitogenesis or carcinogenesis (64,65). Another possible pathway is that a *p53* mutation (an apoptotic factor) was noted frequently in HCC patients with diabetes rather than non-diabetics, this might provide an evidence for a molecular mechanism involving this common association (66).

According to WHO statistics 2008, an estimated 7.4% of Egyptian females and 7% of Egyptian males above the age of 25 years are said to have elevated blood glucose. An Egyptian study revealed high prevalence of DM in liver cirrhosis and HCC but no statistically significant difference in prevalence of DM between HCC and liver cirrhosis patients (54).

Nonalcoholic fatty liver disease (NAFLD)

NAFLD is being diagnosed with increasing frequency as a manifestation of the metabolic syndrome, obesity and diabetes mellitus type 2. The key process in NAFLD that predisposes patients to HCC is the development of NASH. The diagnosis of NASH relies on a biopsy with a histopathology showing features of steatosis, hepatocellular injury (ballooning, Mallory bodies), and fibrosis (67). The presence of NASH places patients at risk for progressive fibrosis and subsequent cirrhosis. The pathophysiology of hepatic carcinogenesis in patients with NAFLD-NASH has not been completely elucidated (68). But initial research suggests that excess fatty acid supply and hepatocellular steatosis elicit increased fatty acid oxidation with subsequent enhanced reactive oxidative stress (69). This process further promotes the release of proinflammatory cytokines, prooncogenic signals and

epigenetic changes. Importantly, these cascades of events may take place in the absence of cirrhosis. In fact, case reports have been published where HCC arose in patients with NASH in the absence of cirrhosis (70).

Most population-based cohort and case-control studies support the link between NAFLD and HCC by showing that patients who are obese and have diabetes mellitus type 2 are twice as likely to develop HCC compared to non-obese and nondiabetic patients (71-74). An Egyptian epidemiological study over last 15 years including 1,759 HCC patients found that 5.3% of patients had suffered from NASH (75).

NAFLD-NASH is an emerging risk factor for HCC with the potential to contribute and eventually overtake HCV as the main risk factor for HCC given the galloping rates of obesity and diabetes in the world (76). Efforts should continue to better understand the link of NAFLD-NASH with HCC.

Iron overload

Hereditary hemochromatosis, a rare autosomal recessive genetic disorder characterized by excess iron absorption, is caused by mutations in the *HFE* gene and/or other mutations in the iron metabolism machinery (77). The estimated prevalence of Hereditary hemochromatosis in Egypt is around 0.5% (78). The altered iron metabolism seen in hereditary hemochromatosis leads to excess iron storage in the liver and the subsequent development of liver cell damage. Several studies have shown that the diagnosis of hereditary hemochromatosis confers a consistent and markedly elevated risk for the development of HCC (79-81). An Egyptian study revealed that the frequencies of *HD* and *DD* genotype of *H63D* mutation were significantly increased among HCC patients compared to control group and to cirrhosis group (82).

In fact, patients with excess total body iron secondary to other etiologies such as β thalassemia or iron overload in people of African descent have been shown to have a higher risk of HCC in the absence of genetic hemochromatosis (83,84). Regardless of etiology, surveillance for HCC should be undertaken in case of iron overload (85).

Autoimmune hepatitis (AIH)

AIH is a disease of unknown etiology affecting females mainly (86). It is an inflammation of the liver that occurs when immune cells mistake the liver's normal cells for

harmful invaders and attack them. The risk of HCC among AIH patients with cirrhosis is 1.9% per year. This is comparable to HCC risk among patients with cirrhosis secondary to HBV, HCV or alcohol-related liver disease (87). In Egypt, an epidemiological study over last 15 years including 1,759 HCC patients found that 0.5% of patients had suffered from AIH (75). HCC incidence of about 1% has been reported from different geographic areas among chronic AIH dependent liver cirrhosis (88-90).

Others

Epidemiology studies revealed that severe alpha1 antitrypsin deficiency (A1ATD) is a significant risk factor for cirrhosis and HCC unrelated to HBV or HCV infections. However, predisposition to HCC in moderate A1ATD is rare, and probably occurs in combination with HBV and/or HCV infections or other unknown risk factors (91). It is proposed that accumulation of polymers of A1ATD variants in endoplasmic reticulum of hepatocytes leads to damage of hepatocytes by gain-of-function mechanism (92). The increased frequency of mutant A1AT deficiency alleles together with the existence of *HFE* mutant alleles among HCV liver cirrhosis Egyptian patients may warrant us to do further studies assessing their relevance for risk stratification for disease progression (93).

Hereditary Tyrosinemia is an autosomal recessive inborn error of tyrosine metabolism caused by a deficiency of fumarylacetoacetate hydrolase (FAH). Hepatomegaly with focal hepatic lesions is the commonest presentation. It is increasingly recognized among Egyptian children; this may be explained by the high rate of consanguinity among Egyptians (94). Tyrosinemia might be complicated by the development of HCC (95). Thus, dietary or pharmacological management of hereditary tyrosinemia might offer a strategy for prevention of HCC in these cases (96).

Conclusions

As in many developing countries, Egypt is undergoing an epidemiologic transition. With increasing urbanization, smoking rates, environmental exposures, aging and life style changes, in addition to the heavy burden of HCV, it is likely that HCC will continue to rise in the next few years. However, with wider use of Hepatitis B vaccination, the importance of HBV will decrease in the future. As HCV related HCCs are on the increase in many geographical areas, a safe and effective vaccine that prevents and treats

HCV infection is urgently required. Other possible risk factors of HCC such as DM and obesity deserve more concern for their rapid increasing worldwide. Such review should help define the complex aetiology of HCC, enabling policy makers to create targeted and more efficient prevention and screening programs. Our review produced important preliminary insights that can be used to develop more refined, prospective analyses of HCC magnitude and risk in Egypt.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Status of hepatocellular cancer in Europe

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Abstract: Hepatocellular cancer (HCC) accounts for 47,000 deaths per year in Europe and the incidence is expected to increase over the next 10-15 years. The highest incidence is found in Southern Europe, mainly attributable to chronic hepatitis C infection. The most widely used staging system used is the Barcelona-Clinic Liver Cancer (BCLC) classification according to which, 30-40% patients are suitable for potentially curative therapies including transplantation, resection or ablative therapy while the remainder are offered palliative therapy with transarterial therapy, systemic therapy or supportive care. Here we review the indications and outcomes of these interventions as applied to the European population.

Keywords: Hepatocellular cancer (HCC); liver resection; liver transplantation; ablative therapy; transarterial therapy; Europe

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Etiology and epidemiology of hepatocellular carcinoma (HCC) in Europe

HCC is a leading cause of cancer death worldwide. It represents the fifth commonest cancer worldwide and over 500,000 new cases are diagnosed per year (1). There is marked variation in the geographical incidence of HCC reflecting the contribution of different viral, genetic, metabolic and environmental factors. In Europe, HCC accounts for around 47,000 deaths per year and the incidence is comparatively low with the exception of Southern Europe where the age-standardized incidence rate in men is 9.8 per 100,000 as compared with 3.8 in Northern Europe, 4.6 in central and Eastern Europe and 7.2 in Western Europe (1) However, in the UK, mortality rates from HCC are expected to rise by 14% between 2006 and 2025 (2) representing the largest increase in any male cancer. Cirrhosis of any cause is an important risk factor for the development of HCC with up to 90% of HCC developing within cirrhotic livers and HCC is also the leading cause of death in cirrhotic individuals. Chronic hepatitis B affects 0.5-0.7% of Europeans and the prevalence of chronic

Hepatitis C ranges between 0.13-3.26%. NAFLD is present in 2-44% of the general population and 43-70% of those with type 2 diabetes (3). Mortality from alcohol related liver disease also varies across Europe being highest in Hungary at 49 per 100,000 and lowest in Uzbekistan and Israel. Overall, in Europe, hepatitis C is the major risk factor accounting for 60-70% cases of cirrhosis while alcohol is the causative factor in 20% and hepatitis B in 10-15%.

Surveillance for HCC

When HCC presents symptomatically with abdominal pain, ascites, weight loss or distant metastases, the prognosis is extremely bleak with a median survival time of only 6 weeks. Consequently most centers offer a surveillance strategy to detect early tumors in high-risk individuals including those with cirrhosis or hepatitis B infection. In Europe the recommended surveillance comprises six-monthly ultrasound (4,5) and some centers also monitor AFP although sensitivity and specificity of blood markers for early disease is low and the benefit unproven. Ultrasound surveillance has never been subjected to a randomized

clinical trial in Europe but it is clear that six-monthly surveillance leads to better outcomes whilst there appears to be no distinct advantage to shortening the surveillance interval to three months (5,6). Thus the standard of care in Europe is biannual ultrasound.

Diagnosis and staging of HCC

Most HCC arising in a high-risk setting such as cirrhosis can be diagnosed noninvasively using dynamic contrast enhanced CT or MRI. The classical imaging features of HCC are a lesion that demonstrates increased enhancement compared to the background liver in the hepatic arterial phase of the scan. In addition to arterial hyper-vascularity a lesion must also show washout in the venous or delayed phase of the scan to be defined a HCC. The combination of arterial hypervascularity and washout in the context of a high risk setting (cirrhosis or hepatitis B) is highly specific for HCC and biopsy is not required for these lesions if greater than 1 cm in diameter (7). For lesions that do not display classical imaging criteria either a second dynamic imaging study can be applied or the lesion can be biopsied. Some small HCC however are hypovascular and therefore do not conform to the classical imaging criteria and can only be diagnosed on biopsy. Hypovascular HCC are usually well differentiated and therefore some authorities would recommend enhanced surveillance for this group of patients given that most of these lesions will acquire classical imaging characteristics as they grow. Conversely an aggressive approach to biopsy is advocated by some as these lesions have the best chance of cure if treated early (8). The differentiation of very early HCC from regenerative nodules can be difficult and it is recommended that pathological analysis of biopsies takes place in specialist centers.

Given that most HCC arise within the setting of pre-existing liver disease, an accurate assessment of prognosis is dependent on both the degree of liver dysfunction and the tumor characteristics. A number of staging systems have been proposed but, in Europe, the most widely used is the Barcelona-Clinic Liver Cancer (BCLC) classification. The BCLC system incorporates characteristics of the tumor, the background liver function and also the patient's performance status. It has been externally validated as a prognostic classification and can also be used to guide treatment decisions (9). However, in practice, European centers often deviate from these guidelines. AFP is increasingly used to inform decisions about transplantation and resection (10), tumors greater than 2 cm in diameter

are resected with good outcomes (11) and TAE may be used rather than transarterial chemoembolization (TACE) (12). The guideline also has no place for transarterial radioembolization (TARE) which is increasingly used in Europe (13). It is also recognized that the BCLC B stage is very heterogeneous and proposals have been made to sub-classify this group (14,15).

Liver resection for HCC

In patients without cirrhosis, the treatment of choice for HCC is surgical resection. In Europe, individuals with HCC suitable for resection make up only 5% of the total number of HCC patients (16). Surgical resection may also be offered to patients with well-compensated cirrhosis but these individuals must be selected carefully to avoid the risk of postoperative decompensation (17). In Europe, the decision to offer surgery for HCC in cirrhosis relies on the measurement of a normal serum bilirubin and the absence of clinically significant portal hypertension as measured by a hepatic venous pressure gradient measurement of <10 mmHg (18,19). If these guidelines are followed then the risk of decompensation of the liver disease following resection is extremely low. Functional tests of liver reserve such as indocyanine green clearance studies also have a role in determining both suitability for resection and the extent of resection (20). Outcomes for surgical resection vary but most centers report 5-year survival rates of between 50% and 70%; Recurrence rates however are high even after resection of small tumors. A recent multi-center French study has reported equivalent outcomes in patients undergoing laparoscopic resection and this may be favored in selected patients (21). According to the BCLC classification, tumors traditionally thought suitable for treatment with resection are limited to those of early stage (i.e., Single tumors of 2 cm or less with normal portal pressure and serum bilirubin). Outcomes in these patients following resection are usually excellent with 5-year survival exceeding 90%. However the occurrence of these early stage tumors is rare with only 75 cases reported from a large volume center over a 20-year period. Whilst 5-year survival in these cases was generally excellent, recurrence rates were high at 68% reflecting the more aggressive nature of small tumors in European patients (22). Recently the restriction of resection to patients with very early or early stage disease has been challenged. In response to the publication of single center reports of resection in patients with intermediate stage (large or multiple) or advanced (portal vein invasion) stage tumors, the HCC East-West study group performed a

multi-centric study of resection outcomes for HCC across all BCLC categories (11). A total of 2,046 patients were studied from ten centers across three continents. The majority of the patients had BCLC stage very early or early disease but 36% and 14% were from BCLC intermediate or advanced stage. The results of the study confirm that, for early stage disease, outcomes are generally good with 5-year overall survival of 61% and disease free survival of 21%. For patients with intermediate or advanced stage tumors the disease free survival was poor at 5 years (12-26%) but overall survival at 5 years was surprisingly good at 55% for intermediate and 31% in advanced stage disease. In some centers, resection is also considered as a bridge to transplantation to avoid drop out on the waiting list or even as an alternative to transplantation with 'salvage transplantation' offered in the case of recurrence. Belghiti and colleagues have shown that patient selection is key to achieving satisfactory outcomes with this approach (23,24).

Liver transplantation for HCC in Europe

For those patients not suitable for resection due to advanced underlying liver disease the only curative surgical option is liver transplantation. The Milan criteria remain the most widely used means of selecting patients for transplantation in Europe and its application is associated with a five years survival of around 70% (25). According to data from the European Transplant Registry, almost 6,000 liver transplants are performed each year and the primary indication is HCC in around 20% cases (26). The majority of liver transplantation in Europe occurs from deceased donors, therefore the main limitation for transplantation is donor shortage resulting in a prolonged waiting time which, in Europe, is responsible for a dropout rate of between 15% and 35% (27,28). Deceased donor rates vary widely across Europe with Spain having the highest rates of 34.2 per million (in 2008) as compared with 20-25% per million for the most other European countries (26). To reduce the rate of progression beyond Milan criteria, many centers apply 'bridging' interventions including RFA or TA(C)E while on the waiting list. Evidence suggests that this approach is indicated when waiting times are longer than six months but the unpredictability of waits for individual patients often results in wider application (29,30). Post-transplant recurrence may be reduced by effective embolization (31) and the response to pre-transplant loco-regional therapies may also select those patients with a favorable biology (32,33). In patients transplanted after demonstrating a response to

down-staging protocols, histology in the explanted livers was found to be favorable with all residual tumors being well to moderately differentiated and without microvascular invasion (34). Partly based on these findings, the UK transplant criteria for HCC have been extended beyond the Milan Criteria to include those with a period of stability over six months, where the maximum dimension for a single tumor does not exceed 7 cm or five lesions are present with a maximum dimension of 3 cm. Allocation of donor organs in Europe is usually based on MELD score (35). This system results in patients who are sickest in terms of liver disease receiving highest priority. Allocation by MELD may disadvantage patients with HCC and well compensated cirrhosis and therefore patients within the Eurotransplant allocation scheme receive MELD exception points in order to increase priority for transplantation and mitigate the risk of drop out on the waiting list. Other centers in Europe allocate organs in a center specific manner which allows a degree of donor recipient matching although this tends to result in HCC patients receiving more marginal organs which may compromise outcomes (36). Expansion of the donor pool using live donor transplantation or grafts from donors after determination of circulatory death (DDCD) is utilized in some European centers and could potentially increase the number of grafts available for patients with HCC. However numbers of patients undergoing live-donor liver transplantation remains relatively small (300/year) and the use of DDCD grafts results in inferior outcomes due to increased rates of primary non function and biliary structuring disease (26,37).

Despite the improved survival following the implementation of the Milan Criteria, recurrent disease remains a problem and at present there are no evidence-based treatments that have been shown to be effective in post-transplant HCC. Therefore interest has focused on the prevention of recurrence and particularly the role of excess immune suppression which may increase recurrence rates (38). Recently the role of mTOR inhibitors has been examined in the prevention of HCC recurrence. A randomized trial of sirolimus in patients with HCC is underway but yet to report, however a recent meta-analysis suggests that this molecule may have a role in immunosuppressive regimens in HCC patients due to an observed reduction in HCC recurrence (39).

Ablative therapy

According to the most recent EASL-EORTC practice

guidelines, local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC A tumors not suitable for surgery (4). Precautious ethanol injection (PEI) is cheap and has been widely used for over 20 years but there is increasing evidence that radiofrequency thermal ablation (RFTA) may be superior. PEI was introduced as a treatment for HCC in the early 1980s and induces tumor necrosis by causing cellular dehydration, protein denaturation and chemical destruction of blood vessels. It is performed under local anesthetic using ultrasound guidance and requires 4-6 sessions depending on the tumor characteristics. Histological complete necrosis is found in 70% tumors measuring less than 3 cm and the 5-year survival for patients with well compensated cirrhosis ranges from 47-60% (40-42). Although there have been no randomized trials comparing PEI with best supportive care, the historical survival of this group of unresectable patients is in the order of 20% (43). The risks of PEI are small and in one recent series from a single center reporting on 270 patients treated over 20 years, there were no deaths and the most common toxicities were fever, pain and elevation of ALT. The rate of seeding was 1.9%. There have been no randomized trials comparing PEI with surgery but a non-randomized prospective comparison of PEI versus surgery in patients with tumors smaller than 3 cm in size and less than three in number demonstrated almost identical survival at five years of 59.0% for PEI and 61.4% for surgery (44).

A potential disadvantage for PEI is that ethanol does not extend beyond the capsule and there is therefore the risk of not treating the satellite deposits present outside the main tumor rim. Cancer is the cause of death in 60% of Child Pugh A patients following PEI and 28% of recurrences have been reported as occurring solely in the same liver segment (42). For this reason, particularly in tumors greater than 2 cm there has been increasing interest in RFTA which can destroy a rim of tissue around the tumor. The aim of RFTA is to cause local tissue destruction at the tip of an electrode by thermal injury as a result of the deposition of electromagnetic energy. Initially the monopolar electrodes used were only able to induce ablation zones of 1.6 cm but the development of multipronged retractable electrodes has allowed ablation of much larger volumes with a single insertion. As with PEI image guidance is required but many centers use general anesthesia as the procedure is more painful than PEI.

Initial non-randomized trials reported 5-year survivals of 33-40% at five years. The first trial comparing PEI and RFTA randomized 102 patients with HCC less than

5 cm or no more than three tumors less than 3 cm each. Although there was no significant difference in 2-year survival (88% versus 98%) there was a significant difference in terms of 2-year relapse free survival (62% versus 96%) in favor of RFTA. Furthermore, an average of 1.1 sessions of RFTA was required compared to 5.4 for PEI. Longer term survival has now been reported in a prospective trial and found to be 41% at 5 years according to intention to treat. Recurrence rate was 80% but local tumor progression was only 10% and for patients with Childs A cirrhosis and a single tumor five years survival was 61% (45). Subsequently, there have been further randomized trials published (46-49) and three meta-analyses (50-52) and these provide evidence that RFTA is superior to PEI in terms of survival for HCC >2 cm.

However not all lesions are suitable for RFTA and two of the reported trials excluded about 10% patients because the tumor was within 1 cm of the liver hilum, close proximity to the gall bladder or to the gastrointestinal tract and in these circumstances PEI may be the favored option.

Pain is a common side effect of RFTA but the rate of major complications in the reported randomized trials is between 2% and 5% and includes intraperitoneal bleeding, hemothorax, skin burns, and perforated viscous (45-48). The rate of malignant seeding varies between 0% and 3%.

Transarterial therapy

Embolic therapy

For good performance patients with unifocal disease, not suitable for resection or ablation, or multifocal disease without vascular invasion or extrahepatic spread, transarterial therapy is recommended. Historically, there has been considerable heterogeneity in the approach to transarterial therapy (53) and there have been no large randomized trials against best supportive care. The EASL-EORTC practice guidelines recommend TACE based on the results of two small randomized trials (54,55) and a meta-analysis of seven trials including 545 patients (56). Of the two positive trials, one was performed in Hong Kong and randomized 80 patients to treatment with TACE using an emulsion of cisplatin and lipiodol and gelatin sponge particles or to symptomatic care (SC). The actuarial survival was significantly improved in the treated group (31% at 2 years versus 11% in the untreated group) (55). The second trial, from Barcelona, randomized 112 patients from a screened population of 903 into three groups;

TACE using a doxorubicin/lipiodol emulsion and gelfoam fragments, TAE using gelfoam fragments alone and SC. Again there was a significant difference in two years survival between the TACE group and the SC group (63% versus 27%) (54). However no significant difference in survival was demonstrated between TAE- and TACE-treated patients or between the TAE- and SC-treated patients. More recently drug eluting beads (DEB-TACE) have been evaluated. Doxorubicin is directly loaded onto embolic micro-beads and leaches into the tissue following transarterial injection. The peak plasma concentration and AUC of doxorubicin is reduced compared to conventional lipiodol-based TACE (57) and the systemic toxicity is reduced as a consequence. A randomized comparison of DEB-TACE versus conventional TACE confirmed reduced systemic toxicity with DEB-TACE but a survival benefit has not been demonstrated (58). Overall, the importance of chemotherapy remains questionable and no trial has yet shown a benefit of TACE over bland embolization (TAE). A meta-analysis including 582 patients from five randomized trials demonstrated no difference in survival between TAE and TACE treated patients (12) and a recent randomized comparison of DEB-TACE with bland bead TACE also failed to show any survival advantage for DEB-TACE (59).

Transarterial radioembolization (TARE)

TARE can be delivered in the form of Iodine-131 labeled lipiodol or using Yttrium-90 conjugated resin or glass microspheres but the lack of randomized trials has prevented TARE becoming established in the therapeutic algorithm. The only reported randomized trial was conducted in France and compared ¹³¹I-Lipiodol with TACE. There was no difference in terms of survival or response but ¹³¹I-Lipiodol was better tolerated (60) and similar findings were reported for a cohort comparison of these two modalities (61). A cohort comparison of ⁹⁰Y-microspheres with TACE conducted in 245 patients demonstrated similar survival of around 17 months in the both groups with intermediate stage disease but there was reduced toxicity in the TARE treated patients (62). A potential benefit of TARE over TACE is that there is no embolic effect and TARE appears to be safe in patients with portal vein occlusion (63,64). Randomized trials comparing sorafenib with TARE in patients with liver confined disease but portal vein thrombosis are on-going and may help define the place of TARE in the management of HCC. However the delivery of TARE is not straight forward and

requires expertise and dedicated infrastructure.

In summary, there are a number of locoregional therapies that are used in Europe for liver confined HCC but there are few comprehensive surveys that define their application. A recently published Italian study surveyed 134 centers of which 65% responded. Of 8,959 procedures performed in 2011, 31% were ablations of which about three quarters were RFTA and the remainder PEI. Transarterial treatments accounted for 67% of procedures of which 13% were TAE and the remainder TACE. Of those treated with TACE, DC Beads were used in 46%. Only 16.7% of responding centers performed TARE which constituted 2% of procedures overall (65).

Systemic therapy

The European Agency for the Evaluation of Medicinal Products (EMA) approved the use of sorafenib for HCC in October 2007. This decision was made in light of the findings of the SHARP trial (66); a multi-center, randomized, placebo-controlled trial which allocated 602 patients with advanced HCC to sorafenib 400 mg BD or placebo. Investigators reported an overall survival benefit of nearly three months with sorafenib (10.7 vs. 7.9 months). Although a multi-center trial, the majority of patients were recruited from Europe, making the results applicable to the population in question here. Importantly, the underlying etiology of liver disease was also reflective of the European population, with Hepatitis C and alcohol being the most frequent causes of underlying liver disease (28% and 24% of all patients recruited respectively). Sorafenib has become established as the standard systemic treatment for patients with advanced HCC, as defined by the BCLC staging system (9). The European Society of Medical Oncology (ESMO) has published clinical practice guidelines which recommend the use of sorafenib in patients with advanced stage HCC and preserved liver function (i.e., Child-Pugh A or B) or intermediate stage patients who have progressed following loco-regional treatments (67). Sorafenib is also indicated in patients with early stage HCC who are ineligible for radical treatment because of poor performance status or co-morbidity (67).

In both the SHARP trial and subsequent Asia-Pacific trial (68), the vast majority of patients had well preserved liver synthetic function confined to Child-Pugh Class A (97% for both studies). GIDEON is a global, prospective, non-interventional study partially undertaken to provide more data from real life clinical use of sorafenib in HCC,

including data from Child-Pugh B patients (69). Additionally, it provides further information on the differences between patient populations and their management according to region. The first interim analysis looked at 511 patients across five different regions, namely Europe, Latin America, USA, Japan and Asia-Pacific. As expected, the etiology of underlying liver disease varied according to region, with HCV infection and alcohol being the commonest in Europe and HBV infection being the commonest in Asia-Pacific. There was also geographical variation in the number of patients who received locoregional treatments (LRT) prior to commencing sorafenib. In Europe only 45% of patients had previous LRT prior to sorafenib treatment as compared to 100% in Japan and 68% in Asia-Pacific (69). Differences were also observed in the underlying disease characteristics by region. In Europe, patients commencing sorafenib tended to have less advanced disease according to BCLC status, with 14%, 22% and 51% of patients having BCLC stage A, B and C disease respectively as compared to 1%, 11% and 74% in the Asia-Pacific population. Additionally, with the exception of Japan, Europe had the greatest proportion of Child-Pugh A patients at 70%, as compared to 60%, 44% and 41% for Asia-Pacific, Latin America and USA respectively.

Following the results of SHARP, Iavarone *et al.* conducted a prospective observational study of all HCC patients treated with sorafenib in six liver centers across Italy (70). Their primary objective was to assess safety, but they also gathered data related to survival and time to radiological progression. In a notable difference to the SHARP trial, they used the modified RECIST (mRECIST) criteria, which consider vascularized tumor dimensions (71). In their population of 296 patients, 75% had BCLC stage C disease and 88% were Child-Pugh Class A. Overall, 56% of patients had received previous LRT treatment, and 38% had not received any previous anti-HCC therapy prior to sorafenib. The incidence of adverse events (AEs) was 91%, with 45% of patients experiencing grade 3/4 AEs. The most common grade 3/4 AEs included fatigue (39%), hand-foot skin reactions (HFSR) (18%) and diarrhea (14%). This is in contrast to the registration trial (66) in which no grade 4 AEs were reported and the grade 3 AEs were most commonly diarrhea (8%) and HFSR (8%) and hypertension (2%). Overall survival data was consistent with previous trials at 10.5 months, and sub-group analysis suggested that survival was improved in BCLC-B patients as compared to BCLC-C (20.7 *vs.* 8.5 months). Time to radiological progression in this population was improved compared to the registration trial (9.2 *vs.* 5.5 months), which may reflect

the use of mRECIST criteria. Despite this, the radiological response rate was similar to the registration trial (8% *vs.* 2% respectively) and the majority of patients (73%) achieved stable disease only. Another notable difference is that 54% of patients required dose reduction due to AEs as compared to 26% in the registration trial. In fact, 26% of all patients received half dose sorafenib for >70% of the treatment period despite a broadly similar patient population in terms of performance status. This may be related to the increased numbers of Child-Pugh B patients, as the GIDEON study also commented on a higher rate of sorafenib discontinuation in Child-Pugh B patients as compared to Child-Pugh A (40% *vs.* 25%) (70). Indeed the results are consistent with a large retrospective audit of 400 patients treated with sorafenib across 13 centers in the UK (72). Again, although the majority of patients were Child-Pugh A (84%), a significant minority had Child-Pugh B disease (16%). Furthermore, in comparison to the SHARP trial, patients in this UK audit received a lower average daily dose of 585 mg and had a shorter time on treatment of 3.2 months.

Ozenne *et al.* have also conducted a retrospective study looking at a cohort of 50 patients with HCC treated with sorafenib at a single center in France (73). In keeping with previous studies, the majority of patients were Child-Pugh Class A (66%) and BCLC-C (76%). They reported grade 3/4 AEs in 18% of their patients, and 38% of patients required dose reduction. Together with the Italian study, this suggests that dose reductions are being used more frequently in clinical practice across Europe than suggested in the registration trial. Although the proportion of patients who discontinued treatment due to AEs was similar between Child Pugh A and B classes, median duration of treatment for Child-Pugh B patients was only 1.8 months. In keeping with previous trials, the majority of patients (67%) demonstrated stable disease with only a minority (11%) demonstrating objective radiological response to treatment. Median overall survival was 5.5 months with a trend towards increased survival in Child-Pugh A patients compared to Child-Pugh B (8.9 *vs.* 2 months). However, Child-Pugh status also correlated with performance status and stage of HCC and, after multivariate analysis, the only factor significantly related to survival was BCLC stage.

Despite the inclusion of some Child-Pugh B patients, the majority of published experience with sorafenib in Europe still pertains to those patients with relatively well preserved liver function. One center in Germany has reported a prospective study of 34 patients with advanced HCC who

were treated with sorafenib regardless of Child-Pugh score (74). Of the 34 patients treated, only four were Child-Pugh C with the remaining patients being split equally between Child-Pugh A and B. High rates of AEs and dose modification were reported (100% and 47% respectively), with the majority of AEs being at Grade 1/2. The toxicity profile is consistent with previous studies and is similar across Child-Pugh groups, with a trend towards an increase rate of diarrhea and skin reactions in Child-Pugh C patients. Worsening liver function was significantly more frequent in Child-Pugh B and C patients (73% and 75% respectively) and all Child-Pugh C patients experienced deterioration in their Child-Pugh score whilst on treatment, with three out of those four patients dying on therapy.

There is little published data pertaining to the use of chemotherapy in advanced HCC in Europe in clinical practice. Gish *et al.* performed the only randomized controlled trial using chemotherapy in a Western population (75). They randomized 445 patients to receive either the thymidylate synthase inhibitor nolatrexed or doxorubicin and found that survival was improved in those patients receiving doxorubicin (7.4 *vs.* 5.1 months). In parallel to the SHARP trial, Abou-Alfa *et al.* compared patients receiving doxorubicin alone to those receiving it in combination with sorafenib in 97 patients recruited across North and South America and Europe (76). Overall survival was improved in the combination group as compared to doxorubicin alone (13.7 *vs.* 6.5 months) and a further trial comparing sorafenib with sorafenib plus doxorubicin is ongoing.

Sorafenib was a major advance but the absolute impact on patient survival is limited and there remains an urgent need to improve outcomes for patients with advanced HCC. Since the approval of sorafenib progress has been disappointing and there have been a series of large phase three that have failed to demonstrate equivalence or superiority of an experimental arm. As with other cancers, the focus for the future will be to understand better, the drivers of oncogenesis in HCC and to develop strategies that target these drivers and prevent the emergence of resistance. Traditionally, diagnosis of HCC has not required histology and this must change in order to increase our molecular understanding of the disease. The relative rarity of HCC in Europe requires functional collaboration between centers within and between member states.

Conclusions

HCC is a relatively uncommon cancer in Europe yet the

prognosis remains dismal. Reductions in incidence seen in the Far East as a consequence of vaccination and screening have not been observed in Europe, perhaps due to the varied etiology. Improved selection has resulted in better outcomes for transplantation and resection but, for patients treated with palliative intent, the current interventions remain unsatisfactory. Relapse or progression following locoregional therapy is common and the benefit of systemic therapy limited. Major initiatives for the future include early detection so that more patients can be cured, and improved systemic therapy that can increase the cure rate following radical therapy and improve outcome for those with advanced disease.

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Footnote

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Current status of hepatocellular carcinoma in the United States

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Abstract: Hepatocellular carcinoma (HCC) represents a challenging malignancy of worldwide importance and is the third most common cause of cancer-related death globally. While most of the burden of HCC is borne in Southeast Asia, particularly China, and sub-Saharan Africa, there have been several interesting trends of HCC in the United States in the past decades. First, the latest epidemiology trend has shown that the incidence rates for HCC in the United States have been rising. While most cancer related mortality is decreasing in the United States, deaths from HCC are increasing and at a rate faster than deaths from any other types of cancer. Second, early diagnosis of HCC continues to be challenging and most patients would present with unresectable disease. Third, the management of HCC is evolving with many new treatment modalities applied in clinical practice. In addition, multidisciplinary team efforts with increasing role of oncologists have emerged in the management of HCC in most centers in the United States. In this review, the author will highlight the key trends and current status of HCC in the United States.

Keywords: Hepatocellular carcinoma (HCC); treatments; United States

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Hepatocellular carcinoma (HCC) represents a challenging malignancy of worldwide importance and is the third most common cause of cancer-related death globally (1). While most of the burden of HCC is borne in Southeast Asia, particularly China, and sub-Saharan Africa, there has been several interesting trends of HCC in the United States in the past decades. First, the latest epidemiology study has shown that the incidence rates for HCC in the United States have been rising (2,3). Second, early diagnosis of HCC continues to be challenging and most patients would present with unresectable or metastatic disease. Third, the management of HCC is evolving with many new treatment modalities applied in clinical practice. In this review, the author will highlight the key trends and current status of HCC in the United States.

Epidemiology

While the incidence of HCC in Asia is starting to plateau or decrease (4), it is increasing in the US (2,3). In 2013, HCC

and intrahepatic cholangiocarcinoma have risen to become the fifth cancer related mortality in men and ninth in women in the States (5) (*Table 1*). Based on the SEER data, age-adjusted HCC incidence rates tripled between 1975 and 2005 (6,7). The greatest proportional increase in cases of HCC has been seen among Hispanics and whites between 45 and 60 years of age. It is worth noting that while most cancer related mortality is decreasing in the States, deaths from HCC in the US are increasing and at a rate faster than deaths from any other types of cancer (8).

What contributes to the recent rising incidence of HCC in the United States? In contrast to the endemic regions in Southeast Asia and sub-Saharan Africa where hepatitis B (HBV) infection is responsible for the majority of HCC, chronic hepatitis C (HCV) infection is the major driver to account for the increased incidence of HCC in the States. It is estimated that approximately 4.1 million people in the United States are infected with HCV (9). In comparison to HBV, HCV causes more severe liver inflammation. Approximately 70-80% HCV-infected patients will develop

Table 1 Hepatocellular carcinoma (HCC) in the United States

Fifth cancer related mortality in men and ninth in women
Rising incidence in past three decades, likely contributed by:
Hepatitis C infection
Metabolic syndrome related to obesity, diabetes mellitus, and non-alcoholic fatty liver disease
Hepatitis B infection from immigrants from Asia and Africa
HCC related mortality is increasing
Most patients present with unresectable or metastatic disease

chronic HCV infection and 15-20% will eventually develop cirrhosis. Once cirrhosis develops, HCC will develop at a rate of 1-4% per year. The estimated risk of HCC is 15-20 times as high among HCV-infected patients compared with those who are not HCV-infected, and the risk is largely related to those with advanced hepatic fibrosis or cirrhosis. HCV infection occurred in large numbers of young adults in North America in the 1960s and 1970s, as a result of sharing contaminated needles by users of injection drugs and from blood transfusions. HCV infection can be found in up to 30% to 50% of patients with HCC in the United States. Judging from the epidemiology trend of HCV related HCC in Japan, it has been projected that cases of HCV-related HCC will continue to increase in the United States over the next two to three decades. Alcohol is another important risk factor for HCC and a cofactor in patients with HCV infection.

Worldwide, HBV infection is responsible for the majority of HCC. It is important to appreciate that HBV vaccine is available and primary prevention through HBV vaccination is a feasible strategy to prevent HCC development. The success of this approach was first demonstrated by the nationwide Taiwanese vaccination program against HBV, which showed decreased incidence of HCC in children and the extended benefit into early adulthood (10). In the States, HBV infection in Asian and African immigrants deserves attention. The number of immigrants from Asia and Africa may contribute to the HCC incidence in large cities in the States and these patients should receive HBV vaccination and anti-HBV treatment timely.

In the States, about 20-40% of HCC patients do not have underlying HBV/HCV infection or alcohol, suggesting the presence of other causes of HCC. Some of these patients were more likely to have metabolic syndrome related to obesity, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) (11). Given the high prevalence of the metabolic syndrome in the United States, even small

increases in HCC risk related to obesity or diabetes could translate into a large number of cases of HCC, which will likely have significant impact on the trend of HCC incidence in the States in the coming decades (11). In population based cohort studies in the States, HCC was 1.5-2.0 times as likely to develop in obese persons as in those who were not obese (12). Case control and cohort studies have shown that HCC is twice as likely to develop in patients with type 2 diabetes as compared with those who do not have diabetes (13,14). Despite the clinical suspicion, there is a paucity of data supporting the direct link between progression of NAFLD and HCC development. Therefore, this potential correlation between metabolic syndrome/NAFLD and HCC warrants further investigation.

Diagnosis

Diagnosis of HCC can be rendered relatively easily in the right clinical setting for patients with well-defined risk factors, the presence of cirrhosis, and characteristic imaging findings on CT scan or liver MRI. These coupled with the use of serum alpha-fetoprotein (AFP), judicious use of biopsy, and careful interpretation of pathology will lead to the diagnosis of HCC in most cases. In patients with cirrhosis and a focal hepatic lesion larger than 2 cm in diameter, the diagnosis can be established with confidence on the basis of the presence of typical imaging features showing areas of early arterial enhancement and delayed washout in the venous or delayed phase of four-phase multidetector CT (the four phases are unenhanced, arterial, venous, and delayed) or in dynamic contrast-enhanced MRI. For lesions 1-2 cm in diameter, concordant findings from CT and MRI are recommended in order to diagnose HCC with confidence. In the United States, the guidelines for making HCC diagnosis with non-invasive methods are the same as in Europe or Asia (15). However, in the United States, tissue diagnosis with liver biopsy is

Table 2 Trends of HCC management in the United States

Surgical resection, liver transplant and ablative therapy represent curative treatment options
Novel liver directed regional therapies being developed and increasingly used:
Drug eluting beads TACE
Radioembolization
Radiation (stereotactic body radiotherapy, proton etc.)
Sorafenib remains the only approved agent in advanced HCC
Active clinical trials testing molecularly targeted agents
Multidisciplinary care of HCC has become the main theme
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

performed more often than other regions in the world. Obtaining tissue diagnosis has several advantages. First, despite the strong clinical suspicion, the distinction between HCC and intrahepatic cholangiocarcinoma or the mixed HCC-cholangiocarcinoma is not always straightforward, as a result, up to 10-20% patients could be misdiagnosed. Second, other primary liver tumors or metastatic disease, or benign lesions could be the underlying diagnosis. Third, when patients present with metastatic disease, the radiologic features may not be very characteristic. Finally, tissue diagnosis will provide the critical material for molecular testing, which will potentially provide useful information in the era of personalized medicine. AFP is the most commonly used serum biomarker in the United States. Despite the wide use of des-gamma carboxy prothrombin (DCP) and lectin-bound AFP (AFP-L3) in other regions of the world (16), they are not routinely used in clinical practice in most centers in the United States.

Despite the availability of well established diagnostic tests, it remains challenging to diagnose HCC at early stage in the United States. As a result, most patients will present with unresectable or metastatic disease. This is particularly true for certain racial/ethnic groups (17) and in patients with NAFLD or no clear underlying risk factors (18). For reasons outlined above, tissue diagnosis should be obtained more often both for diagnostic purpose and for research related issues.

Staging

The heterogeneity of HCC, contributed by various factors including tumor burden, the presence and severity of underlying cirrhosis and performance status, contributes to the complexity of patient care and evaluation (19). Staging systems are useful for stratification of patients based on

their prognosis prior to treatment, allocating specific treatment based on the stage, and allowing comparison of clinical outcomes from different clinical studies. Although many different staging systems have been developed, which include Barcelona Clinic Liver Cancer (BCLC) (20), Cancer of the Liver Italian Program (CLIP) (21), tumor-node-metastasis (TNM) (22), Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH) (23), Chinese University Prognostic Index (CUPI) (24), and Japanese Integrated Staging (JIS) (25), there is currently no universally accepted staging system. The BCLC staging classification is increasingly used in the United States and it has tried to capture the tumor features, severity of cirrhosis, performance status, and a recommended treatment algorithm for each stage. However, due to the geographic variation of different risk factors, one staging system may perform better than others in certain regions. In addition, depending on the stage of the disease, certain staging system may be more prognostic, as suggested by a study comparing the various staging systems for patients with advanced disease (26). In this study, the BCLC system was found to be less informative than the GRETCH and CLIP classifications (26). In the United States, TNM, BCLC and CLIP represent some of the more commonly used staging systems. Currently, there are a lot of research and efforts trying to incorporate molecular classification into the existing staging systems (27).

Management

There are several interesting trends for the management of HCC in the United States in the past decade (*Table 2*). First, there are continued efforts refining the indications for surgical resection and liver transplant and to develop new surgical techniques. Second, novel local and regional liver directed therapies are being developed and increasingly

applied in clinical practice. Third, following the successful approval of sorafenib, there have been renewed and ongoing interests and active efforts developing other molecularly targeted agents in this disease. Fourth, multidisciplinary management of HCC has become the theme for patient care in most hospitals in the United States.

Curative treatments: surgery, transplantation, ablative therapy

Surgical resection remains the curative treatment choice for patients with resectable HCC and adequately preserved liver function. Major resections can only be performed with low rates of life-threatening complications in non-cirrhotic patients. By contrast in cirrhotic patients this procedure requires well-defined selection criteria (solitary tumors and Child-Pugh's A patients without portal hypertension) and a skilled surgical team. In these cases, perioperative mortality should be below 3%, blood transfusion requirements of less than 10%, and 5-year survival rates of at least 50-60%. In the United States, liver resection tends to be performed by experienced surgeons specialized in hepatobiliary surgeries in major medical centers. The experience of laparoscopic resection of HCC has been expanding. In general, the laparoscopic resection is only applicable to selected patients and it may have better postoperative quality of life than those with open resection.

Tumor recurrence complicates 50-80% of cases, and there is no established standard adjuvant therapy. More than 15 randomized controlled trials (RCTs) assessing loco-regional and systemic therapies have been published including chemoembolization, internal radiation, chemotherapy or adoptive immunotherapy, retinoids or interferon. Despite the early evidence of efficacy signal such as internal radiation with ¹³¹I-labelled lipiodol, retinoids or adoptive immunotherapy, these results were not confirmed in large randomized phase III trials and the strength of evidence was not convincing enough to become the standard of care. As a result, patients will be observed for surveillance after surgical resection without additional adjuvant therapy. In the United States, many centers and investigators have participated in the phase III randomized trial evaluating sorafenib as adjuvant therapy in the prevention of recurrence of HCC (STORM). This study has completed the enrollment of the targeted more than 1,000 patients and the results are eagerly awaited.

Liver transplantation is the first treatment choice for patients with single HCC ≤ 5 cm or up to three nodules each

≤ 3 cm or those with advanced liver dysfunction. When these criteria are met, transplant would achieve 70% survival at 5-year with a recurrence rate below 15% (28). Due to the scarcity of donors up to 10-20% of the candidates would dropout from the waiting list before receiving the procedure. Bridging therapy using either radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) are commonly used in the States, however, none of the treatments applied whilst on the waiting list have been tested in the setting of randomized investigations.

Although the Milan criteria is the generally accepted standard criteria in the States, attempts to assess the transplant outcomes in patients who exceeded the Milan criteria has been explored. Other criteria including UCSF criteria have been used in selective centers in the States (29). In the States, cadaver transplant is more common than living donor transplant. Genomic translational studies enabling the identification of the best candidates based on molecular profiles are currently conducted in the States, and might better define the ideal subpopulations.

Several local ablative treatment options exist. Generally, RFA and percutaneous ethanol injection (PEI) are more commonly used to treat small HCCs that are either solitary or a few lesions. Complete responses are achieved in more than 80% of tumors smaller than 3 cm in diameter, but in 50% of tumors of 3-5 cm in size. In the United States, there is a general agreement in that RFA provides better local control of the disease as compared with PEI as shown previously (30), and thus is considered the treatment of choice. Other ablative treatment modalities including microwave ablation and irreversible electroporation (IRE) are also being tested in many centers in the States.

Liver directed regional treatment

Patients at intermediate stages of this disease present a natural outcome of 16 months of median survival (31). Chemoembolization is generally used in patients with multifocal or unresectable HCC without portal vein invasion and can improve median survival to up to 20 months in selected patients based on two randomized studies and a systematic review of six RCT (31-33). In the United States, TACE is also often used in patients with multifocal HCC and segmental portal vein thrombosis despite the lack of level 1 evidence. The added value of doxorubicin in TACE remains controversial as suggested by a randomized single blind controlled trial comparing beads versus doxorubicin-eluting beads for HCC (34).

It is encouraging that many other local treatment modalities have been explored in HCC including intra-arterial injection of Yttrium-90 microspheres, drug-eluting beads and external beam radiation in the United States. Many centers have expanded on the initial clinical experience of radioembolization with Yttrium 90 microspheres (35). Encouraged by the initial experience in Asia with liver radiation, many centers are exploring the use of radiation (SBRT, protons etc.) to the liver in the States (36). How these different local treatment approaches would compare with TACE and whether each technique will find its unique application in selected patient populations remain to be determined with randomized studies.

Perhaps the most active area of clinical research in local regional therapy in HCC in the States is the ongoing efforts combining sorafenib or other targeted agents with TACE, radioembolization or radiation. In parallel with the efforts worldwide, many investigators in the States have conducted the initial studies testing the tolerability, safety and early evidence of efficacy of sorafenib with TACE (37). Currently, ECOG 1208, a randomized phase III study assessing the combination of sorafenib or placebo with DEB-TACE in HCC, is ongoing in the United States.

Systemic treatment

In a landmark international, phase III, placebo-controlled Sorafenib HCC Assessment Randomized Protocol (SHARP) trial, sorafenib demonstrated improved OS and time to tumor progression (TTP) compared with placebo (38). Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio for the sorafenib group, 0.69; $P < 0.001$). Based on these results, sorafenib is the only approved agent in advanced HCC in the States. As sorafenib is gaining more clinical experience, several important pictures have emerged. First, the clinical benefits are still modest and transient. This highlights the importance of understanding the mechanism of action of sorafenib and identification of predictive markers. Second, sorafenib related toxicities including hand and foot skin reaction, diarrhea, and fatigue need to be carefully monitored and timely managed. Third, since the agent was tested only in patients with underlying Child A cirrhosis in the registration trials, the benefits of sorafenib in patients with worsening hepatic dysfunction remains uncertain.

In the United States, there are active clinical trial efforts in various settings. For patients for newly diagnosed advanced HCC, current clinical studies are assessing the

role of sorafenib in combination with other targeted agents or chemotherapy in advanced HCC. CALGB80802, a phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced HCC, is ongoing in an attempt to assess the added value of doxorubicin when combined with sorafenib (39). Many molecularly targeted agents are being tested in patients with advanced HCC who failed or could not tolerate sorafenib. There are also significant efforts testing novel agents in phase I trials in HCC in the States. Despite the failure of several phase III trials in the past few years, these vigorous clinical trial efforts will hopefully lead to additional approved agents in this challenging disease.

In conclusion, HCC has emerged as an important malignancy in the United States with rising incidence and high mortality. The development in all forefronts including prevention, surveillance, early diagnosis, and more effective treatment for patients with different stages of disease holds promise to further improve the outcomes for patients with HCC. Given the complexity of HCC, multidisciplinary team efforts are critical to optimize the care of HCC and have become the main theme of care in the United States. While more molecularly targeted agents are under active investigation in HCC (40), it is important to identify more relevant therapeutic targets based on our further understanding of hepatocarcinogenesis and molecular classification, to optimize the trial design and patient resources, and to develop and validate surrogate and predictive molecular markers.

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Footnote

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Profiling HBV integrations in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide. In this context, chronic viral hepatitis B (HBV) infection represents the most common etiology of HCC. Notably, although other common causes of HCC including chronic viral hepatitis C and chronic alcoholic liver disease are mediated by progression through cirrhosis, the pathogenesis of HCC in HBV infection does not entirely depend on this mechanism. A major proposed pathway by which HCC may arise from chronic HBV infection is the integration of HBV DNA into the host genome, resulting in oncogene activation, tumor-suppressor gene inactivation, or other predisposition to chromosomal instability (1).

Since the 1980's, many studies have detected evidence of HBV DNA integrated not only into normal hepatocytes, but specifically into HCC cells, supporting the hypothesized role of HBV DNA integration in hepatocarcinogenesis. However, early studies observed viral DNA integration in a non-recurrent pattern, meaning that the integration was not found to occur at predictable and reproducible sites in the host genome. It is important to note that these initial studies were limited by technological constraints to the analysis of only certain portions of the host genome, and also constrained by small sample size.

Over the past several years, the new technology of next-generation sequencing (NGS) has resulted in an explosion of studies in which somatic aberrations in cancer cells have been explored with much greater efficiency and accuracy (2). Specifically, NGS has been increasingly used as a powerful means to help pinpoint the genomic events implicated in hepatocarcinogenesis, and to design preventive and therapeutic interventions tailored to target these events (3).

In a recent study, Sung and colleagues used NGS to

construct a genome-wide HBV DNA integration map at single-base resolution by analyzing tumor and paired non-tumor liver tissues from 81 HBV-positive and 7 HBV-negative Chinese HCC patients (4). The authors identified 399 integration breakpoints in 75 HBV-positive and 1 HBV-negative patients. They found that viral integration occurred more frequently in tumors (344 events) than in paired non-tumor tissues (55 events). Of the 344 integrations into tumor tissue, 179 were found in known coding genes and were over-represented in the exons and promoter regions of these genes. Furthermore, they identified specific sites of recurrent integration, or "hotspots", of HBV DNA at breakpoints in the host genome within particular genes including *TERT*, *MLL4*, *CCNE1*, *SENP5*, and *ROCK1*. The findings are in line with previous studies using PCR- or hybridization-based techniques showing that HBV integrations commonly reside in *TERT* on chromosome 5, and *MLL4* on chromosome 19 (5-9).

Sung *et al.* went on to further characterize the consequences of HBV DNA integrations at these breakpoints, and found that mRNA expression levels of *TERT*, *MLL4* and *CCNE1* genes were significantly higher in tumor tissues carrying recurrent HBV DNA integrations at these breakpoints. In addition, the authors noted integrations at these sites were associated with dramatically increased copy number variations of the host genes, substantiating the link between HBV DNA integration and chromosomal instability. Finally, the authors reported an association between the total number of all detected integration sites and important clinical characteristics of the patient population including AFP levels, age at HCC diagnosis, and overall survival.

Collectively, these findings confirmed *TERT* and *MLL4*

genes as HBV integration hotspots in HCC patients. Moreover, they suggested that recurrent HBV DNA integration into the host genome is an important driving event in HBV-related hepatocarcinogenesis, as well as a potential target for individualized therapies.

Another key finding of the study by Sung *et al.* is that approximately 40% of the integration breakpoints on the HBV genome occurred within a 1,800-bp range, an insertion hotspot region harboring several essential viral genes. This is consistent with the results of another recent study by Jiang and colleagues who applied high-depth whole genome NGS to sequence tumor and adjacent normal liver tissues from 3 HBV-positive HCC patients and 1 HBV-negative HCC patient (10). Interestingly, although Jiang *et al.* also confirmed the link between HBV integration and elevated expression of host genes, there was only one shared recurrent integration site (*MLL4*) between that study and the one by Sung *et al.* This discrepancy may be partially explained by sample size limitations and individual variations. It may also be accounted for by potential intra-tumor heterogeneity, a major challenge in the design and analysis of current NGS studies, despite the commonly recognized theory of clonal expansion in cancer development (11,12). Neither study reported a detailed procedure of HCC sampling (4,10), and therefore it is possible that differences in sampling could have introduced bias into the findings.

Another difference between the two studies relates to sequencing depth. Sung *et al.* identified a total of 344 integration sites from 76 HCC tumors through a >30× depth of coverage, whereas Jiang *et al.* observed 148 integration sites from 3 HCC tumors by a >80× deeper sequencing of samples containing >80% tumor content. Jiang *et al.* further compared the results from the >80× depth to an even higher coverage of >240×, and found the number of detected integration sites were proportional to sequencing depth. Assuming the actual average numbers of integrations per sample were comparable between the tumors in these two studies, the fact that Jiang *et al.* identified a much higher number of integrations per sample might be due to the different stringencies in detection criteria used in the two studies, as well as differences in potential sequencing errors, analysis biases and artifacts. Furthermore, it could have reflected the presence of tumor heterogeneity that resulted from the inclusion of normal tissues in the tumor samples and thus reduced the sequencing sensitivity in the study of Sung *et al.* Further in-depth assessments of allelic bias and number of integration

sites that were shared across samples in each study may provide additional clues to these observations.

In addition to constructing HBV integration maps, NGS has been widely applied to survey HCC genomes to identify other aberrations such as mutations, small insertions and deletions, copy number variations, and structural variations. As a result, many frequently mutated genes have been discovered and linked to HCC development, including *TP53*, *AXIN1*, *ARID1A*, *ARID2*, *CTNNB1*, as well as others (13-17). However, a causative link between HBV integration sites and specific gene mutations remains to be demonstrated. Moreover, although Sung *et al.* reported a significant association between the overall numbers of integration sites and patient survival, it is unknown whether this association was particularly prominent in patients with recurrent integrations in hotspot genes. Sung *et al.* (4) reported sequencing data on the largest HBV-positive HCC patient population to date, which may offer pivotal insights into the mechanism of malignant transformation from HBV infection to HCC. A thorough understanding of HBV DNA integration into the host genome, and the resulting aberrant gene expression and cancer development will likely necessitate even higher-depth sequencing coverage in larger patient populations, in order to tackle the heterogeneity issue and yield statistically robust findings. Due to the rapid decrease in NGS cost and increase in computational capacity, it will not be long before future studies like Sung's and Jiang's pave new roads for researchers to establish a comprehensive understanding of HCC genomes, eventually facilitating the development of novel targeted and personalized therapeutic options to prevent and treat this devastating disease.

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Footnote

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Cellular and molecular mechanisms of hepatic fibrogenesis leading to liver cancer

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Introduction

Currently, hepatic fibrosis is considered a model of the wound-healing response to chronic liver injury (1). The excessive extracellular matrix (ECM) deposition that distorts the hepatic architecture by forming fibrotic scars, and the subsequent development of nodules of regenerating hepatocytes defines liver cirrhosis (2-5). The clinical importance of liver cirrhosis is related to the associated hepatocellular dysfunction and increased intrahepatic resistance to blood flow, which result in hepatic insufficiency and portal hypertension, respectively, and to the occurrence of hepatocellular carcinoma (6). The incidence of hepatocellular carcinoma (HCC) is rising in North America, Europe, and Eastern countries such as China and Japan (7). This increase is largely due to the emergence of hepatitis C virus (HCV), the continued problem of hepatitis B virus (HBV) infection control, and the liver pathologies associated with obesity and chronic alcohol abuse. The increasing levels of obesity in these countries is a particularly significant epidemiological factor that will ensure further worldwide rises in HCC incidence over the next decade (8). There is therefore an urgent need to understand how HCC develops in the diseased liver. In this respect, it is often overlooked that 90% of HCC cases have a natural history of unresolved inflammation and severe fibrosis (or cirrhosis). Approaches to HCC prevention should therefore focus on the molecular regulators of a disease process that we could define as the inflammation-fibrosis-cancer (IFC) axis.

Mechanisms involved in the inflammation-fibrosis-cancer axis

The final event of chronic liver injury, independently from the aetiological agent, is hepatic fibrosis and this process may consequently and directly lead to cancer development (*Figure 1*). Thus, the current review will focus the attention on the mechanisms contributing to fibrosis and cancer.

Role of oxidative stress

At the molecular level, a series of studies have shown that oxidative stress is commonly induced in all forms of chronic liver injury and plays a crucial role in hepatic fibrogenesis (9-12) and cancer development (13,14). Exogenous reactive oxygen species (ROS) released by damaged parenchymal cells directly contribute to cell degeneration process and would also activate redox-sensitive intracellular pathways in HSCs, inducing their activation and increasing collagen synthesis (11,15). Furthermore, HSCs are also an important source of ROS in liver fibrosis (15-17). Cytochrome P450 2E1 is the main source of ROS in hepatocytes, while phagocytic and non-phagocytic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is the key source, respectively, in Kupffer cells and HSCs (12,18,19). The phagocytic form of NADPH oxidase expressed in Kupffer cells has several important functions: besides its defensive effect against bacterial products reaching the liver through the portal system, NADPH oxidase in Kupffer cells is also activated by several stimuli (i.e. alcohol metabolites and tumor necrosis factor- α) to produce ROS. Kupffer cells-

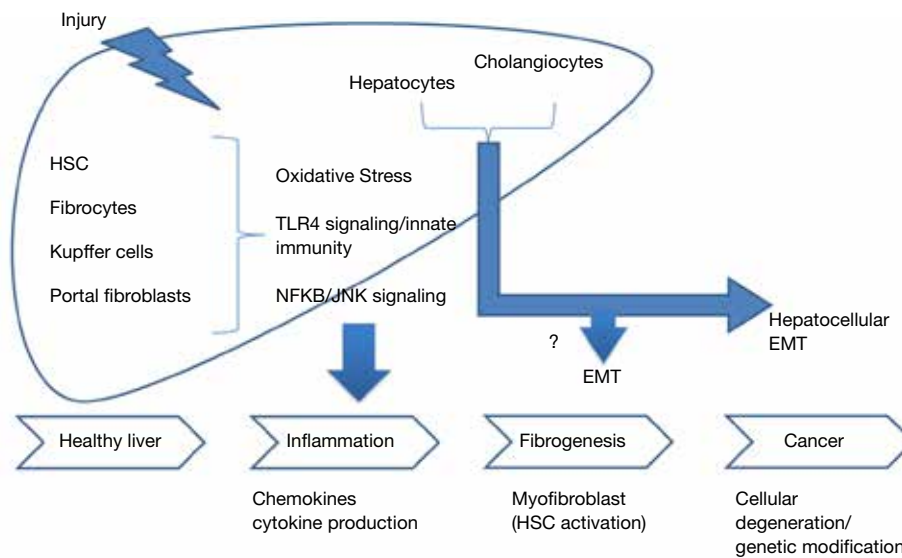


Figure 1 Fibrogenetic/hepatocarcinogenic mechanisms in the liver.

derived ROS consequently drive proinflammatory effects and sensitize hepatocytes to undergo apoptosis, being involved in fibrogenesis and carcinogenesis. Conversely, recent data indicate that HSCs express the non-phagocytic form of NADPH oxidase and demonstrate that ROS participate in the activation and fibrogenic actions of HSCs *in vitro* (12,18,19). Thus in summary, several sources of ROS in parenchymal and non-parenchymal cells actively contribute to the development and activation of pathways involved either in fibrogenic or in cancer processes.

Role of cytokines

Classical studies using experimental models of chronic liver injury in rats and mice have revealed cytokines and growth factors that are critical in hepatic fibrogenesis (20-22) as well as in cancer development (1,13). As occurs in most tissues, transforming growth factor- β 1 (TGF- β 1) is the major fibrogenic cytokine in the liver (23) and it has been clearly demonstrated to play an active role in the process of myofibroblast activation (1). In addition to TGF- β 1, other molecules exert a pro-fibrogenic activity involving different mechanisms: vasoconstrictor substances [e.g., norepinephrine (NE), angiotensin II] (24), platelet-derived growth factor (PDGF) (the most potent mitogen) (25) and adipocytokines such as leptin involved in hepatic inflammation (26,27). As in hepatic fibrosis, TGF- β levels in HCC increase in line with collagen deposition and the

reduction in proteolytic degradation (23). For example, connective tissue growth factor (CTGF) promotes tumor growth, angiogenesis, migration and invasion (28). Human HCC cell lines produce high levels of CTGF to form highly stromagenic tumors. If CTGF is knocked down in such cells, tumors show little stroma (29). Blocking the TGF- β signaling pathway with the TGF- β inhibitor LY2109761 inhibits CTGF production and tumor growth. Based on these observations, cancer associated fibroblasts (CAF) are considered a possible source of CTGF in response to paracrine signals from cancer cells, such as TGF- β (30). It appears that CAF can originate from endothelial cells and can be a source of the endothelial-to-mesenchymal transformation (30). Also, in pancreatic cancer they can originate from stellate cells and can contribute to resistance to chemotherapy or radiation (31). Thus, it is possible that HSC may be the source for the CAF cells in HCC.

Role of NF κ B

NF- κ B transcription factors are key regulators of innate and adaptive immune responses, inflammation, and cell survival (32,33). Many proinflammatory stimuli activate NF- κ B, mainly via I κ B kinase-(IKK) dependent phosphorylation and degradation of the κ B inhibitor (I κ B) proteins. IKK consists of two catalytic subunits, IKK α and IKK β , and a regulatory component, NEMO/IKK γ . IKK activation occurs primarily through IKK β (34), whose absence

increases susceptibility to tumor necrosis factor- α -(TNF- α) induced apoptosis (35). Tumor initiation means cellular immortality, which happens through DNA mutation, but the relationship with NF- κ B activation has not been considered in detail for this process. However, the first clue linking NF- κ B to cancer was recognizing that c-rel, which is a v-rel oncogene cellular homologue, encodes an NF- κ B subunit and that all of these proteins share the Rel homology DNA-binding domain (36). Not surprisingly, overexpression of normal Rel proteins promotes oncogenic transformation. Participation of NF- κ B activation in the carcinogenic promotion and progression stages has become clear in recent years. The promotion of carcinogenesis is mainly related to the involvement of NF κ B in the regulation of different processes such as: proliferation, apoptosis, angiogenesis, invasion, and metastasis (36,37). TNF α , which is a strong NF- κ B-activating factor, is produced by macrophages and plays a central role in inflammation but has also been suggested as an accelerator factor of cell proliferation (13,37). Anti-apoptosis is also important for maintaining cancer cells: a large number of antiapoptotic factors, such as cIAPs, c-FLIP, and BclX, are controlled by NF- κ B activation (38). Finally, invasion and metastasis are pivotal processes for prognosis: matrix metalloproteinases (MMPs) are produced by inflammatory cells and on the other hand tumor cells are key players in the degradation of the extracellular matrix and basement membranes; thus, they are important in tumor invasion.

Role of JNK

The c-Jun NH₂-terminal kinase (JNK) belongs to a family of mitogen-activated kinases (MAPKs), together with extracellular regulated kinases (ERKs) and p38. The JNK subgroup of MAPKs is encoded by three loci; Jnk1 and Jnk2 are ubiquitously expressed, and Jnk3 is expressed primarily in heart, testis, and brain (39). JNKs are activated by stress signals and proinflammatory stimuli, and their activity increases following phosphorylation by the MAPK kinases, MKK4, and MKK7 (40). In the liver, JNK plays a pivotal role in the development of metabolic syndrome including NAFLD (20). Hepatic steatosis, inflammation, and fibrosis have been examined in mice fed a choline-deficient L-amino-acid-defined diet. The results showed less hepatic inflammation and less liver fibrosis despite a similar level of hepatic steatosis in JNK1-deficient mice compared with wild type, suggesting that JNK1 may be associated with the induction of diet-induced steatohepatitis and

liver fibrosis (41). In addition to these data, JNK function is critical in the carcinogenic promotion and progression stages, as JNK phosphorylates a variety of genes associated with carcinogenesis. Growth factors activate receptor tyrosine kinases, and phosphorylated receptors transmit the signals through JNKs (42). There is also participation in the transcriptional regulation of growth factors such as EGF through JNK activation (24). Numerous studies have considered the proliferative effect following JNK activation. For example, in a liver regeneration mouse model, the number of Ki67-positive proliferating hepatocytes in Jnk1-/- mice was reduced by 80% compared with that in controls at 48 hours after a partial hepatectomy (43). The expression of several angiogenic factors is also regulated by JNK: Vascular endothelial growth factor (VEGF) promotes proliferation and migration of endothelium cells. VEGF expression is also controlled by JNK activation (44,45).

Role of TLRs

Innate immunity represents the first line of protection against microbial pathogens and is mediated by macrophages and dendritic cells. Although it was initially suggested to be a nonspecific response, innate immunity discriminates a variety of pathogens through the function of pattern-recognition receptors (PRRs) such as TLRs. These receptors recognize microbial components known as pathogen-associated molecular patterns (41,46). Thirteen mammalian TLRs have been described; 10 are expressed in humans, and each is responsible for recognizing distinct bacteria, virus, and fungi microbial structures: the two most largely studied are TLR2 and TLR4, the PRRs for gram-negative and gram-positive bacterial products, respectively. TLR4 is also the major receptor recognizing endogenous ligands released from damaged or dying cells (41,42). The liver may be exposed to bacteria from the intestine via the portal vein, leading to an uncontrolled innate immune system that may result in inflammatory liver disorders (47). Many factors are capable of activating TLRs in the liver. Among them, HBV, HCV, alcoholic liver disease, and NASH are important etiologies for HCC (48). The TLR ligands TLR4 and 9 inhibit viral replication in HBV-transgenic mice (49). In the absence of HBsAg, HBV replication is associated with upregulation of the TLR2 pathway, leading to increased TNF α production, demonstrating a potentially important interaction between HBV and the innate immune response (42,50). HCV can activate innate immune systems to produce inflammation.

The HCV core and NS3 proteins activate TLR2 on monocytes to induce cytokines in a NF- κ B- and JNK-dependent manner (51). The NS3 protein interacts directly with TBK1, resulting in decreased TBK1-IRF3 interaction and inhibition of IRF3 and IFN transcription. The NS3 protein also impedes both IRF3 and NF- κ B activation by reducing functional TRIF abundance (52). Many other *in vitro* studies have been reported, but the *in vivo* condition is still unclear. Excessive alcohol intake is associated with increased intestinal permeability and elevated endotoxin levels (50). LPS activates TLR4 on Kupffer cells and increases proinflammatory cytokine production. Antibiotic treatment reduces the sensitivity of alcoholic liver disease (53). Intestinal bacteria seem to be important in NASH pathogenesis. In NASH, ob/ob mice exhibit increased hepatic sensitivity to LPS and developed steatohepatitis (54). In a methionine/choline-deficient NASH model, TLR4-deficient, but not TLR2-deficient mice, exhibited less intrahepatic lipid accumulation (53). All of the diseases described above are associated with the development of HCC. Therefore, it seems clear that TLRs are involved in the development of HCC. Mice deficient in TLR4 and MyD88, but not TLR2, have a marked decrease in the incidence, size, and number of chemically induced (DEN) liver cancer tumors, indicating a strong contribution of TLR signaling to hepatocarcinogenesis (55). It is assumed that dying hepatocytes following DEN may activate myeloid cells such as Kupffer cells via TLRs and induce proinflammatory cytokines and hepatomitogens, which enhance the development of HCC.

Role of EMT

Epithelial to Mesenchymal Transition (EMT) may also occur in the liver. Fetal liver exhibits characteristics of EMT in that some fibroblast-like stromal cells co-express both epithelial [a-fetoprotein(AFP), albumin(Alb), cytokeratins CK18 and CK7] and mesenchymal markers (a-SMA, osteopontin, and collagen I) (56,57). In adult liver, EMT does not occur without stress or injury (56). Transformation of biliary epithelium into fibroblasts is best documented in metastatic hepatocellular carcinoma, while is more controversial in the field of liver fibrosis. Evidence of EMT in liver fibrosis was reported in a patient with primary biliary cirrhosis (PBC), a condition characterized by loss of biliary epithelial cells and progressive fibrosis (58). Analysis of liver biopsies from this patient revealed that a number of

biliary epithelial cells expressed markers of EMT (e.g., an early fibroblast marker FSP1, vimentin, nuclear Smad2/3 and a-SMA), suggesting that biliary epithelial cells may undergo EMT and potentially contribute to the fibroblast population (58). In mice, EMT was observed in response to bile duct ligation (BDL)-induced injury (59). BDL causes chronic obstruction and concomitant proliferation of the bile duct, outgrowth of periductal myofibroblasts and fibrosis. Expression of EMT markers (collagen type I, a-SMA, and cytokeratin 19) by periductal myofibroblasts supported a notion that biliary epithelial cells may undergo EMT (59).

On the other hand, scientifically relevant data demonstrate the absence of EMT in liver fibrosis: the report by the Wells laboratory provides the strongest evidence against EMT in the liver as a source of myofibroblasts (60). The study uses lineage tracing generated by crossing the alpha-fetoprotein (AFP)-cre mouse with the ROSA26YFP stop mouse to trace the fate of any cell ever expressing AFP. As expected, all the cholangiocytes and all the hepatocytes were genetically labeled, because they are derived from AFP-expressing precursor cells. Furthermore, AFP progenitor cells were also irreversibly genetically marked. The critical result is that after inducing liver fibrosis by a variety of methods, none of the resulting myofibroblasts originated from the genetically marked epithelial (AFP) cells. This important article confirms the results obtained in two previous studies demonstrating the contribution of epithelial cells to myofibroblasts in liver fibrosis (61,62).

While EMT in hepatic fibrosis play a controversial role, the importance of this process in the development of HCC is relevant and is known as hepatocellular EMT. Hepatocellular EMT has been recognized not only in experimental animal model but also in humans and it is mainly defined as the expression of epithelial markers in cancer cells. In fact, while hepatocytes of well-differentiated human HCC samples and adjacent non-cancerous liver parenchyma show E-cadherin at the plasma membranes, cytoplasmic localization or frequent loss of E-cadherin is displayed in poorly differentiated HCC. These data suggest a disruption of E-cadherin/ β -catenin complexes at cell boundaries that is characteristic for hepatocellular EMT and comparable to observation of experimental HCC in mouse (63). The reduced expression of E-cadherin is accompanied by (partial) nuclear translocation of β -catenin, and significantly correlates with intrahepatic metastasis and poor survival of patients.

Experimental models of liver fibrosis/cancer and future directions

Although the number of studies on the field of liver fibrosis and HCC degeneration, there is an important need of a model that could be used in basic research, able to resemble the human characteristics of HCC development starting from a condition of liver disease, as it happens in humans. The models existing in literature are not completely accurate and do not entirely recreate the human conditions: the limitations are mainly related to the lack of a tool that could summarize all the features in a single experimental model.

Concerning experimental models of HCC: genetic models, conditioned knock-out or transgenic models are mainly used to study the involvement of specific protein in the carcinogenetic process (64,65). On the other hand, the HCC models induced by chemotoxic agents (such as DEN model) allow a broader involvement of different pathways, providing a technique to study the interaction of different effects in the specific organ. However, chemotoxic-induced HCC models do not completely resemble the human disease.

The DEN is the most important and most used agent in literature. Such a compound allows to obtain HCC development in a time and dose dependent manner, being also easy to reproduce. The DEN model has been largely used to study the pathophysiology of the pure HCC tumor model (66,67). However, in this model the sequence of events leading to steatohepatitis, fibrosis, cirrhosis and tumor, is completely skipped. Based on this, recent manuscripts evaluated other models able to better recreate the conditions leading to HCC development in cirrhotic patients (68). In the current view, the diet model could be a good option, allowing researchers to study not only the mechanisms involved in tumor progression, but also the early events involved in tumor formation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Alcoholic liver disease - Hepatocellular carcinoma transformation

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Introduction

In the DDC feeding mouse model where liver cells proliferate, Mallory-Denk bodies (MDBs) form and later, after DDC withdrawal, hepatocellular carcinomas (HCCs) develop (1). Similarly, patients who abuse alcohol develop alcoholic liver disease (ALD), MDBs form (2) and later, after alcohol abstinence, the patients develop HCCs (2). Also MDBs form in many of the HCCs, both in the mouse model and in ALD. Because of this, it has been suggested that MDBs are a preneoplastic change formed in balloon hepatocytes which transform into cancer cells (3-6). But there may be other links to the preneoplastic process in ALD-induced HCCs such as the role that macrophages play in the TLR4 pathway response to LPS (4) or the transformation of stem cells seen in both cirrhosis and the associated HCC in ALD (7). In this review the role played by the following is discussed: (I) cell cycle arrest, (II) TLR signaling macrophages and stem cell transformation to form cancer stem cells, (III) ballooned hepatocytes that form Mallory-Denk bodies as progenitor pre-cancer cells in the pathogenesis of the ALD/HCC transformation.

Cell arrest

Alcohol-induced cell cycle arrest plays a role in the ALD-HCC transformation. It also plays a major role in alcoholic hepatitis (AH) as determined in liver biopsies from AH patients. Our hypothesis is based on the observation that the expression of both PCNA and cyclin D1 is increased in almost all of the hepatocytic nuclei in liver biopsies taken from AH patients. The stain for Ki-67 was positive

in only a very few hepatocytes in the same biopsies. Both p21 and p27 positive nuclei were very numerous in these liver biopsies of patients with AH or NASH (7) (*Figure 1*). This indicates that p21 and p27 inhibition of the cell cycle at both the G1/S growth phase and the G2 phase (8,9) was the reason. Because of the cell cycle arrest, regeneration of liver cells is impeded and apoptosis, genome instability and oncogenic effects result (9). P53 dependent and independent mechanisms of p21 and p27 induction exist. Stress from liver injury increases the expression of p53 and mitochondrial stress, both increasing p21 expression, which leads to cell cycle arrest (10,11). It has been reported that p21, but not Ki-67 expression, is increased in the liver cell nuclei of patients with AH, but not in NASH (12,13). This means that the cell cycle progression is arrested and regeneration of the liver is prevented in AH. A similar phenomenon occurs in decompensated cirrhosis where oxidative stress induces p21 up regulation (14-16). Rats fed ethanol chronically have up regulation of p21 and p27 in liver cell nuclei and this explains how ethanol inhibited liver regeneration after partial hepatectomy (15).

The increase in PCNA positive nuclei in AH has been reported previously (12,13). The mechanisms by which p21 regulates cell cycle progression are complex. Inhibition of cyclin/CDK kinase activity by p21 induces cell cycle arrest (17). P21 can directly inhibit PCNA-dependent DNA replication (16,18). In response to mitogen, p21 is induced during the G1 phase and plays a role in normal cell cycle progression (19,20). Activated p53 binds DNA and activates WAF-1/Cip-1 encoding for p21, which binds to the G1-S/CDK2 and S/CDK complexes (molecules that are important for the G1/S transition) inhibiting their

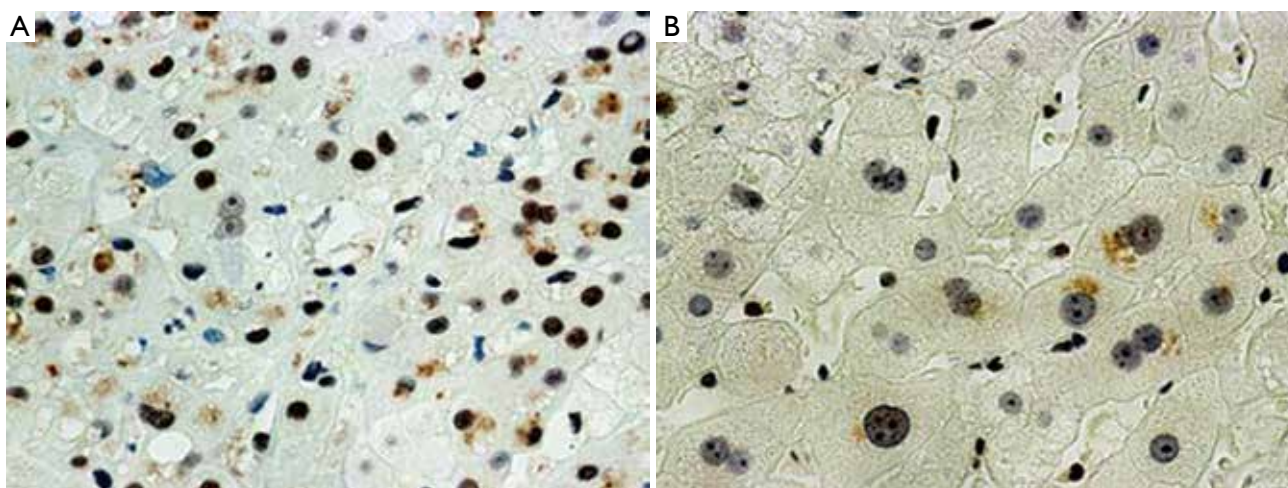


Figure 1 Liver biopsy from a patient with alcoholic hepatitis showing (A) an immunostain of numerous p27 positive nuclei (700 \times); (B) MDBs also stain positive (arrows) (1,050 \times)

activation. When p21 (WAF 1) is complexed with CDK2 the cell cannot continue to the next stage of the cell cycle.

PCNA positive nuclei are markedly increased in hepatocytes in AH (7,21). PCNA is important for both DNA synthesis and DNA repair (22,23). PCNA becomes post-translationally modified by ubiquitin (24). Polyubiquitin-mediated degradation of cell cycle proteins such as p21 is bound to PCNA by the E3 ligase CRL4 (Cdt2 ubiquitination and the 26s proteasome). This promotes several DNA repair processes when p21 is degraded by the proteasome. PCNA is then freed for the repair process of the DNA (25). If the U3 ligase/proteasome digestion mechanism fails to degrade p21, the cell cycle progression is arrested. This may turn out to be the mechanism involved in HCC formation in ALD, since chronic ethanol feeding leads to inhibition of the 26S proteasome activity in the liver (26). Chronic infection can also induce p21 levels in the liver where the balance of the liver cell proliferation/growth arrest leads to changes in the levels of Gadd 45B, PCNA, cyclin D1, Gadd 45r, p53 and activated caspase 3 (27).

P21 and p27 are up regulated in cirrhosis and HCCs (28) and up regulated by deacetylase inhibitors such as vorinostat (SAHA) used in chemotherapy (29). The implication is that histone acetyltransferases regulate p21 and p27 expression such as HADC1 (30). HADC1 is over expressed in the nuclei of hepatocytes forming Mallory Denk bodies in alcoholic hepatitis (31). P27 has oncogenic effects (32). Therefore, p21 and p27 may play important roles in the pathogenesis of HCCs in ALD patients, probably because of the DNA damage that develops during cell cycle arrest caused by p21 and p27 over expression.

The role of macrophages TLR4 signaling and stem cell transformation to form cancer stem cells in the pathogenesis of ALD-HCC transformation

Liver cell injury in AH is in part, due to macrophage generated proinflammatory cytokines and sinusoidal obstruction. The function of some macrophages (Kupffer cells) causes injury to hepatocytes by way of innate immune injury in response to endotoxin. This was found in rodent models of early alcoholic liver disease and possibly in AH in humans (33). However, these changes are increased in response to acute alcohol ingestion. They are responses that are reversible when ethanol ingestion is stopped in experimental alcohol fed rodent models. The question is: What has happened to the macrophages in chronic alcohol ingestion in humans who have AH? Plasticity and functional polarization are hallmarks of different types of macrophages i.e. M1i, M2a, M2b, and M2c which might be involved in AH.

This differential modulation of the macrophage chemokine system integrates polarized macrophages in pathways of resistance to or promotion of immune-regulation, tissue repair and remodeling (34). The T cell response to chemokines and cytokines differs when M1 and M2 macrophages are compared. M1 has a Th1 response to IFN α and LPS. M2a, b and c give a Th2 response of immune-regulation, matrix deposition and remodeling. M2a is a response to IL-4 and 13, M2b is a response to TLR/IL-1R agonists, and M2c responds to 1L-10 and suppresses immune responses to tissue remodeling (34,35). The type of macrophages in the sinusoids determines the inflammatory

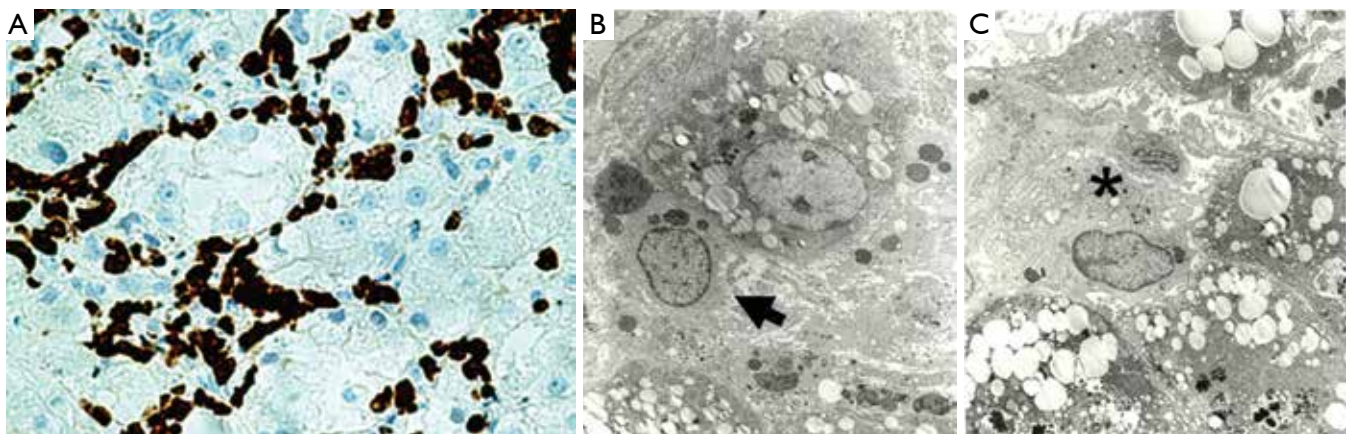


Figure 2 CD-163 positive macrophages fill all the sinusoids in a liver biopsy from an AH patient $\times 612$ (A); EM of the same liver as A showing 2 types of macrophages in the sinusoids, phagocytic on the left (B arrow) and (C) secretory on the right $\times 1973$

process in AH. We have done preliminary studies on the type of macrophages that occupies the sinusoids in liver biopsies of AH. We did IHC stains for CD-68 and CD163 to determine the degree of macrophage infiltrate in the sinusoids in AH (Figure 2A). We were surprised to find that the sinusoids were diffusely filled with macrophages (obstructed) all of which stained heavily for CD163 and not so heavily for CD68. The CD163 (M2c) plays an immuno-regulation role (34). The soluble form of CD163 can be measured in the serum to assess the degree of macrophage activation since CD163 is an activated macrophage marker (35). To assess the sinusoidal macrophages morphologically, we performed electron microscopy (Figure 2B, C). The morphology was that of two types of macrophages. The first type was smaller and filled with phagocytic bodies (secondary lysosomes). The second type was much larger and less common and contained lysosomes and rough ER (Figure 2).

The marked increase in the activity of CD163 positive macrophages involves a cascade of intracellular signals which lead to the secretion of IL6 and CSF1. CD163 positive macrophages are positive for the CD14 and CD16 subunits. CD-163 expression is down regulated by proinflammatory mediators like LPS, IFN γ and TNF α . IL-6 and IL-10 strongly up regulate CD-163 (36). Thus, up regulation of CD-163 as noted in the livers of AH implies that the positive staining macrophages are functionally anti-inflammatory (36).

The link between the activated macrophage in the sinusoids in the liver of patients with AH and the development of HCC is through chronic activation of TLR4 in response to a “leaky gut” increase in LPS into the portal vascular system (4). The link to HCC pathogenesis was first developed using a model of alcohol-fed NSSA Tg

mice with a diet supplement of LPS. The combination, over time led to synergistic liver damage and liver tumor formation due to alcohol-induced endotoxemia (37). In this mouse model, Nanog, a stem cell/progenitor cell marker, was up regulated by TLR4 activation. CD133/Nanog positive cells were found in the mouse liver tumors that formed (38). These observations supported the concept that the synergism between alcohol abuse and HCV leads to liver tumorigenesis through TLR signaling up regulation of the Nanog expressing stem cells, causing them to transform into cancer stem cells in HCC formation (TISCs). Nanog is up regulated by TLR4 activation. CD133/Nanog positive cells are consequently found in the HCCs of affected Tg mice (39) (Figures 3, 4, 5). CD133, a marker for cancer stem cells, is regulated epigenetically by TGF β (40). In fact there is compelling evidence that TGF β signals the expansion of progenitor liver stem cells, which lead to HCC formation and stimulate the progression of the HCCs (41-43). It’s a paradox that the cytostatic, tumor suppressor, TGF β becomes a tumor promoter, which stimulates the transition from stem cells to progenitor cells to cancer stem cells (39,42,43). Yap1 and Igf2bp3 that are Nanog-dependent genes inhibit TGF β signaling in TISCs (39). Yap1 and Igf2bp positive cells are present in the livers of ALD and associated HCCs (Figures 3, 4, 5). Taken together, TLR4 expression may be a universal proto-oncogene responsible for the genesis of TLR4-Nanog dependent TISCs (39).

The role of chronic inflammation of the liver in the development of liver cancer has long been suspected (44). Transcription factors such as TLR4, JNK, NF κ B, STAT3, IL-6, IL-1 α and EGF receptor are involved in inflammation associated HCC development (44,45). TLR4 and TLR2 signaling activated by inflammation up regulate NF κ B

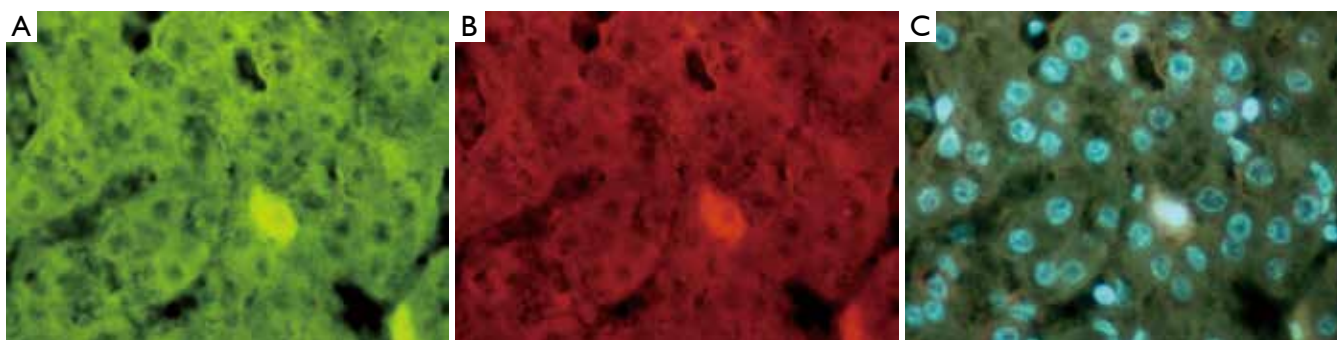


Figure 3 Immunostain (IHC) of liver showing an HCC. A. Shows a positive stained cell for YAP1 (green); B. Same cell stained positive for IGF2bdr3 (red); and C. tricolor combining A and B (x654)

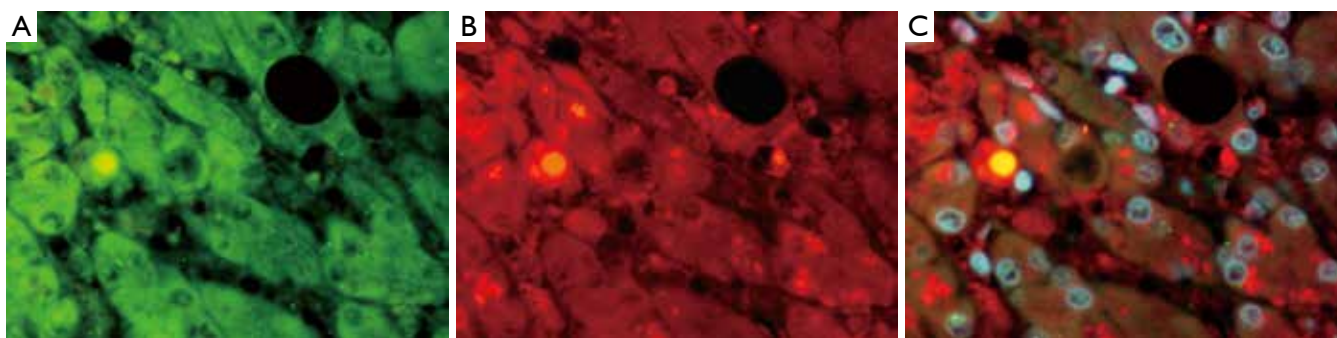


Figure 4 Liver from a patient with alcoholic liver disease showing alcoholic hepatitis and cirrhosis, immunostained for Oct 3-4 (A green), ubiquitin (B red) and (C tricolor) combining A and B. Note the co localization of Oct 3-4 and ubiquitin in the nucleus (x654)

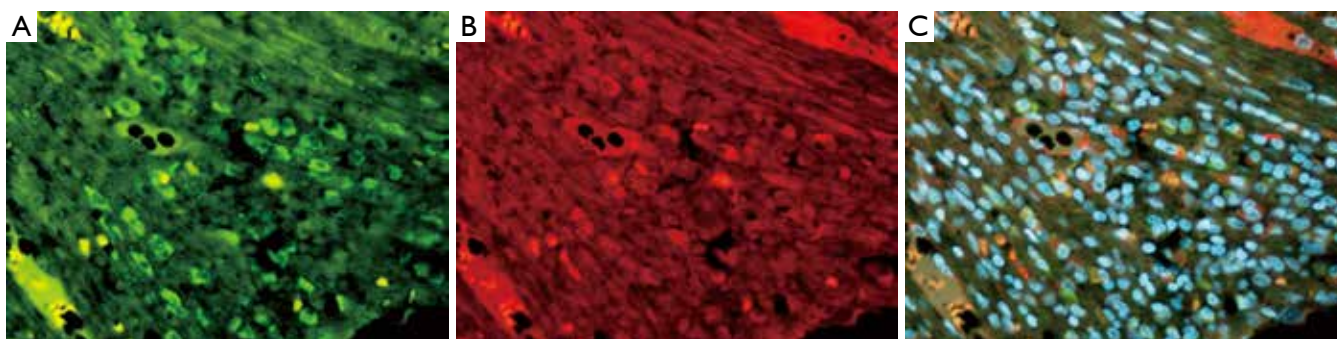


Figure 5 Liver from a patient with alcoholic liver disease showing cirrhosis and HCC. The photos are of a fibrous septa in the cirrhosis. A. Shows numerous Nanog (green) stem cells; B. One cell staining positive for SOX2 (red) (arrow); C. is tricolor combining A and B (x436)

and JNK cytokine expression. In experimental alcoholic liver disease TLR4 signaling in mice fed ethanol is increased through a MyD88 independent pathway (46). However, in rats fed ethanol by intragastric tube, where high blood alcohol levels are achieved, TLR4 expression increased as well as MyD88 protein levels indicating that the MyD88 signaling pathway was activated (47). When S-adenosylmethionine was fed with ethanol the up

regulation of TLR signaling was prevented indicating that the changes in TLR expression were the result of epigenetic mechanisms. Chronic alcohol feeding also up regulated CD34, FOS, IRF-1, Jun, TLR1, 2, 3, 6 and 7 and Traf6. IL-6, IL10 and IFN γ were also up regulated. Both IL-6 and IL-10 are cytokines that are up regulated by Kupffer cells (M2) in ALD (48). TL-6 activates STAT3. STAT3 acts as a proinflammatory signal (34). The activation of the TLR

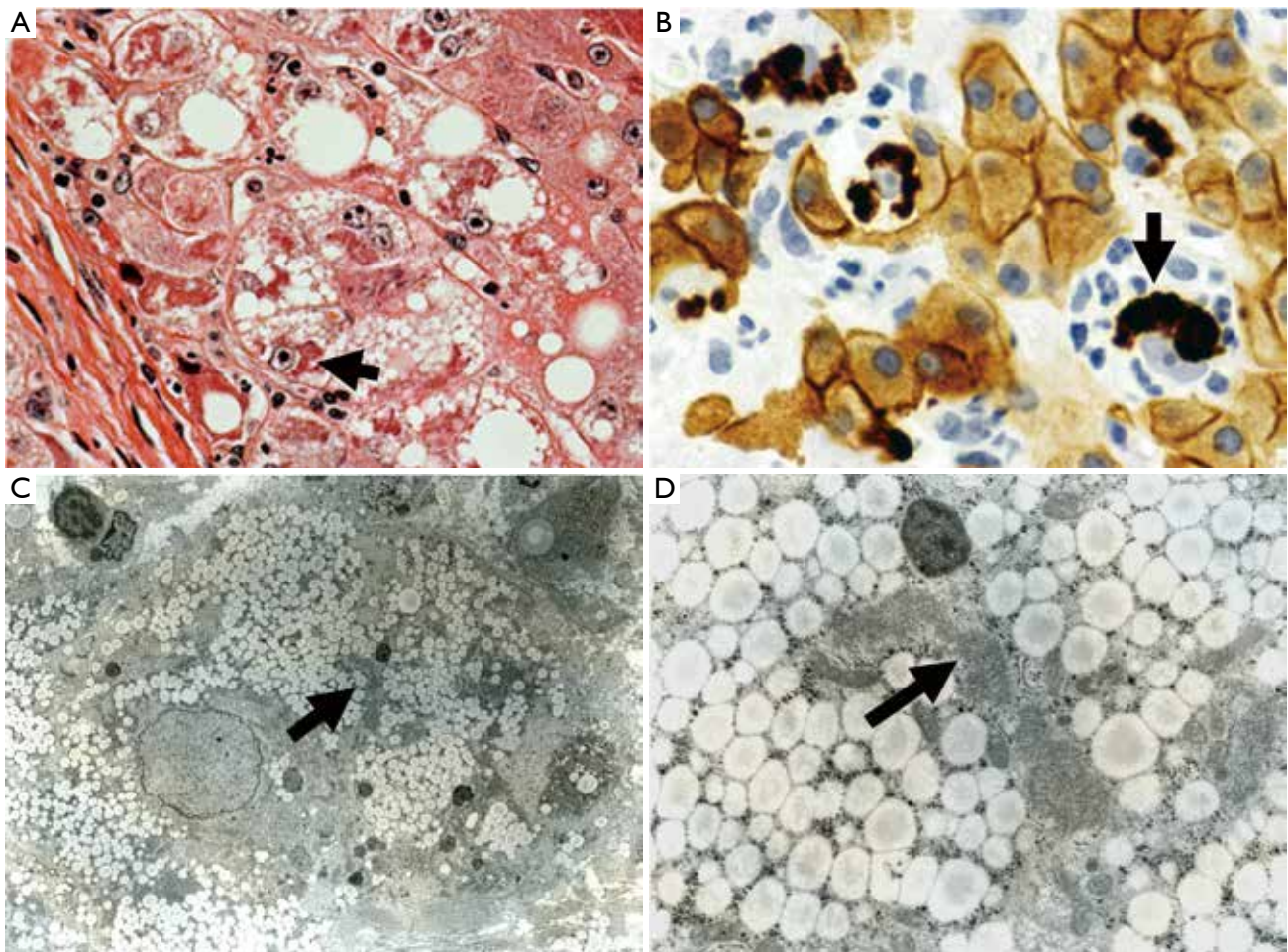


Figure 6 Liver biopsy stained for H&E (A) $\times 700$ and CAM5.2 (B) $\times 1,050$ for keratin 8 and 18. Balloon cells that formed in alcoholic hepatitis are shown where they have formed MDBs. Note that the balloon cells are devoid of keratin except for the MDBs which stain intensely. (C) $\times 1,875$ and (D) $\times 7,500$ electron micrographs of an hepatocyte balloon degeneration cell which had formed an MDB (arrow)

signaling pathway leads to the up activation of NF κ B which stimulates cytokine expression in chronic liver diseases, including ALD and this triggers, over time, the formation of HCC (49).

The role of ballooned hepatocytes that form Mallory-Denk bodies (MDB) as progenitor precancer cells

Balloon cell differentiation (BCD) with (MDB) occurs in chronic hepatitis and cirrhosis due to diverse causes such as alcoholic hepatitis (5). Their occurrence associated with HCC is well established (3). In an experimental mouse model where BCD/MDBs develop in large numbers similar to alcoholic hepatitis, liver tumors develop many months after the withdrawal of the carcinogen DCC. This is similar

to the development of the HCCs that develop years after alcohol abstinence in ALD patients (1). In the mouse model BCD/MDBs are associated with the development of preneoplastic changes (48). MDB forming hepatocytes express the same preneoplastic hepatocyte phenotype in both mice (50) and humans (4). The basic morphology of the MDB forming BCD is the same in the human liver and the liver in the mouse model of MDB formation (7) (*Figure 6*).

The first change that occurs when the balloon cell degeneration occurs is the disappearance of the keratin 18/8 cytoskeleton and rounding up of the cell. The balloon cell then differs from the normal polyhedral-shaped cell of neighboring hepatocytes (5). Electron microscopy of balloon cells (*Figure 6B, C*) shows micro-vesicular fat, reduced numbers of mitochondria, reduced glycogen and loss of the normal organelle arrangement due to the loss of

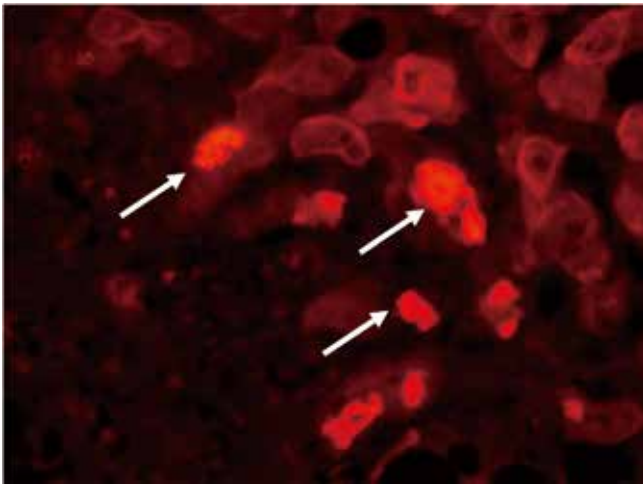


Figure 7 Liver from a patient with alcoholic hepatitis immunostained for SOX2 (red). Note that numerous MDBs stained positive for SOX2 (arrows) (2,224x)

the keratin filament structure. The most dramatic change is in the nucleus, which is large, with euchromatin and vesicular with a prominent nucleolus. When the balloon cell nucleus was immunostained for H3K27me3 the fluorescent intensity was low compared to the surrounding normal liver cell nuclei as shown by morphometric comparison (7). Similarly, pEZH2 was increased in the balloon cells that had formed (7). PEZH2 was increased in the liver when measured by Western blot. These observations supported the working hypothesis that the balloon cell change is due to epigenetic alteration of gene expression where the nuclear DNA methylation was reduced and gene expression was up regulated globally (1).

The working hypothesis is that balloon cells are phenotypically changed due to a failure of the H3K27me3/EZH2 to repress gene expression (51). The hallmark of the balloon cell/MDB forming cell is the loss of keratin intermediate filaments which normally span from the plasma membrane to the nuclear membrane (52). Keratin protein regulates protein synthesis and epithelial cell growth in keratinocytes (53). When MDBs form in the balloon cells in AH, the bile canaliculi disappear and organelles become randomly arranged. In an electron microscopic autoradiography study of synthesis of keratin filament protein using radio labeled S35 methionine as a marker, we showed that the nascent keratin proteins went to MDBs preferentially compared to the normally formed intermediate filaments (54).

Most relevant to the role of the BCD/MDB cells linking them to the formation of HCCs is the fact that HCCs often form MDBs in large numbers in humans and in the

mouse model (7). In the mouse model the BCD/MDB cells (FAT10+ cells) have a growth advantage compared to the normal neighboring cells in response to liver cell injury (1). They show an increased expression of α -fetoprotein, have a decreased expression of DNA repair enzyme glycosylase OGG1, have decreased levels of DNA 5' methyl cytosine, decreased nuclear levels of DNA methyltransferase enzyme DNMT36 and have a large increase in the expression of the mouse form of FAT10 (UBD). Fat10 is over expressed in human HCCs (1,55,56). The markers for the MDB associated preneoplastic phenotype, which indicate that the BCD/MDB cells are preneoplastic; include A2 macroglobin, gamma glutamyl transpeptidase, GSTmu2, fatty acid synthase, glypican-3, p38 and AKT, as well as AFP (1). The BCD cell as well as the MDBs stain positive with an antibody to SOX2 (Figure 7) a marker for hepatic stem cells, suggesting that these cells are stem cell/progenitor cells which have the potential to transform into cancer stem cells, which drive the formation of HCCs (57).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Viral hepatitis, non-alcoholic fatty liver disease and alcohol as risk factors for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a common cancer worldwide, with significant increase in the incidence observed in the past two decades in the United States. Majority of cases of HCC are due to chronic viral hepatitis B and C infections; however non-alcoholic fatty liver disease, associated with obesity and diabetes emerges as an important risk factor for HCC, in particular in the developed countries. Here we will review viral characteristics associated with increased risk for development of HCC and role of antiviral therapy in decreasing risk of HCC in those with viral hepatitis and cirrhosis. Association of alcoholic cirrhosis and non-alcoholic fatty liver disease with liver cancer will be reviewed as well as possible measures to decrease the risk of HCC in these highly prevalent populations.

Keywords: Hepatocellular carcinoma (HCC); hepatitis B; hepatitis C; non-alcoholic fatty liver disease; alcoholic cirrhosis; cancer surveillance

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Liver cancer and viral hepatitis

Worldwide, liver cancer is the fifth most commonly diagnosed cancer (1), with over half a million new cases diagnosed annually (2). The number of deaths per year, attributed to the liver cancer is almost identical to its incidence (1), making it the second leading cause of cancer-related mortality in the world, and the ninth leading cause of cancer death in the United States (3-5). Hepatocellular carcinoma (HCC) accounts for 70-85% of the total liver cancer burden (6), thus representing the major histological subtype of primary liver malignancies.

Almost 80% of cases of HCC are due to underlying chronic hepatitis B and C infection (7,8), not surprising, considering that 1 in 12 individuals worldwide lives either with hepatitis B or C infection. The relative risk of HCC in patients with chronic hepatitis B or chronic hepatitis C infection is about 25-30 times that of those without the infection. The disease burden is the highest in the hepatitis B-endemic areas (hepatitis B surface antigen prevalence $\geq 8\%$),

with over 80% of all cases of HCC occurring in sub-Saharan Africa and Eastern Asia, and over 40% in the People's Republic of China (8,9).

Significant increase in the incidence of HCC that has been observed over the past two decades in the United States has been mainly attributed to the large reservoir of long-standing chronic hepatitis C (10,11). As was demonstrated by El-Serag, the rate actually began to accelerate in the mid-1980s, most likely due to the increased incidence of cirrhosis due to chronic hepatitis C infection and non-alcoholic fatty liver disease (NAFLD), combined with large influx of immigrants from hepatitis B-endemic areas, including East Asia (12). As a consequence of high hepatitis C virus (HCV) infection rates in the United States between 1960 and 1980, and the average lag time between HCV acquisition and the development of cirrhosis and HCC of 20-30 years, the incidence of HCC is expected to continue to rise.

While HCC is more common in men, the age distribution of HCC cases depends on the dominant viral hepatitis and age at which it was acquired. In the regions with

high HCC incidence (where hepatitis B virus transmitted at birth is the most common cause), HCC is usually diagnosed a decade earlier compared to North America and Europe, where most HCC is related to HCV acquired later in life (2). In majority of cases (80-90%) HCC occurs in the setting of cirrhosis (13).

Hepatitis B and HCC

Chronic hepatitis B is the most common cause of viral liver disease worldwide, with over 350 million infected individuals (or 5% of the world population). HCC is one of the major consequences of chronic hepatitis B, and variety of viral and host factors contribute to its development. In hepatitis B virus (HBV)-related cirrhosis, the 5-year cumulative risk of HCC is 15% in high endemic areas and 10% in the West (14). In the recent study from the United States, the death rate from HCC was twice that of decompensated cirrhosis in individuals with chronic hepatitis B infection; with HCC death representing 70% of all cancer-related death in males and 37% in females (15). While only 16% of cases of HCC in the United States are attributed to HBV, worldwide HBV accounts for 54% of all cases of HCC, which is not surprising considering that almost half of the world's population lives in the areas with high HBV prevalence. It is important to keep in mind, that while 70-90% individuals who develop HCC in the setting of HBV infection will have cirrhosis (16,17), HCC can also develop in the absence of cirrhosis, including inactive HBV carriers (18).

Men with chronic hepatitis B, appear to be at higher risk for HCC compared to women (19-21), with cumulative lifetime incidence of HCC of 27% vs. 8%. Family history of HCC, older age, male sex, Asian or African ancestry, alcohol consumption, cigarette smoking, elevated serum alanine aminotransferase (ALT) levels, and the presence of core and pre-core mutations, also appears to increase the risk of HCC in chronic hepatitis B (17,20,22-27).

Viral factors of hepatocarcinogenesis in HBV infection

Although cirrhosis is the major risk factor for HCC in the setting of chronic hepatitis B, over the years several other risk factors have been identified, including the viral load, the presence of hepatitis B e antigen (HBeAg), and hepatitis B surface antigen (HBsAg).

The landmark REVEAL study (28), a large community-based study in Taiwan that included 3,653 HBsAg-positive

and HCV-negative patients enrolled between 1991 and 1992, demonstrated that the risk of HCC was much greater in individuals with high serum levels of HBV DNA compared to those with low levels (defined as HBV DNA <10,000 copies/mL). In this relatively young cohort (median age 45 years), at enrollment, 85% were HBeAg-positive, 94% had normal ALT levels, and only 2% had cirrhosis. During a mean follow-up of 11 years, HCC developed in 164 patients (4.5%), with higher incidence of HCC associated with a higher HBV DNA at the study entry. Cumulative incidence of HCC of 14.9% was noted among those with HBV DNA >1 million copies/mL, while it was much lower at 1.3% among those with an HBV DNA level <300 copies/mL, at baseline. The HBV DNA level remained an independent predictor for HCC even after adjusting for sex, age, cigarette smoking, alcohol consumption, HBeAg status, serum ALT level, and the presence of cirrhosis at the baseline, i.e., all the other known risk factors for development for HCC. It is important to keep in mind, however, that most of the individuals in this study, likely acquired HBV perinatally; it is not clear if these data can be applied to those who acquired HBV as adults.

Yang *et al.*, in the one of the largest prospective studies that tested for HBsAg and HBeAg, detected 111 cases of HCC after following 11,893 Taiwanese men for approximately 10 years (29). The prevalence of HBeAg was 39% among the men who were positive for HBsAg. The cumulative incidence of HCC was much higher among men who were positive for both HBsAg and HBeAg, than among those who were only positive for HBsAg and even higher than among those who were negative for both ($P < 0.001$ for both comparisons). After adjusting for other risk factors, the relative risk (RR) of HCC was 9.6 for men who were positive for HBsAg alone and 60.2 for those who were positive for both HBsAg and HBeAg, as compared to men who were negative for both.

Increased risk of HCC in inactive carriers of HBV (HBV DNA <10,000 copies/mL), was demonstrated in another population-based study from Taiwan, that included 20,069 individuals with HBV; 1,932 of them were HBsAg-positive (HCV-negative), HBeAg-negative, had normal ALT and serum HBV DNA <10,000 copies/mL. During an average follow-up of 13 years, the annual incidence of HCC was higher in HBsAg-positive patients than in controls (0.06% vs. 0.02%) (18).

Moreover, as has been shown in the study that followed 1,271 Alaskan Natives with chronic hepatitis B for an average of 20 years (30), the incidence of HCC, although

lower among those who cleared HBV infection (i.e., became HBsAg negative) compared to those who remained HBsAg-positive (37 *vs.* 196 per 100,000 person-years), was still higher than among the general population. Not surprising however, it appears that the risk of developing HCC in those who cleared HBsAg, at least among Asian patients, is related to the age at which the infection was cleared, with the likelihood of developing HCC higher in those who cleared HBsAg after 50 years of age (31).

Hepatitis B genotype also appears to have an impact on the risk of HCC. As has been shown by studies from Taiwan, Shanghai, and Japan (32-34), where genotypes B and C are the predominant strains, genotype C is associated with more severe liver disease including cirrhosis and HCC (32,35); this is not surprising since patients with genotype C tend to have higher frequency of HBeAg-positivity, higher serum HBV DNA, delayed HBeAg-seroconversion, and basal core promoter mutations (all factors associated with higher risk of HCC). It appears, though, that genotype B is actually associated with the development of HCC in young non-cirrhotic population (35,36). In Western Europe and North America, where genotypes A and D prevail, genotype D appears to be associated with a higher incidence of HCC and development of HCC in young carriers without cirrhosis (2).

As has been demonstrated by several studies from Asia and Europe, co-infection with HCV (particularly in those who are HBeAg-positive), hepatitis D virus (HDV) and human immunodeficiency virus (HIV), also appears to increase the risk of HCC (14,24,37-39).

Prevention of HCC in chronic hepatitis B: anti-viral therapy

Prevention is the best treatment for any condition and HCC is not an exception to the rule, especially in view of the high mortality. Development of HBV vaccine has been a major success in reducing the incidence of HBV and subsequent development of HCC. Benefits of vaccination have been demonstrated by the countries and regions like Taiwan, where 25 years after the adoption of the universal hepatitis B vaccination program, HBV carrier rate among children has decreased to 1.2% and incidence of HCC among vaccinated children decreased by 70% (40). Vaccine is recommended for all newborns, pregnant women at their first neonatal visit and high-risk individuals. Neonates of HBV-infected mothers should get a dose of hepatitis B immunoglobulin (HBIG) in addition to vaccination. It

is estimated that >90% of countries routinely vaccinate newborns against HBV, and approximately 70% are now delivering 3 immunization doses (8).

What about those individuals that have chronic hepatitis B infection? First real prove of benefit of an antiviral therapy in reducing the risk of HCC came from a multicenter, randomized, placebo-controlled, parallel group study of lamivudine in patients with advanced liver disease by Liaw *et al.* (41). After a median of 32.4 months of therapy, HCC occurred in 3.9% of those on lamivudine (100 mg daily) and 7.4% of those in the placebo group (hazard ratio, 0.49; P=0.047). Since then, several systematic reviews also suggested that the relative risk of HCC is reduced by approximately 60% following treatment with interferon or nucleos(t)ides (42-44), although benefit seems to be restricted to those with advanced fibrosis or cirrhosis, and is not seen in those who developed nucleos(t)ide resistance. While most of the data on the benefits of oral antiviral therapy comes from the studies on lamivudine and adefovir, a recent retrospective cohort study from Japan demonstrated reduction in the incidence of HCC with long-term use of entecavir, with cumulative 5-year rates of 3.6% *vs.* 12.3% in those on no anti-viral therapy (45).

Analyzing the Taiwan Health Research database, Wu *et al.* demonstrated that nucleoside analogues reduce the risk of recurrent HBV-related HCC following liver resection (46). Authors demonstrated a 6-year HCC recurrence rate of 45.6% compared to 54.6% in untreated individuals, as well as a 6-year reduction in overall mortality (29% *vs.* 42.4%), with number needed to treat (NNT) 12 to prevent one HCC over 6 years, and 6 to prevent 1 death over that same period of time.

As demonstrated by the above data (41-45), the risk of HCC is reduced, but is not completely eliminated by anti-viral therapy. In the recent meta-analysis, lamivudine treatment significantly reduced the incidence of HCC compared to no treatment, however HCC still developed at a rate of 1.3 per 100 patient years in chronic hepatitis B patients receiving lamivudine (47). This finding highlights the need for continued surveillance for HCC, especially in those without adequate suppression, older age and cirrhosis. While, it is not yet clear whether treatment of non-cirrhotic patients with chronic hepatitis B, if instituted early enough could eliminate the risk of HCC altogether, and as pointed in the recent editorial by Sherman (48), performing such a study will be difficult (and might never be done), anti-viral therapy should be provided to the individuals with active HBV.

Hepatitis C and HCC

Approximately 2% of world population has evidence of HCV infection (approximately 180 million people) (8). Cohort studies indicate that HCC remains the major cause of liver-related death in patients with compensated cirrhosis, and HCV infection is associated with the highest HCC incidence in persons with cirrhosis, occurring twice as commonly in Japan than in the West (5-year cumulative incidence, 30% and 17%, respectively) (14). Japan has had one of the highest incidence rates of HCC associated with chronic hepatitis C infection; incidence appears to be decreasing in the recent years (49). In the United States, HCV is the leading cause of HCC, where it accounts for 50-60% of cases. HCV infection acquired 2-4 decades ago explains at least half of the observed increase in HCC in the United States, including the fastest increase in white men 45-54 years of age, and HCV-related HCC is expected to continue to increase for another 10-13 years (10,12).

Viral and host factors in HCV-related HCC

HCV appears to increase the risk of HCC by inducing hepatic inflammation and importantly fibrosis, as well as promoting malignant transformation (50). Although the risk for HCC is highest in those with cirrhosis, occurring at the rate of 1-4% per year (51), it is important to keep in mind that HCC has been reported in chronic hepatitis C in the absence of cirrhosis. In the HALT-C trial, HCC developed in 8% of individuals without cirrhosis but with advanced fibrosis (52).

Not unlike the case with chronic hepatitis B, men and older individuals have an increased risk of HCC. Other risk factors for HCC in the setting of chronic hepatitis C are co-infection with HIV or HBV, diabetes and obesity (see below), as well as chronic alcohol consumption.

The level of viremia in HCV does not appear to impact the risk of HCC (at least based on the European and US data), although any HCV viremia does increase the risk. Interestingly, HCV genotype 1b infection appears to almost double the risk of development of HCC compared to all other genotypes, based on a meta-analysis of 21 studies (53). This might be a contributing factor to the high rate of HCV-related HCC in Japan, where 73% of individuals carry genotype 1b HCV infection.

Vitamin D deficiency is common among individuals with chronic hepatitis C, including those with minimal fibrosis, and severe vitamin D deficiency occurs in about 25%

of those with chronic hepatitis C (54). While vitamin D deficiency has been associated with increased risk of colon, breast and prostate cancer (55-59), it remains unclear as to whether vitamin D deficiency is associated with an increased risk of HCC (60). In fact, we were unable to demonstrate an association between vitamin D deficiency and HCC in a case-control study of 51 individuals with HCC and cirrhosis (mainly due to chronic hepatitis C) and age- and liver disease-matched controls without HCC (Samoy, *et al.* 2013; unpublished data). Further studies looking into this association are needed, since they might lead to the preventative and possibly therapeutic strategies.

Antiviral therapy for chronic hepatitis C and the risk of HCC

Randomized and non-randomized studies, including a recent meta-analysis on the role of antiviral therapy in HCV-related HCC, have shown a 57-75% reduction in the risk of development of HCC with achievement of sustained virologic response, both in those with and without cirrhosis (61-67), and possibly even in those with decompensated cirrhosis (68). It is important to remember however, that individuals with advanced fibrosis who clear HCV viremia with anti-viral therapy (aka achieve sustained virologic response) have a reduced but not eliminated risk of HCC and should continue to undergo surveillance (2,65). This was again recently demonstrated by a study from Sweden (69), showing significantly decreased risk of HCC, liver decompensation and death in patients with HCV-related cirrhosis after sustained virologic response, however long-term risk of development of HCC remained up to 8 years of follow up.

Interestingly, low pre-operative HCV viral load predicted better long-term surgical outcomes in patients undergoing resection for HCC independent of serologic eradication of HCC (70). Both 5-year recurrence-free (36.1% *vs.* 12.4%) and 5-year overall survival rates (76.6% *vs.* 57.7%), were significantly higher in the lower viral group compared to the high viral load group, with reported tumor recurrence hazard ratio of 1.87 in the high viral load group. Moreover, recently published analysis of the 2,237 anti-viral naïve HCV patients with curatively resected HCC from the Taiwan National Health Insurance Research Database, suggested that postoperative peg-interferon plus ribavirin (for at least 16 weeks after surgery) reduced recurrence of HCC (71). After 5 years of follow-up, the recurrence rate of HCC was significantly lower in the treated than matched

untreated cohort: 52.1% *vs.* 63.9%, with NNT 8 to prevent one HCC recurrence at 5 years. Interestingly, the greater risk reduction of recurrent HCC was observed among younger patients (<60 years), and those without cirrhosis or diabetes.

While antiviral treatment for chronic hepatitis C is very efficacious and will become even more so with the approval of novel direct acting anti-virals in the next few years, their effectiveness in the community practice, including endemic regions, is quite low due to barriers in access, diagnosis and cost of medications. It was estimated that approximately 45-85% of the individuals with chronic hepatitis C in the United States are unaware that they are infected and thus do not receive needed care and treatment (72). In the effort to improve detection of HCV, US Centers for Disease Control and Prevention, now recommends routine screening for HCV in all individuals born between 1945 and 1965, who represent approximately 76% of those individuals infected with HCV, and 70% of all HCV-associated deaths. This recommendation was recently supported by the US Preventive Service Task Force (USPSTF), that now recommends screening for HCV infection in persons at high risk for infection, including offering 1-time screening for HCV infection to adults born between 1945-1965 (B recommendation) (73). When accompanied by appropriate care and treatment, as suggested by Ward, HCV testing can reduce risk of HCC by 70% (72).

Non-alcoholic fatty liver disease and HCC

While worrisome trend of the rising incidence of HCC in the United States has been primarily attributed to the high prevalence of chronic hepatitis C in this population, and is expected to plateau by 2020, epidemiological studies indicate that up to 50% of all cases of HCC do not have a clear etiology (74,75). HCC has been linked to NAFLD, which has become the most common liver disorder in the United States and other industrialized countries. NAFLD is present in 30% of the general adult population, 90% of morbidly obese adults (BMI ≥ 40 kg/m²), and close to 74% of those with diabetes (76-78).

The exact prevalence of HCC in cirrhotic NAFLD remains unknown; however the risk of HCC due to NAFLD appears to be less than that of chronic hepatitis C. A recent United States study, reported a 2.6% yearly cumulative incidence of HCC in NAFLD and 4.0% in HCV cirrhosis (over a median follow up 3.2 years) (79), while a prospective 5-year study from Japan reported a rate

of HCC of 11.3% among patients with NAFLD-cirrhosis compared to 30.5% among those with HCV-associated cirrhosis (80).

Keeping in mind prevalence of NAFLD and its natural history, however, NAFLD may actually become the primary source of HCC in the United States and other developed countries, thereby offsetting the impact of successful measures on reducing HCV-related HCC (81). This concern might be further demonstrated by a recent study from Germany, identifying non-alcoholic steatohepatitis (NASH) as the most common etiology of HCC (24%), surpassing chronic hepatitis C (23.3%), chronic hepatitis B (19.3%) and alcoholic liver disease (12.7%) (82). While it is estimated that 30-40% of all HCC in industrialized countries occur in patients with cryptogenic cirrhosis (74), as has been demonstrated by several studies, majority of these cases are associated with either prior NAFLD or other features of metabolic syndrome (81). Diabetes and obesity have been established as independent risk factors for HCC, and that association holds true in the setting of NASH (83,84). Of concern, is the growing body of literature suggesting that NAFLD contributes to non-cirrhotic HCC, and that HCC can develop in patients with metabolic syndrome and NAFLD, in the absence of NASH and fibrosis (85); however as demonstrated by a recent systematic review, while there is an epidemiological evidence to support an association between NAFLD or NASH and increased risk of HCC, the risk seems to be limited to individuals with cirrhosis (86).

Prevention of HCC in NAFLD

Since insulin resistance and lipotoxicity are distinct molecular mechanisms that may promote development of HCC in NAFLD, effective treatment of insulin resistance and hyperinsulinemia may be in fact critical to prevent hepatocarcinogenesis in this population (81). Several reports have suggested that the use of insulin-sensitizing agents in diabetes may reduce the risk of HCC (87,88). Interestingly, metformin in addition to improving insulin resistance has direct antiproliferative effects primarily by inhibiting the mTOR oncogenic pathway (89). In a case control study of diabetic patients with HCC, Hassan *et al.*, demonstrated that treatment with metformin or the insulin-sensitizing peroxisome proliferators activated receptor- γ (PPAR- γ) agonist thiazolidinediones (TZDs), resulted in an adjusted risk ratio of 0.3 for HCC, while the use of insulin-secretagogue sulfonylureas was associated with a 7.1-fold

increase in the risk of HCC (compared to non-users) (88). A recent meta-analysis of observational studies by Singh *et al.* (90), demonstrated a 50% reduction in the incidence of HCC with metformin use (OR 0.50), while a 62% and 161% increase in HCC incidence was observed with sulfonylureas (OR 1.62) or insulin use (OR 2.67), respectively. TZDs did not appear to modify the risk of HCC. While noting that anti-diabetic medications may modify the risk of HCC in patients with diabetes, especially in the Western population, study authors expressed caution in interpreting the effect of an individual agent, due to the “inherent cancer-modifying effect of the comparator group”. Finally, another recent study, suggested that insulin-sensitizers might also improve the prognosis of HCC, demonstrating lower mortality in diabetic patients on metformin, who underwent radiofrequency ablation for early HCC (91). As was suggested by Baffy *et al.*, the use of insulinsensitizing drugs and avoidance of treatments contributing to hyperinsulinemia is likely to enhance prevention and improve disease outcomes in HCC (81).

A recent study by Ascha *et al.* (79), demonstrated that among individuals with NASH cirrhosis, older age and alcohol consumption were independent variables associated with the development of HCC. Compared to non-drinkers, individuals who reported any lifetime alcohol consumption were 3.6 times more likely to develop HCC compared to those who had no exposure to alcohol.

While individuals with NASH-related cirrhosis should be enrolled in the surveillance program, more epidemiologic, clinical and molecular biology data are needed to determine the relative contribution of obesity, diabetes, and NAFLD to HCC and to develop a cancer surveillance program for potentially affected population of non-cirrhotic NAFLD (81). In the meantime, prevention of obesity, diabetes and NAFLD, and avoiding any alcohol use in those with NASH cirrhosis, appears to be the best long-term strategy.

Alcohol and HCC

Alcohol abuse may lead to cirrhosis and development of HCC in some individuals with heavy alcohol use. The actual incidence of HCC in those with alcoholic cirrhosis is not very clear, however alcoholic cirrhosis is clearly a risk factor for HCC. The annual incidence of HCC was reported at around 2.5% among Child-Pugh class A or B alcoholic cirrhotics in Spain (92), with higher annual incidence in those 55 years of age and older and platelet count less than 125,000/mm³. In the US and Austrian cohorts, alcoholic

liver disease appears to account for 24-35% of cases of HCC (93-95). Based on the recent data by Welzel *et al.* (94), in the US, the risk of HCC is increased in the alcohol-related disease (OR 4.06) and represents the second greatest population-attributable fraction (PAF) of risk factors for HCC (23.5%), overall and among males (27.8%), whites (25.6%), Hispanics (30.1%), and blacks (18.5%).

Prior exposure to HBV (positive HBcAb in the absence of HBsAg or anti-HCV) in the setting of heavy alcohol use appears to significantly increase the risk of HCC in males with alcoholic cirrhosis based on the earlier epidemiological data from Japan. After prospectively following 91 individuals with alcoholic cirrhosis for a median of 5.9 years, Uetake *et al.* reported cumulative occurrence rates of HCC at 6.4%, 18.0% and 28.7% at the end of the 5th, 7th, and 10th years, respectively (96). When classified by HBcAb status (about 30% of individuals were HBcAb-positive), prior exposure to HBV resulted in much higher rates of HCC: 15.6% *vs.* 2.9% at the 5th year, 28.4% and 13.5% at the 7th year, and 40.4% *vs.* 22.1% at the 10th year, respectively (96). Hepatitis C and diabetes are not uncommon in alcoholics and there also appears to be a synergistic interaction between heavy alcohol consumption (≥ 80 mL ethanol/day) and chronic viral hepatitis (93,97) and diabetes mellitus (93). Interestingly, however, as observed by Serra *et al.* (98), cumulative survival in alcoholic cirrhosis does not seem to be influenced by the presence or absence of markers of HCV infection: the cumulative survival curve in abstinent alcoholics was significantly different from that of “active” alcoholics, and cumulative survival in patients with HCV-related cirrhosis who stopped drinking after the diagnosis was similar to that in HCV-cirrhotic patients who never consumed alcohol. This observation highlights an importance of complete alcohol abstinence in any cirrhotic patient.

Surveillance for HCC in chronic viral hepatitis, NAFLD and alcoholic cirrhosis

As demonstrated by the HCC incidence and prevalence data, the number of death per year attributed to liver cancer is almost identical to its incidence (1,99). Only 1 randomized trial from China showed a 37% reduction in HCC-related mortality with surveillance for HCC with α -fetoprotein (AFP) and ultrasound every 6 months (compared to no-surveillance arm) (100). However, long-term survival after curative-intent treatment at early stages of the disease may now reach 50-70% over 5 years (101),

highlighting the importance of effective surveillance and early diagnosis of HCC.

At this time, with the exception of chronic hepatitis B, the primary indication for surveillance for HCC is cirrhosis of any etiology (99). Surveillance is also recommended for Asian male hepatitis B carriers over the age of 40 and females over the age of 50, hepatitis B carriers with family history of HCC, and African and North American Blacks with hepatitis B. Surveillance benefit is unclear at this time in male hepatitis B carriers younger than 40 and females younger than 50, those with hepatitis C and stage 3 fibrosis and non-cirrhotic NAFLD.

Although the most recent American Association for Study of Liver Diseases (AASLD) guidelines recommend screening for HCC with ultrasound every 6 months for at risk individuals, some feel that using the combination of AFP and ultrasonography, can increase the yield of screening (2), albeit with the increased cost due to increase in false positive results. Computed tomography (CT) and magnetic resonance imaging (MRI) although are better at imaging the liver when compared to the ultrasound, have not been studied as surveillance tools, and are currently indicated for diagnosis and staging of HCC, rather than surveillance. However, as reported by the HALT-C investigators, while absence of screening and follow-up are common and potentially contribute to late-stage HCC in 30% of cases, the most common reason for finding HCC at the late stage was an absence of detection (70%), strongly suggesting that better surveillance strategies are in-fact needed (102).

Screening for HCC in alcoholic cirrhosis is a difficult task due to poor compliance and early death. Recent data from a Danish nationwide cohort study (103), suggests a low risk of HCC (5-year cumulative risk of 1.0%) in Danish citizens with alcoholic cirrhosis, as well as its little contribution to their high mortality (5-year cumulative mortality of 43.7% with only 1.8% of all death HCC-related). The study authors suggested, based on their data, that surveillance for HCC would be expected to have a minimal effect on mortality and unlikely to be cost-effective (103). The current AASLD guidelines accept alcoholic cirrhosis as a significant risk factor for HCC, probably sufficient to warrant surveillance for HCC (104). In his comment on the Jepsen et al paper, Sherman (105) noted the Danish study reported the incidence of HCC at the lower end of reported rates in alcoholic cirrhosis, with rates higher in other geographic areas (96,106,107), suggesting that the risk has to be assessed locally. He

concluded that while the data from Denmark needs further confirmation before alcoholic cirrhosis is “scratched off” the list of screening candidates, it should be moved from the “definitive” to “possible” category (along with NAFLD, diabetes, autoimmune hepatitis, and treated hepatitis C), which includes “those patients for whom the risk of HCC has not been accurately assessed, and for whom no recommendation for or against screening can be made” (105).

Although HCC in NAFLD may have a distinct pathogenesis, presence of cirrhosis in NAFLD results in much higher risk of HCC, similar to other forms of chronic liver disease (108), and cirrhotic patients with NAFLD should undergo screening as currently recommended. However, traditional approach to surveillance for HCC in NAFLD poses several problems. If we were to accept that obesity and diabetes (109,110), are the major risk factor for HCC (even in the absence of cirrhosis), then as observed by Baffy *et al.* (81), in the United States alone it will imply consideration for surveillance for HCC for every 3rd adult, or for the 26 million of diabetics (many of whom also have NAFLD). On the other hand, as has been observed by Caldwell *et al.* (111), since cryptogenic cirrhosis develops insidiously and individuals do not have pre-existing well-recognized risk factors such as viral hepatitis B or C, or alcoholic liver disease, underlying liver disease might go “unrecognized” in the majority of the affected individuals. This was in fact confirmed by a single-center study from US, where only 47% of those with cryptogenic cirrhosis and HCC, had prior histological diagnosis of NASH or clinically suspected NAFLD; not surprisingly then, was the finding, that much less individuals with cryptogenic cirrhosis were enrolled in the HCC surveillance program (23% vs. 61%, P=0.01), or diagnosed with small, early stage disease, impacting on their success of therapy (112).

Obviously, better understanding of the relative contribution of obesity, diabetes mellitus and NAFLD to HCC, as well as molecular pathways that can accelerate hepatocarcinogenesis in these conditions, is needed in order to develop cancer surveillance recommendations and programs in this vast population.

Conclusions

Chronic viral hepatitis remains a major risk factor for HCC worldwide. Vaccination of infants at birth for hepatitis B is highly effective in decreasing the incidence of HBV and development of HCC. Antiviral therapies demonstrate

possible decreased but not completely eliminated risk of HCC in both hepatitis B and C individuals and surveillance for HCC needs to continue, especially in those with cirrhosis, even after viral eradication. However, as antiviral therapies continue to improve in efficacy and tolerability and will hopefully lead to decrease in HBV- and HCV-related liver cancer, NAFLD is becoming a leading cause of HCC in developed countries, and with the epidemic of obesity and diabetes on the rise, other parts of the world will likely to follow suit. While we need better understanding of which individuals with NAFLD require surveillance for HCC, as well as better screening modalities to improve detection of early HCC, more efforts need to be directed towards prevention of obesity, diabetes and NAFLD, as well as increased awareness of the magnitude of the problem. As was recently demonstrated by Welzel *et al.* (94), among US persons ≥ 68 years, while the dominant risk factors for HCC differ by sex and race/ethnicity, diabetes and obesity had the greatest population attributable factor of 36.6%, and eliminating diabetes and obesity could reduce the incidence of HCC more than the elimination of any other factors (including HCV, HBV, and alcohol).

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Footnote

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Vitamin E in prevention against hepatocellular carcinoma: right type, right dose and right population

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Globally, cancer has surpassed cardiovascular disease as the leading cause of death. In 2008, more than 7.5 million deaths are attributable to malignant diseases worldwide (1). To the general public, cancer prevention has always been a topic of concern, and strategies such as dietary modification or the intake of health supplements have been thoroughly investigated in the past. Amongst all the natural health supplements, vitamin E is probably the most intensively studied cancer preventive agent because of its renowned anti-oxidant property. Vitamin E consists of a group of fat-soluble compounds including the tocopherols and tocotrienols. Because vitamin E cannot be synthesized in the body, human has to rely on dietary sources of vitamin E. Tocopherols are the major source of vitamin E in the diet. Structurally, the tocopherol family consists of four structurally related compounds namely α -, β -, γ -, and δ -tocopherols. α -tocopherol is most well studied subtype because of its preferential secretion by the liver and higher plasma concentration in the body.

The epidemiological link between vitamin E and cancer risk remains a controversial issue. Inconsistent results have been reported by various case-control and cohort studies. For lung cancers, there have been at least three cohort studies and four case-control studies evaluating the association between vitamin E and the risk of lung cancer (reviewed in reference 2). Five of these studies have demonstrated that dietary vitamin E intake or serum tocopherol levels were associated with a reduced risk of lung cancer, especially in light smokers. Out of the eight cohort or case-control studies that have been performed on the risk of colorectal cancer, only four studies have demonstrated

a protective effect of vitamin E (2). For prostate cancer, more than twenty studies have been conducted to date, and ten of them were considered positive trials (2). Similar inconsistencies are observed in studies on the prevention of breast cancer, with less than half of the fifteen case-control studies suggesting that vitamin E could lower the risk of breast cancer (2). In China, hepatocellular carcinoma (HCC) is one of the most alarming medical problems with an annual incidence and mortality of 39,000 and 32,000 cases, respectively (3). The total caseload of HCC in China accounts for half of the global burden of HCC (4). The association between vitamin E and HCC has been poorly understood. There have been only two reported case-control studies which evaluated the effect of protective micronutrients against HCC, but these studies did not show that vitamin E could protect against HCC (5,6).

In the article by Zhang *et al.* in the *Journal of National Cancer Institute* (7), the investigators aimed to study the association between vitamin intake and the risk of HCC. By analyzing data from two cohorts which comprised of 132,837 participants in China, Zhang *et al.* calculated the vitamin intake of participants through a comprehensive food questionnaire. The authors have also identified new cases of HCC by rigorous methods including regular surveys, establishing linkage with independent population-based databases and also cross-checking by oncologists. After a median follow-up of 10.9 years for women and 5.5 years for men, a total of 267 participants developed HCC. The most salient finding of this study is that the oral intake of vitamin E, either from the diet or vitamin supplements, are associated with a reduced risk of HCC development.

In addition, this statistically significant association between vitamin E and a lowered risk of HCC remained after adjusting for the influence from self-reported liver diseases and family history of liver cancer. On the other hand, other micronutrients including vitamin C were found to have no impact on the risk of HCC. The authors concluded that a high intake of vitamin E, either from the diet or as supplements, is related to a lower risk of HCC.

How should we interpret the results of this study? Compared to the two previous case-control studies (5,6), the cohort study by Zhang *et al.* is unique in several aspects. First, the paper is based on cohorts consisting of more than 130,000 participants (7). This large sample size has enabled robust statistical analysis and optimization of the study's power. Second, the study subjects are based on general population rather than selected subjects from institutions or clinics (7). This is reflected by the close similarity of the calculated annual incidence of HCC in Zhang's study (women: 14.9/100,000; men: 44.1/100,000 population) and the incidence figures reported by other cancer surveys in China (women: 14.2/100,000; men: 37.9/100,000 population) (8). Hence, we are confident that the results are applicable to the general population in most urban cities in China. Third, the two previous studies were conducted in predominantly non-Asian subjects, while the current paper is the only study based on Chinese population (7). In China and other parts of Asia, more than 80% of HCC cases are due to chronic hepatitis B virus (HBV) infection (9,10). Nowadays, it has become increasingly clear that the HBV-related HCC is genetically different from the Western counterparts (11,12). Therefore, the results of Zhang's study provide the first relevant data on the role of vitamin E which is specific to an endemic area of HBV-related HCC.

Should we proceed to an interventional trial to test the hypothesis of vitamin supplementation for the prevention of HCC? This question is not straight-forward if we consider the lessons learnt from previously reported phase III trials in other cancers. Over the past decades, several international cancer-prevention trials on oral vitamin E have reported disappointing results in prostate, lung and breast cancers (review in reference 2). For example, the 'SELECT' study which recruited 35,533 healthy men from more than 420 study sites from 2001 to 2004, addressed the question of whether vitamin E and/or selenium might protect against prostate cancer (13,14). In this study, participants were randomized into four groups, namely vitamin E supplement and matched placebo, selenium supplement and matched

placebo, both vitamin E and selenium supplements, or placebo only. After more than 7 years of follow-up, vitamin E supplementation was unexpectedly found to increase the risks of prostate cancer (13,14). One of the possible explanations of this result was the differential efficacy of the different subtypes of tocopherols in cancer prevention. In most of the interventional studies including the SELECT study, α -tocopherols are the main components of oral vitamin E supplements. Recently, there are growing preclinical evidence showing that γ - and δ -tocopherols are the more important vitamin E subtypes than α -tocopherols in the prevention of cancer (15,16). In fact, a number of recent preclinical studies suggested that α -tocopherols did not have cancer-preventing properties (17,18). It is possible that the wrong choice of vitamin E subtypes had been evaluated in some of the negative trials. Further studies are necessary to delineate the role of different subtypes of vitamin E in prevention of HCC before further large-scale studies on vitamin E should be conducted.

The dose of vitamin E used in cancer prevention studies may also be an important consideration when interpreting the results of these studies. For adults, the recommended daily dietary allowance of vitamin E is about 15 mg/day (19). On average, the amount of vitamin E in an ordinary daily diet is in the range of few mini-grams (e.g., one kiwifruit, one medium-sized tomato, and 100 g of broccoli consists of 1.1 mg, 0.7 mg and 1.3 mg of α -tocopherols, respectively). On the contrary, commercially available vitamin E tablets are usually composed of high 'supra-nutritional' levels of α -tocopherol, typically at a range of few hundred mini-grams. For instance, in the 'SELECT' study (13,14), the daily dosage of vitamin E was 400 IU of all *rac*- α -tocopherol acetate (approximately equivalent to 280 mg), which was much higher than the daily amount as derived from an ordinary diet. Further analysis of the 'SELECT' trial found that participants taking the vitamin E supplements had very high plasma level of α -tocopherol, which was associated with a reduction in the plasma level of γ -tocopherols (14). This finding suggests that the supra-nutritional dosage of α -tocopherol supplements could paradoxically deplete the level of other more 'protective' tocopherols, thereby increasing the risk of prostate cancer in the study. If we review the daily dosage of vitamin E in Zhang's study, the lowest quartile is 9.977 mg/day while the highest quartile is 16.176 mg/day (7). It is reasonable to deduce that the sources of vitamin E in most participants are mainly derived from natural food types rather than commercially available vitamin supplements. Although Zhang's study tells us that

dietary vitamin E intake is beneficial in lowering HCC risk, it is not clear whether additional supplements of vitamin E could protect against HCC. Therefore, it is too early to recommend to the general public to take extra vitamin E supplements based on the result of this study.

Finally, a large proportion of HCCs in China are etiologically linked to HBV infection. In patients with chronic HBV infection, hepatocarcinogenesis is accompanied by chronic process of necroinflammation in the liver (20). Large-scale cohort studies by different groups, including ours, have demonstrated that HBV viral load is a strong risk factor for HCC, and the use of anti-viral therapy against HBV infection, such as the nucleot(s)ide analogues, could significantly reduce the risk of HCC (21,22). Zhang *et al.* have elegantly shown in a subgroup analysis that the benefits of vitamin E remain valid in both populations with and without viral hepatitis (7). However, the study cohorts in Zhang's study were collected from 1997 to 2006, a period when potent antiviral nucleot(s)ide analogues were not yet widely available in the most parts of China. Nowadays, patients with chronic HBV infection in China will have more access to various antiviral treatments, and their viral loads should be lower compared with HBV-infected patients in Zhang's cohort. Since viral load is a powerful risk factor for HCC, it is unclear whether vitamin E may still offer added protection in populations where vaccination against HCC and anti-viral therapies are readily accessible. Before one can extrapolate the results of this study in HBV-endemic regions, further studies are crucial to determine the role of vitamin E in the prevention of HCC amongst selected populations of HBV-infected individuals with different levels of viral load.

In summary, the study by Zhang *et al.* provides solid epidemiological data on the protective role of dietary source of vitamin E on the risk of developing HCC. This study should re-ignite interests in the chemo-prevention of HCC using vitamin E. Future studies should be directed at the identification of the optimal subtype and dosage of vitamin E, as well as the target population which will most benefit from such intervention. Without the advancement of knowledge in these areas, it seems premature to head towards a randomized interventional trial, or recommending the routine use of vitamin E to prevent HCC at this point in time.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Nutrition and metabolism in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma is the fifth most common human cancer worldwide, with an overall 5-year survival in the range of 10%. In addition to the very substantial role of chronic viral hepatitis in causing hepatocellular carcinoma, nutritional status and specific nutritional factors appear to influence disease risk. This is apparent in the increased risk associated with non-alcoholic hepatic cirrhosis occurring in the context of obesity, the metabolic syndrome, and type 2 diabetes. Specific nutrients and ingested toxins, including ethanol, aflatoxin, microcystins, iron, and possibly components of red meat, also are associated with increased hepatocellular carcinoma risk. Other dietary components, including omega-3 fatty acids and branched chain amino acids, may have protective effects. Recent data further suggest that several metabolic regulatory drugs, including metformin, pioglitazone, and statins, may have the potential to decrease the risk of hepatocellular carcinoma. The available data on these nutritional and metabolic factors in causing hepatocellular carcinoma are reviewed with the goal of identifying the strength of current knowledge and directions for future investigation.

Keywords: Hepatocellular carcinoma; obesity; type 2 diabetes; branched-chain amino acids; metformin; statins

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Hepatocellular carcinoma (HCC) is a globally important disease by any measure. As the most frequently occurring primary hepatic malignancy, it represents the fifth most common human cancer and the second most common cause of cancer death worldwide (1), accounting for an estimated 500,000 fatal outcomes per year. These prevalence figures highlight a need for improved preventive strategies for HCC, especially in individuals known to be at increased risk. The medical challenges presented by HCC lie not just in the high incidence of the disorder, but also in its generally unfavorable clinical course, which includes a current overall mean 5-year survival from the time of diagnosis in the range of 10% (2). These unfavorable survival statistics clearly define a need for improved medical treatments and improved medical adjuncts to surgical treatment in patients diagnosed with HCC.

There is substantial clinical knowledge about factors predisposing to the development of HCC and potentially

influencing the response to treatment. Multiple epidemiological studies have established a particularly strong association between chronic hepatitis B (HBV) and hepatitis C (HCV) infection and the development of HCC. It is estimated that approximately 80% of HCC worldwide occurs in the context of infection by these viruses (3). The risk of developing HCC in chronically virus-infected individuals correlates not just with viral infection, but with the presence of chronic hepatic cirrhosis. This association may be a mechanistic consequence of inflammatory processes typically present in hepatic cirrhosis, as well as associated changes in hepatocyte turnover and differentiation following liver cell injury.

Beyond HBV and HCV infection, there is compelling evidence for the increased incidence of HCC in association with hepatic cirrhosis resulting from other causes. These non-viral causes include the genetic disorder hereditary hemochromatosis, in which hepatic inflammation and cirrhosis develop secondary to iron overload. While relatively

uncommon, hemochromatosis provides valuable insight into the potential for a metabolite or nutrient, in this instance the micronutrient iron, to induce an injury response in the liver leading to inflammation, cirrhosis, and increased risk of HCC. More common non-viral causes of HCC may similarly result from toxic effects of nutrients or metabolites in the liver, although the mechanisms are less well defined. Such disorders include chronic alcoholism, obesity, the metabolic syndrome, and type 2 diabetes.

A role for nutrients or metabolites in causing primary liver cancer may ultimately have its basis in the central role of the liver in the processing of ingested nutrients, the synthesis, degradation and storage of body fuels, and the clearance of ingested toxins. In addition to the effects of nutrition and metabolic factors in predisposing to the development of HCC, it is of interest to consider the role of nutrition and metabolic processes in influencing responses to treatment of established HCC. This includes the potential for nutritional status to influence responses to surgical or medical treatments, and the possibility of purposefully utilizing nutritional or metabolic factors as adjuncts to treatment.

Nutritional and metabolic factors in the genesis of HCC

HCC develops most commonly in the setting of chronic hepatic cirrhosis. In hepatitis virus-associated HCC, 70-90 percent of HCC patients with chronic HBV and an even higher percentage of HCC patients with chronic HCV infection are reported to have hepatic cirrhosis (4,5). There is evidence that the specific mechanisms of progression to HCC may differ in these two types of viral infections, with a stronger role for elevated oncogene levels in HBV and more prominent inflammation-driven cell turnover responses in HCV (6,7). Irrespective of these initiating mechanisms, it is thought that the association of HCC and hepatic cirrhosis ultimately reflects their shared development as consequences of accelerated hepatocyte proliferation and turnover, with progressive emergence of sclerotic, dysplastic nodules in the liver parenchyma containing poorly differentiated hepatocytes that can transition to cancerous cells.

Hepatic cirrhosis and an associated increased risk of developing HCC independent of viral hepatitis frequently occurs consequent to fatty liver disease, which often has a nutritional basis. A well recognized example of this is the increased risk of HCC in alcohol-induced liver cirrhosis. Ethanol represents a specific macronutrient with metabolic

properties overlapping those of dietary fat. While its metabolism in the liver generates caloric energy, ethanol also exerts toxic effects that can cause cellular injury and a reactive response culminating in hepatic cirrhosis. The extent of hepatic injury and the resulting proliferative and fibrotic response appears to be influenced by genetic factors and also by the not infrequent co-occurrence of HCV infection in individuals with chronic alcoholism. Epidemiologic data have raised the possibility that chronic alcohol exposure and HCV infection may not only have individual effects, but that these two factors may act synergistically to further augment risk of developing HCC (8).

Nonalcoholic fatty liver disease (NAFLD) has more recently been recognized as another important nutrition-related disorder associated with increased risk for hepatic cirrhosis and HCC. NAFLD is defined as the accumulation of hepatic intracellular triglycerides in individuals consuming less than 20 gm of alcohol per day (9). NAFLD often develops in the context of obesity, and it is particularly associated with central (visceral) obesity and with other features of the metabolic syndrome, including hypertension, dyslipidemia, and type 2 diabetes mellitus (1,10). As the prevalence and severity of obesity have increased worldwide in association with population level increases in daily calorie intake and decreases in exercise, the prevalence of NAFLD has become progressively more common, such that it now is the most frequently reported liver disorder in industrialized countries (11). Although the pathogenesis of NAFLD has not been fully elucidated, insulin resistance is thought to have an important mechanistic role in driving the accumulation of lipid stores in the liver (12). The frequent occurrence of insulin resistance in individuals with obesity and the metabolic syndrome thus may explain the epidemiological association of NAFLD with these disorders. While NAFLD may be a relatively benign abnormality in many individuals, a substantial subset of patients with NAFLD develop an associated inflammatory response. This disorder, which is designated nonalcoholic steatohepatitis (NASH), appears quite similar to alcoholic hepatitis on liver biopsy. As with alcohol-induced steatohepatitis, NASH progresses to cirrhosis and liver failure in a substantial percentage of patients, and it represents an important risk factor for the development of HCC (13). The mechanistic processes driving hepatocyte proliferation, dedifferentiation, and evolution to HCC in NASH are not well understood, but may involve the combined effects of insulin resistance (with altered insulin and insulin-like growth factor pathway signaling), inflammation, and oxidative injury. The exact

prevalence of NASH in individuals with NAFLD is difficult to establish, because the diagnosis of NASH requires liver biopsy, and this is not routinely done in NAFLD. It is likely, however, that the subset of individuals with NASH largely accounts for the increased incidence of HCC in obesity-associated NAFLD. Both NAFLD and NASH occur in association with type 2 diabetes, and it is thought that the development of NASH and its progression to hepatic cirrhosis is a major factor accounting for the approximately 2-fold increased risk of HCC in type 2 diabetes documented in several meta-analyses (14-16).

There is a need for better understanding of the metabolic events that lead to liver fat deposition and the transition from steatosis to steatohepatitis in the context obesity and the metabolic syndrome. In this regard, studies in mice genetically engineered for deficiency in the rate-limiting enzyme for hepatic triglyceride and glycerophospholipid synthesis, glycerol-3-phosphate acyltransferase 1 (GPAT1), have demonstrated protection of these animals against hepatic fat accumulation during high-fat diet feeding (17). The *Gpat1*^{-/-} mice have not only decreased liver fat accumulation on a high-fat diet, but also decreased formation of hepatic foci, adenomas, and HCC (18). This mouse model offers the potential to further examine whether the decrease in GPAT1 enzyme activity is protective against the development of HCC through the lowering of levels of specific toxic lipid metabolites or a more general effect on hepatocyte turnover (19). Perhaps more importantly, the recognition that the activity of a specific enzyme can profoundly influence the amount of hepatic fat accumulation on a lipogenic diet could prove to have practical relevance to human hepatic steatosis and the progression to steatohepatitis. A better understanding of human genetic variability in the *GPAT1* gene and genetic factors controlling expression of the *GPAT1* gene and related pathways might lead to strategies for identifying individuals particularly at risk for developing hepatic steatosis or progressing from steatosis to steatohepatitis and HCC. It can be further hypothesized that the GPAT1 protein, plus related endogenous factors influencing hepatic lipid synthesis, such as the bile acid-activated farnesoid X receptor (20), may prove useful as targets for the development of new drugs that can decrease the development of fatty liver or the transition to steatohepatitis and HCC in susceptible individuals.

In considering the mechanisms leading from hepatic steatosis to steatohepatitis and HCC, it has been hypothesized that specific toxic lipid metabolites may drive both the inflammatory response, and the altered

hepatocyte proliferation and differentiation characteristic of steatohepatitis. In a sense, such toxic lipid metabolites might be seen as endogenously generated equivalents of ingested micronutrients and toxins with known links to the development of HCC. The role of ingested toxins in causing HCC has been well established though the examples of the fungal toxin, aflatoxin, and the blue-green algae toxin, microcystin (21,22). While exposures to these toxins are common only in specific geographic locations and uncommon worldwide as causes of HCC, their powerful effects illustrate the potential for specific toxins to induce HCC. In contrast to these toxic substances, which are not normally part of the human diet, iron represents an ingested micronutrient in the normal diet with the potential to cause HCC when absorbed in excess. High levels of ingested iron in certain populations, for example among Sub-Saharan Africans, has been associated with a substantially increased risk of HCC (23). The impact of iron overload as a cause of HCC has been most extensively investigated in the context of hereditary hemochromatosis, which results from a genetic defect causing increased absorption of dietary iron. Hepatocellular oxidative injury resulting from elevated iron levels is thought to mediate hepatic cirrhosis and inflammation in hereditary hemochromatosis, leading to a 20-fold or greater increased risk of HCC (24). Studies on hemochromatosis have further shown that the prevention or remediation of iron overload with chelating agents can decrease the risk of developing HCC (25). One can speculate that additional yet unidentified macronutrients or micronutrients may explain the reported increases in HCC risk associated with the consumption of red meat or saturated fats (Freedman *et al.*, Cross *et al.*) (26,27).

Role of nutritional and metabolic interventions in reducing HCC risk

It is of interest to consider potential protective effects of nutritional factors in decreasing risk for developing HCC. Multiple epidemiological studies have demonstrated increased risk of HCC in association with obesity, but it is important to appreciate that weight loss in obese individuals has not yet been convincingly shown to decrease HCC risk. While this appears logical given the positive association between obesity and HCC, adequately powered studies comparing HCC incidence in individuals who have achieved and maintained weight loss in comparison with persistently obese subjects are needed. The widespread use of bariatric surgical procedures and the marked degree of

weight loss achieved in most of these patients may provide an opportunity to test the effects on HCC risk, as would more effective weight loss drugs.

In contrast with obesity treatment, which involves decreasing overall nutrient intake, there are intriguing data suggesting that increased intake of branched chain amino acids (BCAA), as specific nutrients, may protect against the development of HCC. This concept has its basis in the long-standing observation that the BCAA/aromatic amino acid ratio is typically decreased in hepatic cirrhosis. There may thus be a relative deficiency of BCAA in cirrhotic patients, which is hypothesized to result from the combined effects of changes in nutritional intake, catabolic processes, and ammonia detoxification in association with compromised liver function (28). The administration of BCAA-enriched nutrition in the context of hepatic cirrhosis has been shown to decrease insulin resistance (29) and also has the potential to alter hepatic redox state and augment immune system function (30). These consequences of BCAA supplementation in a state of relative BCAA deficiency might be predicted to lower the risk of HCC.

In a study published several years ago, the oral administration of 12 gm BCAA/day, in comparison with a diet matched in energy and protein intake, to patients with cirrhosis and liver dysfunction appeared to decrease incident HCC in a subgroup of the BCAA-treated subjects with a relatively high BMI and elevated alpha-fetoprotein levels (31). Further evidence for this effect of BCAA feeding is provided in a more recent controlled, prospective study on patients with both compensated and decompensated cirrhosis and no prior history of HCC (32). In 56 BCAA-treated subjects, oral administration of 12 gm BCAA per day as a dietary supplement for at least 6 months resulted in a decrease in HCC incidence in the BCAA-treatment group in comparison with 155 controls (hazard ratio 0.46, CI, 0.216-0.800, $P=0.0085$). While the magnitude of the effect is substantial, it will be important to confirm this finding in a larger number of subjects and investigate different population groups. In addition, longer term studies are needed to better distinguish between the potential alternative actions of BCAA supplementation in affecting the emergence of new foci of HCC *vs.* delaying the presentation of pre-existing HCC.

As additional specific dietary factors that should be further investigated, the ingestion of fish and omega-3 fatty acids have been associated with decreased risk of HCC through mechanisms that are not yet understood (33). Similarly, coffee ingestion has been associated with decreased risk of HCC in

two meta-analyses (34,35). This could hypothetically result from either antioxidant effects or a decrease in hepatic cirrhosis and hepatocyte turnover mediated by components of coffee. Understanding the potential role of such dietary interventions in modifying HCC risk in vulnerable individuals is limited in general by a lack of prospective, controlled studies. The challenge is to design studies of adequate power and duration in the context of slow and variably progressive cirrhosis and development of HCC.

As an alternative approach to modifying the metabolic milieu in individuals at increased risk for HCC, there is substantial current interest in the potential for metabolic regulatory drugs to decrease the risk of HCC as well as several other cancer types. As noted above, type 2 diabetes is associated with an approximately 2-fold increased incidence of HCC (14-16). It is hypothesized that insulin resistance, which is commonly present in type 2 diabetes and obesity, may be a causal factor in the development of HCC through mechanisms that could include direct trophic actions on hepatocytes (36) and indirect effects in promoting hepatic lipid deposition, NAFLD, and NASH (37). Metabolic regulatory drugs that decrease insulin resistance and lower insulin levels may therefore have the potential to decrease the risk of HCC in insulin resistant states. This concept is supported by recent observational and retrospective case-control studies that have shown a very strong inverse correlation between use of the insulin-sensitizing drug metformin and the development of HCC in patients with type 2 diabetes, with a relative risk on the order of 0.15 (38,39). The magnitude of the metformin effect is compelling even in the absence of prospective, controlled trials on metformin and HCC, which have not yet been reported. Metformin might lower HCC risk by decreasing insulin resistance and ameliorating hyperinsulinemia, and there also are multiple other molecular mechanisms that could contribute to anti-tumor effects of the drug. These include potential direct anti-tumor actions from metformin activation of AMPK, leading to increased levels of the LKB1 tumor suppressor, or modified signaling via cell growth regulatory pathways, such as mTOR (40,41). Additionally, metformin has the potential to decrease the development of HCC indirectly by suppressing hepatic fat deposition, or through anti-oxidant, anti-inflammatory, growth inhibitory, or anti-angiogenic actions (42-44).

More limited data on a second insulin-sensitizing drug, the thiazolidinedione, pioglitazone, further support the potential role of insulin resistance and insulin sensitizing drugs in modifying HCC risk. In a recently published large

population-based study in Taiwan, the incidence of HCC was confirmed to be increased in type 2 diabetes, with an adjusted hazard ratio of 1.7, and this risk was decreased in individuals on pioglitazone (hazard ratio 0.56) (45). The same study also showed decreased risk of HCC with metformin (hazard ratio 0.49). Further investigation will be required to confirm the metformin and pioglitazone effects and to examine the multiple possible causal mechanisms.

As another class of metabolic regulatory drugs, there has been recent interest in a role for statins in decreasing the risk of developing HCC. Observational studies initially suggested that statins may decrease risk for multiple cancer types (46-49), although these anti-tumor effects of statins have not been confirmed in meta-analyses of randomized trials (50-54). Data specifically on HCC risk with statin treatment are more limited, but also have been conflicting. A population based study in Taiwan showed decreased HCC risk in association with statins (55), whereas no association was observed in a Danish study (47). A nested case-control study reported that statin use in diabetes patients was associated with decreased risk of HCC (56). Most recently, a very large population-based study in HBV patients in Taiwan showed a significant decrease in HCC incidence with statins, which appeared to be dose-related (hazard ratio of 0.34 with statin use for more than 365 days) (57). Potential mechanisms proposed for decreased HCC risk with statins include disruption of the generation of geranylgeranyl pyrophosphate and farnesyl pyrophosphate (thus interfering with the growth of malignant cells), inhibition of the proteasome pathway (and consequent interference with mitosis), and inhibition of cholesterol synthesis (resulting in slower HBV replication) (57).

Nutritional and metabolic factors in HCC treatment

In patients with established HCC undergoing treatment, optimal nutritional management has potential benefits on morbidity and mortality. The treatment of choice for HCC, when feasible, is complete tumor resection. This often requires removal of a significant portion of cirrhotic, functionally compromised liver. Postoperative nutrition support appears to be an important factor in the success of such surgical procedures (58,59), possibly serving to both improve hepatocyte survival and promote a regenerative response in remaining liver segments. Preoperative nutritional status, as well as postoperative management, may also be a key determinant of success in liver resection,

although this has been less extensively investigated (60). Since preoperative nutritional status might simply serve as a surrogate index for the state of advancement of liver disease in association with HCC and the extent of remaining viable liver function, more data are needed to clarify the potential benefits of preoperative nutritional interventions in promoting survival and recovery from HCC resection surgery.

For patients with advanced HCC who are not candidates for resection, further study is needed to evaluate several nutritional or metabolic interventions with theoretical potential for clinical benefit. These include modifications in macronutrient composition of the diet, such as the use of BCAA supplementation (32), and consideration of micronutrient modifications, such as iron chelation even in the absence of hemochromatosis (61). There also is a need to further investigate opportunities for pharmacologically targeting nutritional and metabolic pathways as adjuncts to the treatment of non-resectable HCC. In this regard, an inhibitor of the nutrient-regulated mTOR pathway in currently is in phase III trials for the treatment of HCC (62). Agents that modify the GPAT-1 linked pathways or the bile acid-activated farnesoid receptor are of theoretical interest as adjuncts to HCC (see discussion of these pathways above), although clinically practical examples of such compounds have not yet been developed.

Summary and conclusions

There are compelling clinical data implicating nutritional status (exemplified by obesity) and metabolic state (e.g., type 2 diabetes) as risk factors for HCC. The impact of these nutritional and metabolic disorders as causal factors in HCC can be expected to increase substantially, if the prevalence of obesity and type 2 diabetes continue to rise as predicted over the next several decades. It is likely that these and other nutritional factors operate through multiple mechanisms influencing the development of HCC, both in the presence and absence of chronic hepatitis virus infection.

Although nutritional and metabolic mechanisms may have causal roles in the development of HCC, it has not yet been possible to translate current knowledge into mechanistic- or evidence-driven guidelines for nutritional management of individuals at risk for HCC or being treated for HCC (63). It is possible, however, to define specific questions and areas of investigation with considerable promise for informing nutritional and metabolic approaches

to reducing risk of HCC and managing existing HCC. One important goal is determining whether there are strategies for weight reduction in obese individuals that can decrease the risk for HCC. Using NAFLD and NASH as surrogates for HCC risk, and ultimately directly assessing incident HCC, it will be important to link effects on HCC risk to specific patient groups (e.g., obese subjects with or without the metabolic syndrome), as well as the magnitude of weight loss. It also will be important to assess the impact of different strategies for achieving weight loss, including specific diet protocols, bariatric surgery, and a now increasing spectrum of pharmacological agents for weight loss in obesity. Studies currently in progress should help to resolve the question of whether metformin has clinically useful benefit in ameliorating the increased risk of HCC in type 2 diabetes, and whether there may be role for metformin in prediabetes. There is need for a better understanding of the mechanisms of anti-neoplastic effects of metformin, as well as the potential effects on HCC risk of other existing pharmacological agents, such as the thiazolidinedione, pioglitazone. Similarly, more clinical and mechanistic data are needed on the potential effects of statins on HCC risk. This might be helpful not only in determining whether the use of statins to reduce HCC risk is indicated in some groups of patients, but also whether there may be other useful strategies for modifying HCC risk linked to the ingestion or metabolism of complex lipids.

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Footnote

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Multifocal hepatocellular carcinoma: intrahepatic metastasis or multicentric carcinogenesis?

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Abstract: Multifocal hepatocellular carcinoma (HCC) may be multiple HCCs of multicentric origin (MO) or intrahepatic metastases (IM) arising from a primary HCC. Numerous attempts to differentiate the two types of multifocal HCC have been made including the valuation of the clinicopathologic characteristics of MO and IM patients and the recurrence time, loss-of-heterozygosity analysis of specific DNA microsatellite loci to distinguish multiclonal MO from IM of monoclonal origin, and the research of diagnostic and progression markers through genomic and proteomic analyses. These approaches, however, have been unsatisfactory hitherto. Recently, a multi-omic analysis of HBV-related multifocal HCCs, including intergraded genomics and transcriptomics, was performed and the results, validated by a cohort of 174 HCC patients, were correlated with HCC clinicopathological data. The two multifocal HCC types were effectively discerned by multi-omics profiling that could predict HCC clonality and aggressiveness. Further, the dual-specificity protein kinase *TTK* was recognized as a prognostic marker for HCC. Multi-omics strategy potentially opens new perspectives for the diagnosis, prognosis and personalized treatment of multi-focal HCC. Further work aimed at extending this strategy to HCC with other etiology, simplifying the analysis, and reducing its costs is necessary for its routine clinical application.

Keywords: HCC recurrence; multifocal HCC; multi-omics profiling; genomics; proteomics

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Hepatocellular carcinoma (HCC) is a frequent and deadly human disease, with 0.25-1 million new cases per year (1). HCC incidence varies with age, sex, and geographic region, the major number of cases coming from Asia, followed by Europe, Africa, North America, Latin America and Caribbean (2). The distribution of HCC cases among different populations reflects the differences in the exposition to different etiological factors. Hepatitis B virus (HBV) infection is a public health problem with approximately 2 billion people that have been exposed to the virus, and chronic HBV infection is the dominant risk factor for HCC in Eastern Asia and Sub-Saharan Africa (3). In recent years, a better knowledge of mutational and epigenetic events deregulating the signaling pathways involved in tumor progression, and the definition of genetic variants of HCC predicting disease outcome led to the identification of new potential prognostic markers and targets for molecular-

based personalized therapies (4,5). Indeed, biomarkers with acceptable levels of sensitivity and specificity have been used, in recent years, to screen for and diagnose HCC, allowing in some cases early detection of HCC nodules in relatively high percentages of patients (6).

Multifocal hepatocarcinogenesis

Early HCC could be cured by surgical resection. However, a serious problem concerning this treatment is represented by the propensity to multifocal occurrence of this disease, which is responsible for frequent recurrences that largely influence its outcome. Multifocal HCC may be multiple HCCs of multicentric origin (MO), as well as intrahepatic metastases (IM) arising from a primary HCC (*Figure 1*). Different studies have documented that MO recurrences are more frequent than IM (7-9), but a recent report

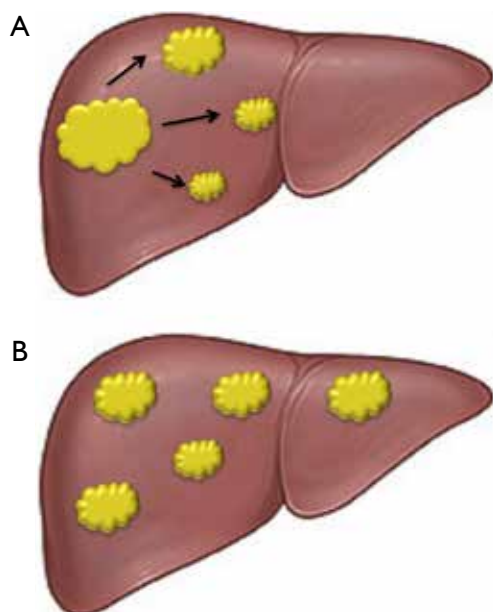


Figure 1 Schematic representation of two types of multifocal liver carcinogenesis. (A) Primary hepatocellular carcinoma with intrahepatic metastatic spreading; (B) development of multiple independent hepatocellular carcinomas.

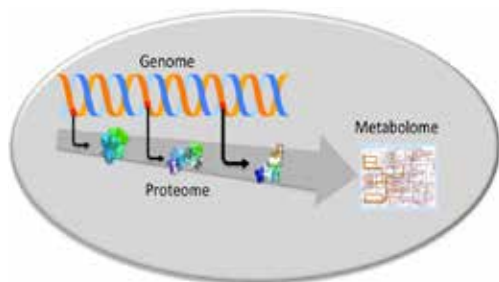


Figure 2 Schematic representation of the multi-omic analysis covering the path from genes, to proteins and metabolism.

claims higher frequency and poorer prognosis of IM-type recurrences (10).

The differentiation of the two types of multifocal HCC is crucial because of their different clinical course and response to treatment. Numerous attempts to a differential diagnosis have been made in recent years. The comparison of clinicopathologic characteristics of MO and IM patients evidenced that MO HCC patients might have a favorable outcome compared to IM patients. Moreover, the presence of hepatitis B surface antigen (HBsAg), cumulative tumor size, tumor nodules location, cirrhosis, portal vein and/

or microvascular tumor embolus and histological grade of the primary tumor may represent important discriminating factors (11). Other diagnostic criteria are based on the recognition of early recurrence, resulting from IM, and late recurrence indicating probable MO (12). The identification of patients at risk of recurrence is of prime importance to increase the chance of performing potentially curative interventions. Loss-of-heterozygosity analysis of specific DNA microsatellite loci has also been performed in the attempt to distinguish IM, of monoclonal origin, from multicentric MO, probably arising from different preneoplastic lesions of cirrhotic liver (13,14) (*Figure 1*).

The omic approach

According to a common opinion the approaches merely based on morphologic and clinicopathologic criteria do not allow an accurate distinction between the different types of multifocal HCC (13,14). Therefore, new efforts have been recently dedicated to the research through omic analysis of new biologic mechanisms and molecular markers to better characterize multifocal HCC. The omic strategy includes the research of diagnostic and progression markers through genomic, proteomic and metabolomic analyses in order to evaluate gene, protein and metabolic deregulations (*Figure 2*).

The DNA microarray technology is currently used to identify specific gene-expression signatures of HCC. Recently this analysis has been exploited to predict early HCC recurrence due to intrahepatic metastasis (15). However, no well-defined predictors for late recurrence have been discovered (15). Some studies focused on the status of non-tumorous liver to predict late recurrence possibly due to *de novo* hepatocarcinogenesis, based on the idea of “field cancerization” (15), but not conclusive results have been obtained so far. In a recent study (16), the gene expression signature of metastatic primary HCCs has been found to be similar to that of their corresponding IMs, implying that genetic deregulation responsible for metastasis initiates in the primary tumors. Adrenomedullin (*AM*) gene has been identified, in the gene expression signature, as a leader gene overexpressed in HCCs with IM (16). A different gene expression profile was observed in multicentric HCCs (16).

One important new trend to delineate HCC biomarkers is the proteomic approach to identify proteins that differ in expression levels in liver tissue or in plasma during the progression from liver fibrosis, cirrhosis or steatohepatitis to HCC (17). The same approach has been used with reference to molecular diagnosis and metastatic recurrence

of HCC (18). However, researches focusing on the study of the pathogenesis of IM and MO by proteomic approach are at their beginning. According to a recent report (19), a total of 1,025 and 900 spots indicative of protein overexpression have been found in expression profiles of patients with IM and MO, respectively. The spots indicative of decreased expression were 52 and 98, for IM and MO cases, respectively. The expression levels of 25 proteins were statistically different between the two groups of patients. Unfortunately this study has been done on a limited number of patients (10 IM and 5 MO cases) and the results have not been validated on a large patients' cohort. Therefore, it is not possible to estimate if the newly identified proteins are actually potential biomarkers for identifying the multinodular HCC of clonal origin and discriminating between IM and MO cases.

A really innovative research, in this field, has been recently published by Miao and coworkers (20) who performed a multi-omics analysis to differentiate the MO *vs.* the IM disease, by decoding molecular differences between the two multifocal HCC models and recognize molecular markers for diagnosis and prognosis, as well as therapeutic targets. They evaluated the intrahepatic HCC lesions, and matched non-cancerous liver tissue and blood obtained from representative patients with HBV-related multifocal HCC who underwent tumor resection and exhibited distinct postsurgical courses. The samples were subjected to multi-omic analyses, integrating genomics and transcriptomics, and the results, further validated by a cohort of 174 HCC patients, were correlated with the clinicopathological data.

Two patients with multifocal HCC were identified. The patient I (PI) was cirrhotic and presented a multifocal poorly differentiated HCC. The patient II (PII) was non-cirrhotic and presented a well-differentiated multifocal HCC. It was hypothesized that PI was affected by an HCC with IM and PII by synchronous primary HCC development, with no spreading or metachronism. Tissues from multiple lesions for PI were: peripheral blood (PI-B), surrounding noncancerous liver (PI-N), primary HCC (PI-P), IM (PI-M1, PI-M2, and PI-M3), and a portal vein tumor thrombus (PI-V). Tissues from PII included: peripheral blood (PII-B), noncancerous liver (PII-N), and two HCCs located in the left (PII-L) and right lobes (PII-R). PI-N, PI-B, PI-P, PI-M1, PI-V, PII-N, PII-B, PII-L, and PII-R were used for next generation sequence, and the same tissues plus PI-M2 and PI-M3 were used for PCR validation. The determination of HBV integration in the different lesions clearly suggested the existence of different

tumor clonality, in agreement with the different patterns of the multifocal tumors, in the two patients analyzed.

The evaluation of genomic alterations showed similar mutation patterns in all tumor tissues of PI, whereas the two HCCs of PII exhibited distinct mutation profiles. Further, significant enrichments of p53 signaling were present in all PI HCCs, whereas no cancer-related pathways were enriched in the PII tumors. Interestingly, the presence of the same deletions and amplifications in PI-P, PI-M1, and PI-V, with some differences between PI-M1 and PI-V, indicated the appearance of further selective mutations in HCC subclones during the formation of metastases. In PII HCCs different copy number variations occurred between PII-L and PII-R.

Importantly, the construction of a phylogenetic tree to predict the temporal development of each tissue, regardless of their germline differences, revealed that PI-M1-3 were phylogenetically most distant from the putative germline, with respect to PI-P, PI-V, or PI-N. Moreover, the sequence of PI HCCs development indicated that the portal vein tumor thrombus (PI-V) developed from the primary PI-I tumor and was followed by the metastatic lesions (PI-M1-3). These observations explained the genomic similarities of all PI HCCs indicating their origin from portal venous blood. Different patterns of the two PII HCCs were found, indicating that they were distant from germline and from each other, which implicates synchronous development of distinct clones.

These observations were in good agreement with the results of transcriptomic analysis that showed a stronger association of gene deregulation between the PI HCCs, indicative of genetic similarities between the metastases and the primary HCC in PI. In contrast, distinct patterns of transcriptomic dysregulation occurred in each PII HCCs, suggesting the existence of non-invasive phenotypes of PII HCCs developing from different premalignant clones of non-cirrhotic liver. Furthermore, it clearly appeared from the analysis of the deregulation of key genes and major signaling pathways, that neither PII HCC displayed molecular signatures of metastasis, which were instead found in PI HCCs. In complex, transcriptomic analysis substantiated the genetic alterations identified by genomic analysis.

Protein analysis also revealed the presence in all PI of similar metabolic alterations regarding changes in coenzyme metabolism and energy generation by mitochondrial oxidative phosphorylation, perturbations of carbohydrate catabolism and aerobic glycolysis, increases in nucleic acid metabolism, protein translation and transport, cell

cycle, cell proliferation, and cell migration. Upregulation of genes involved in metastases formation, such as genes related to cytoskeletal remodeling and extracellular matrix organization was only found in PI-M1. In contrast, metabolic deregulation patterns were prevalently different in PII HCCs.

An important aspect of the study by Miao and co-workers (20) is the validation of the results of the multi-omic approach on a cohort of 174 patients with HBV-related HCC, in the attempt to identify new diagnostic and prognostic biomarkers for HCC. By the use of the BioCarta or KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways databases (21,22), the enrichment of pathways including cell cycle, p53 signaling, histidine metabolism, G2/M checkpoint, and Ran (Ras-related nuclear protein)-mediated mitotic spindle regulation was exclusively found in PI HCCs. Validation analysis confirmed the upregulation of six out of seven genes, such as: Histidine ammonia-lyase (*HAL*), stratifin, 14-3-3 γ (*SFN*), kinesin superfamily protein 15 (*KIF15*), dual-specificity protein kinase (*TTK*), Budding uninhibited by benzimidazoles 1, *s. cerevisiae*, homolog of (*BUB1*), and minichromosome maintenance, *s. cerevisiae*, homolog of, 4 (*MCM4*). Different clinicopathologic features of HCCs were significantly associated with at least one of these genes. In addition, the evaluation of the relationships between the expression of above genes and the metastatic potential and postsurgical recurrence strongly suggested that *TTK* expression could be an independent prognostic indicator of HCC patients.

Conclusions and future perspectives

One of the important results of the multi-omic analysis of multifocal HCC, performed by Miao and coworkers (20) was the possibility to discern between the synchronous development of multicentric primary HCC and the metastatic disease. Furthermore, the integration of genomic and transcriptomic analyses with clinicopathologic features led to the identification of HCC biomarkers, validated with a large number of HCC patients.

In addition to the possibility to differentiate MO from IM, multi-omics profiling could provide essential information to evaluate the aggressiveness of existing lesions and apply personalized therapies, including postsurgical treatment. In this respect, it must be considered that the presence of several nodules in IM cases exhibiting various molecular alterations, indicative of differences in the progression of single lesions, requires multi-omic analysis

of each new nodule in order to identify critical molecular lesions and to try their adjustment. Less aggressive MO cases may take advantage from the treatment of the underlying liver disease and from the resection of recurrences.

Another interesting result of the multi-omic approach performed by Miao and coworkers (20) is that the analysis of a single gene, *TTK*, led to the accurate prediction of early recurrence. This represents a valuable advantage with respect to gene-expression profiling studies that suggest multi-gene scores to predict recurrence and survival. In addition, when a specific genetic alteration predicting early recurrence is diffusely present in the liver, its detection by needle biopsies may allow chemopreventive strategies.

Although the multi-omics strategy potentially opens new groundbreaking perspectives for the diagnosis, prognosis and treatment of multi-focal HCC, it still presents some important limitations. The analysis regarded only HBV-HCC and should be extended to HCC caused by HCV infection, aflatoxin B1, alcoholism and metabolic diseases. Moreover, its clinical application could be seriously limited by the complexity of the analysis and the elevated costs. Nonetheless, the innovative results of the multi-omic approach propose new efforts to overcome these drawbacks.

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Footnote

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Statins: emerging role in chemoprevention for hepatocellular carcinoma?

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Statins have well established efficacy in reducing morbidity and mortality from coronary artery disease in both the primary and secondary setting (1,2). This is almost certainly achieved by reduction in plasma LDL levels and other purported circulatory/anti-atherosclerotic effects (3). Beyond its therapeutic value in cardiovascular disorders, there is now emerging interest in developing statins as an anti-cancer agent. Inhibition of 3-hydroxy-3-methylglutaryl CoA reductase by statins impede the rate-limiting step of mevalonate pathway leading to reduced levels of mevalonate and its downstream products which are important in cellular homeostasis, cell signalling, protein synthesis and cell cycle progression. Growth inhibitory signals exerted by statins in cancer cell lines and tumor-bearing animal models further support potential pro-apoptotic, anti-proliferative and anti-invasive properties (4). Aberrant regulation of cholesterol homeostasis has also been associated with cancer pathogenesis. Interestingly there has been recent genetic link identified between cholesterol and cancer risk further providing rationale for cholesterol targeting as a therapeutic or preventive strategy. Smith *et al.* (5) demonstrated anti-cancer function of cholesterol exporter ABCA1 (ATP-binding cassette transporter AI) in cell lines. Defective cholesterol efflux following suppression of ABCA1 gene expression in response to oncogenic mutations or loss of function mutation has been implicated in malignant cell transformation. ABCA1 deficiency allows for elevated mitochondrial cholesterol which supports cancer cell survival.

A number of epidemiologic studies have investigated the effects of statins on reducing site-specific cancer incidence and overall cancer incidence with contrasting conclusions. A nested case-control study including 6,721 beneficiaries

of health care plan in Quebec selected between 1988 and 1994 found a 28% reduction in risk of any cancers among users of statins compared to bile acid binding resins (rate ratio 0.72; 95% CI, 0.57-0.92). There was however no association between specific cancer sites and statin usage (6). The use of statins was associated with a 47% relative reduction in the risk of colorectal cancer in a case control study in Israel. In this study the use of statins for at least five years was associated with a significantly reduced relative risk of colorectal cancer which remained significant after adjustment for other confounders (7).

In contrast to the above mentioned study by Poyner *et al.* (7), a case-control study based on Cancer Prevention Study II Nutrition Cohort found no association between use of cholesterol-lowering drugs and colorectal cancer incidence among 132,136 men and women. Use of cholesterol-lowering drugs was not associated with colorectal cancer incidence (multivariable adjusted rate ratio =1.03, 95% CI, 0.85 to 1.26). Use of cholesterol-lowering drugs for 5 years or more was also not associated with colorectal cancer incidence (rate ratio=1.09, 95% CI, 0.83 to 1.43) (8). The associations of statins and other-lipid lowering drugs with breast cancer risk were assessed in the Nurses' Health Study. A total of 79,994 women were followed prospectively for up to 12 years. Compared with nonusers, lipid-lowering drug users experienced similar breast cancer risk (multivariate relative risk, 0.99; 95% CI, 0.86-1.13). Current use of statins also was not significantly associated with breast cancer risk (relative risk, 0.91; 95% CI, 0.76-1.08). There was also no association between cancer risk and duration of drug use in this cohort study (9).

The epidemiologic studies all had some limitations regardless of their conclusions. Differences in study

methods and study populations are likely to account for some of the variations in the results observed. Moreover, interpretation of these studies needs to be done with caution due to residual confounding and unaccounted effect modifications.

At least 2 randomized controlled trials investigating the effect of statins on cardiovascular outcomes reported an increased risk of cancer incidence. Lowering the cholesterol levels in patients with prior myocardial infarction with average levels of LDL with pravastatin has been shown to reduce risk of coronary events. The frequency of fatal coronary events was 10.2% in the pravastatin group versus 13.2% in the placebo group, an absolute difference of 3% and a 24% reduction in risk (95% CI, 9-36%, $P=0.003$). This study however showed a higher incidence of breast cancer among patients who received pravastatin compared to the patients who received placebo, 12 versus 1 ($P=0.002$) (10). In another randomized controlled trial, pravastatin lowered LDL cholesterol concentrations by 34% and reduced the incidence of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke to 408 events compared with 473 on placebo (HR 0.85, 95% CI, 0.74-0.97, $P=0.014$) in the elderly. New cancer diagnoses were however more frequent on pravastatin than on placebo (HR 1.25, 95% CI, 1.04-1.51, $P=0.020$) (11).

A number of meta-analyses have also contributed insights into the association between statins and cancer incidence. In contrast to observational studies, the meta-analyses consistently reported a lack of association between statins and cancer risk. Herbert *et al.* (12) reported a meta-analysis of 16 trials that included approximately 29,000 patients with average follow up of 3.3 years, and found no reduction in risk of cancer with statins with a relative risk ratio of 1.03 (95% CI, 0.90-1.17). Dale *et al.* (13) reported a meta-analysis of 26 randomized controlled trials including 86,936 patients, each with a minimum follow up of 1 year and a minimum of 100 patients and found an odds ratio of 1.02 (95% CI, 0.97-1.07) for cancer incidence based on 20 studies and an odds ratio of 1.01 (95% CI, 0.93-1.09) for cancer mortality based on 22 studies. Bonovas *et al.* (14) reported a literature based meta-analysis of 35 randomized control trials including 109,143 individuals with an average follow up of 4.5 years and showed no evidence for association between statin therapy and overall cancer risk (relative risk 0.99; 95% CI, 0.94-1.04). Within the same publication, a separate meta-analysis restricted to trials with a minimum duration of 3 years and which enrolled at least

3,000 patients was performed. A total of 78,000 individuals were included with an average follow up of 5.3 years. Once again there was no association between statins therapy and overall cancer risk (relative risk 1.01; 95% CI, 0.96-1.06). More recently, the Cholesterol Treatment Trialist (CTT) Collaboration (15) reported an individual patient data meta-analysis involving 169,618 individuals. No increased risk of cancer incidence or death was detected after median follow up of 4.9 years.

These randomized controlled trials and meta-analysis do suffer from limitations in assessing the relationship between statins and cancer risk. The trials were not powered to assess secondary outcomes such as cancer and follow up periods were relatively short compared to the long latency period of cancer. Although meta-analysis of randomized trials attempt a more objective appraisal of the evidence and serve as a tool for studying rare and unintended effects of treatment, the results ought to be interpreted with caution. The limitations include short follow up period, inconsistent duration of statins use, failure to evaluate the dose/duration association and perhaps failure to account for different types of statins used.

In summary the findings from numerous observational studies and meta-analysis indicate a lack of association between statins therapy and cancer incidence.

The effect of statins on incidence of hepatocellular carcinoma (HCC) has not been as extensively studied. Tsan *et al.* (16) recently reported that statins exposure may reduce the risk of HCC in patients with hepatitis B virus (HBV) infection in a population based cohort study in Taiwan. 33,413 patients with HBV infection were followed up from 1997 to 2008, of which 8.3% had documented statins usage. The incidence of HCC in patients on statins was 210.9 per 100,000 person-years compared with incidence rate of 319.5 among non-users. After adjusting for potential confounders like age, sex, cirrhosis, diabetes and medications, the hazard ratio for HCC in statins users compared to non-users was 0.47 (0.36-0.61). The authors also managed to show a dose-response relationship between statins use and HCC. The adjusted hazard ratios were 0.66 (95% CI, 0.44-0.99), 0.41 (95% CI, 0.27-0.61) and 0.34 (95% CI, 0.18-0.67) for patients with statins use of 28-90, 91-365 and more than 365 cumulative defined daily dose.

This study has some distinct strengths. The investigators tested the association of statins exposure with HCC in a high risk group of patients who had HBV infection. The study population was taken from a computerized

database in Taiwan with a long follow up period of 328,946 person-years. Credit should also go to the authors for their meticulous analysis of possible confounders. The demonstrated clear dose-response relationship is indeed intriguing.

Nevertheless, this study needs to be interpreted with caution due to unaccounted confounders. The authors acknowledged unmeasured confounders such as alcohol intake, smoking status and body mass index. They however, failed to account for differences in risk of HCC even among patients with HBV infection. HBeAg, in addition to HBsAg, may be a useful marker of the risk of HCC. The incidence rate was 324.3 among those who were positive only for HBsAg and 1,169.4 among those who were positive for both HBsAg and HBeAg. The prevalence of HepBeAg among those who were positive for HepBsAg is highest among patients between 30 and 39 (23%). The study also showed a lower prevalence of HepBeAg with age (17). Of note, there was a difference between statin users and non-statin users in terms of age distribution in the study by Tsan *et al.* 37.7% of the patients with documented statin use was more than 50 years of age compared to only 15.9% among the non-statin users.

The finding from this study is consistent with that of 2 other epidemiological studies (18,19). Beyond the purported mechanistic action of statins as described above, it is perhaps more relevant as chemoprevention in HCC. Statins are selectively localized to the liver and less than 5% of the administered dose appears in the systemic circulation. Such selective hepatic uptake does provide a compelling reason to further investigate its role in HCC.

The long standing debate concerning the association between statins and cancer cannot be resolved with more large scale observational studies or meta-analyses of studies. The numerous epidemiological studies including by Tsan *et al.* (16) are informative but not conclusive. Truly, we need well designed randomized controlled trials to instruct us on the real value of statins in reducing cancer risk.

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Footnote

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Hepatocellular carcinoma: the rising tide from east to west—a review of epidemiology, screening and tumor markers

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Abstract: Hepatocellular carcinoma (HCC) is no longer a disease of the Eastern hemisphere. HCC incidence has tripled in the United States in the past two decades. It is the fastest rising cause of cancer mortality in the U.S. and in parts of Western Europe. In the past the HCC epidemic was fueled by the Hepatitis B virus (HBV) seen mainly in Asia via vertical transmission. In this decade, we are experiencing a rising tide due to the maturation of the Hepatitis C epidemic related to contaminated blood products and, more importantly, intravenous drug experimentation. As the obesity epidemic sweeps across the west the incidence of nonalcoholic fatty liver disease (NAFLD) and its inflammatory component nonalcoholic steatohepatitis (NASH) are becoming the harbinger of HCC yet to come. Worldwide, the incidence of HCC equals the mortality. Five year survival is at best 12%. These grim statistics underscore the need for earlier detection through screening resulting in initiation of early treatment that has the greatest impact on survival. An understanding of the epidemiology, risk factors and screening techniques is an essential first step in achieving this goal.

Keywords: Hepatocellular carcinoma (HCC); liver cancer; screening; hepatocellular carcinoma surveillance (HCC surveillance)

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Introduction

More than half a million individuals per year are diagnosed with hepatocellular carcinoma (HCC). From a global perspective it ranks as the fifth most common cancer in men and the seventh in women (1). Worldwide it ranks third in cancer mortality behind lung and gastric cancer. In the present decade, we are experiencing a shift in incidence that is declining in the Asian-Pacific region, where it is primarily due to vertical transmission of hepatitis B, to an increasing incidence in the Western world due to the maturation of the hepatitis C epidemic. In the U.S. the increase is three fold in the last decade (2). If we understand the epidemiology and risk factors and screen accordingly we can make an impact.

Epidemiology of HCC

Geographic variation in the incidence of HCC for the most part is dependent upon its primary risk factors.

In Eastern Asia and sub-Saharan Africa where the highest incidence rates occur (>20/100,000), hepatitis B infection, mostly from vertical transmission, accounts for 70% of the HCC cases. In Europe and North America, considered low incidence areas (<5/100,000), hepatitis C and alcohol account for 50-60% and 10-20% of the HCC cases respectively. The incidence rates of HCC are decreasing in some areas in China primarily in Hong Kong, Shanghai, and Singapore related to universal vaccination for hepatitis B (3-6). HCC in Japan, where hepatitis C is the most common etiology, is also experiencing a decreasing

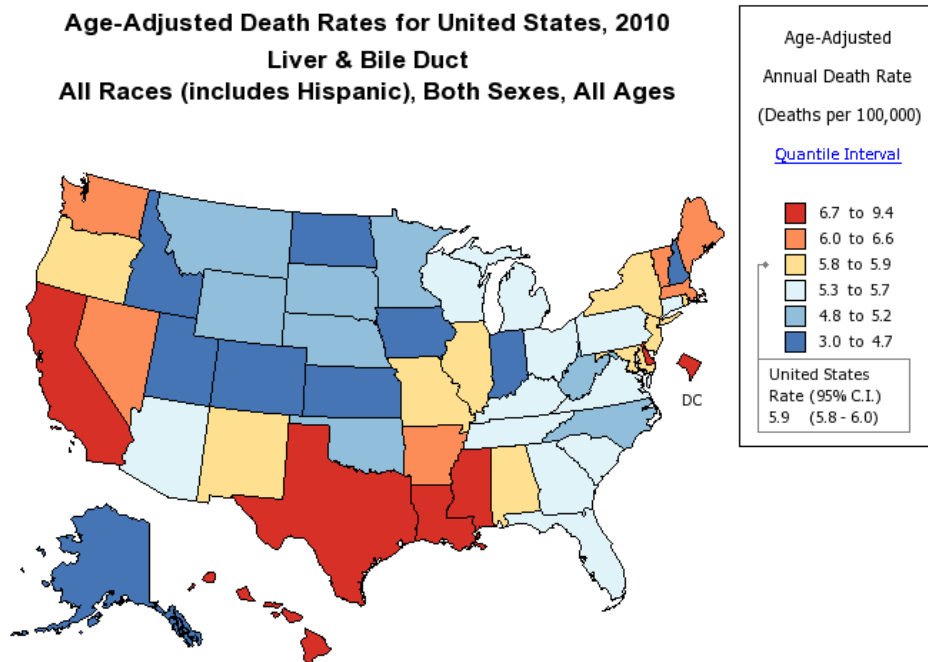


Figure 1 The map is created by statecancerprofiles.cancer.gov on 04/04/2012 8:33 am. Source: death data provided by the National Vital Statistics System public use data file. Death rates calculated by the National Cancer Institute using SEER*Stat. Death rates (deaths per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: <1, 1-4, 5-9, ..., 80-84, 85+). The Healthy People 2010 goals are based on rates adjusted using different methods but the differences should be minimal. Population counts for denominators are based on the Census 1969-2008 US Population Data File as modified by NCI. The US populations included with the data release have been adjusted for the population shifts due to hurricanes Katrina and Rita for 62 counties and parishes in Alabama, Mississippi, Louisiana, and Texas.

incidence. This is secondary to the timing of acquisition where most infections were through blood transfusions 20 years prior to the US epidemic in which IV drug experimentation predominated. HCC incidence in the United States and Europe is increasing. The driving force is predominantly hepatitis C infection. In the U.S., the overall age adjusted incidence and mortality rates tripled between 1975 and 2007 (1). The annual percentage increase was 4.3% per year. HCC has become the fastest rising cause of cancer related death in the United States. There are pockets in the United States where the mortality of HCC is high (Figure 1) (7). These areas include Texas, Louisiana, and Mississippi. In the U.S., the age adjusted HCC incidence for Asian/Pacific Islanders is three times that of Caucasians. However, the annual percentage increase in HCC per ethnicity in the U.S. between 1992 and 2005 was highest among American Indians and Alaskan natives at 5.0%. Black, white, and Hispanics had an annual percentage increase of 4.9%, 4.6%, and 4.0% respectively (8). Regional differences in the incidence of HCC also exist. The

HCC incidence rate among South Texas Latino men and women (17.3/100,000 and 5.4/100,000) is 45% and 42% higher than the incidence of HCC in a comparative U. S. SEER Latino population (9) (Figure 2). This may reflect differences in the incidence of hepatitis C, diabetes, and alcohol consumption. Increasing HCC incidence is linked to increasing cirrhosis. Although noncirrhotic hepatitis B is notoriously linked to HCC, 70-80% of hepatitis B HCC occurs in cirrhosis patients. In hepatitis C, greater than 90% of HCC patients have cirrhosis. In Texas 30-35% of hepatitis C virus (HCV) patients presenting for the first time to the physician's office will have established cirrhosis (10) (Figure 3). This is projected to increase over the next decade. The prevalence of cirrhosis and decompensated liver disease in U.S. veterans doubled between 1996 and 2006. In this same study, the prevalence of HCC increased ten times.

Foreign born persons accounted for almost a third of the U.S. HCC diagnosis between 2000 and 2005. Eighty percent of Asian-Pacific Islanders and 40% of Hispanics HCC patients were born outside the United States during this time

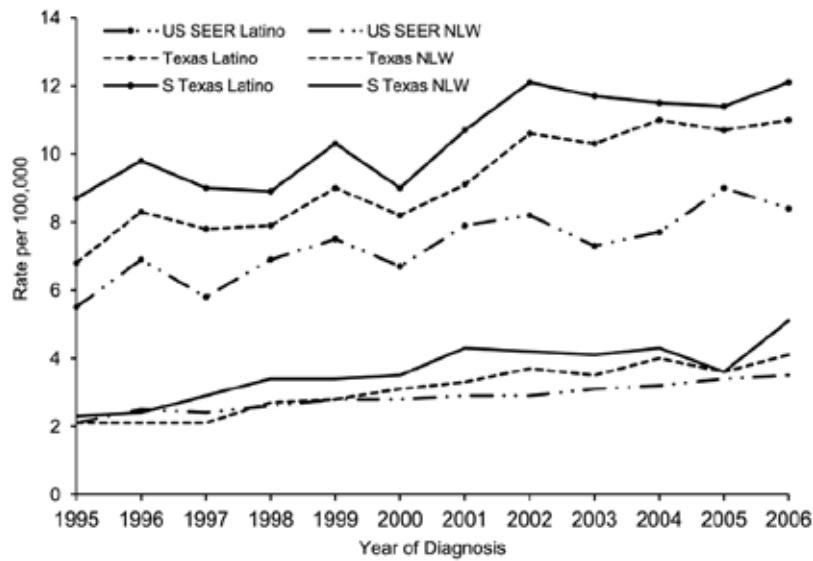


Figure 2 Annual age-adjusted incidence rates of hepatocellular carcinoma by ethnicity, 1995-2006. Annual age-adjusted incidence of HCC increased over the study period and was highest among South Texas Latinos. Data for non-Latino whites (NLW) is included for general comparison purposes. doi:10.1371/journal.pone.0035573.g001.

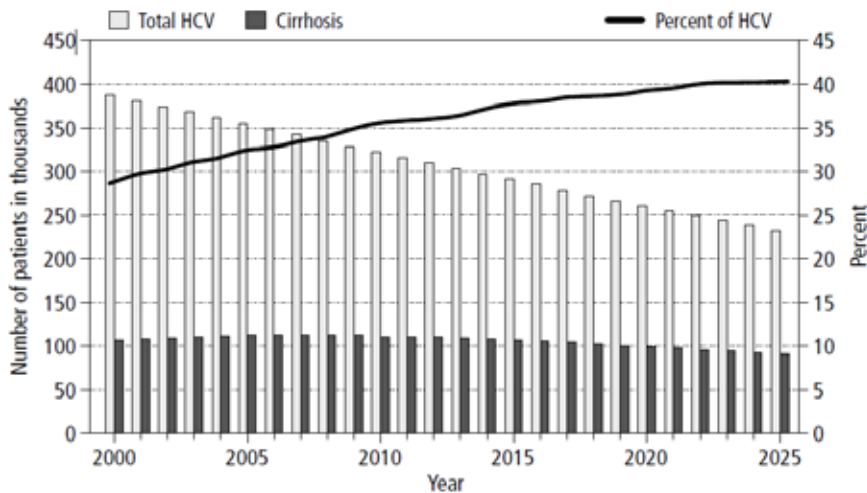


Figure 3 Projected number of all chronic hepatitis C virus (HCV) infections (light bars) and HCV-related cirrhosis (dark bars) in the state of Texas over the next two decades. The proportion of infected cases with cirrhosis is shown as a line (6).

period. Foreign born Caucasians accounted for 17%, blacks for 6%, and American Indians/Alaskan Natives 3% (11).

It is rare for HCC to occur before the age of 40. Female rates peak five years older than the peak age group for males (12). In the U.S. between 2000 and 2005 the majority of the increased incidence of HCC occurred among men age 52-59 years (8). In the U.S. it is becoming more common for

HCC to occur in a younger population. The driving factor behind this is a maturation of the hepatitis C epidemic.

Risk factors for HCC

Risk factors for HCC can be divided into modifiable and non-modifiable risk factors (Table 1). Unfortunately, we

Table 1 Risk factors for HCC

Age
Gender (male)
Cirrhosis
HBV
HCV
Fatty liver (NAFLD/NASH)
Obesity
Metabolic syndrome
Diabetes type II
HIV + HBV/HCV
Dietary
Beneficial (negative influence)
Coffee (mod. strong evidence)
Miso soup/tofu
Selenium
Beta carotene
Retinoic acid
Vegetable/fruit intake
Detrimental (positive influence)
Alcohol
Aflatoxin
Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus.

cannot change our age, gender or race; however, we do have the ability to modify risk factors such as hepatitis C, hepatitis B, HIV, obesity, diabetes, alcohol intake and environmental exposures.

Gender

HCC occurs more often in males (ratio: 2:1 to 4:1) (13). This may reflect that men are more likely to be infected with viral hepatitis, consume alcohol, smoke cigarettes, and have a higher body mass index than women. Gender differences do exist in the liver with the masculinization or feminization occurring early in development peaking at puberty. These sexual differences involve gender specific gene expression, mitochondrial function, microsomal enzyme activity, membrane lipid composition and immune responses (14-16). Higher testosterone levels play a role. Elevated testosterone levels or the intake of anabolic steroids have been associated with increased incidence of liver adenomas

and HCC. Higher serum levels of testosterone have been linked to HCC risk in nested case control studies of hepatitis B virus (HBV) carriers in Taiwan and Shanghai (17). High testosterone levels have been linked to advanced hepatic fibrosis and inflammation in males with chronic hepatitis C infection (18). In animal models androgens have been shown to increase the transcription of hepatitis B genes and bind directly to the viral genome sites (19). Gender disparity in IL6 production may also play a role. IL6 is a known cytokine associated with inflammation and implicated in modeling cell growth. IL6 is increased in HCC patients. Male dominant HCC incidence disappeared when production was blocked in mice (20).

Estrogens may play a role in the incidence of HCC among women. Cases control studies have shown a 5-fold increase in HCC in women with more than five years exposure to oral contraceptives (21-23).

Hepatitis B

Hepatitis B accounts for over 50% of HCC incidence worldwide (24). In endemic areas the transmission is most often vertical (mother to child). Here, the timing of the infection is early thus, the occurrence of HCC appears earlier. Most cases of hepatitis B related HCC occur in patients with cirrhosis. The lifetime relative risk for HCC is 15-20 times greater in HBsAg positive individuals compared to HBsAg negative individuals (25). The individual lifetime risk for persons with chronic hepatitis B infection is between 10% and 25% (26). High viral load, genotype (C in Asia, D in North America), longer duration infection, and co-infection with hepatitis C, HIV, or HDV, increase the risk of HCC (27,28). Active viral replication (HBeAg positivity) confers an increased HCC risk 60 times versus only 10 times in non-replicating HBsAg men. HBV-DNA levels have been correlated in a dose response relationship to the later development of HCC in patients followed for a mean of 11.4 years. The hazard ratio of developing HCC was found to be 1.1 for participants with serum of HBV DNA levels of 300 to 9,999 copies/mL, 2.3 for 10,000 to 99,999 copies/mL, 6.6 for 100,000-999,999 copies/mL and 6.1 for 1 million copies/mL or greater (27,29) (Figure 4). This dose dependent correlation became increasingly stronger in a stepwise analysis sequentially removing patients with elevated serum ALT levels, seropositivity for HBeAg, and cirrhosis. A significant difference is seen in cumulative incidence of HCC in patients whose HBV DNA levels were >10,000 copies/mL (3.75 vs. 1.37) although the

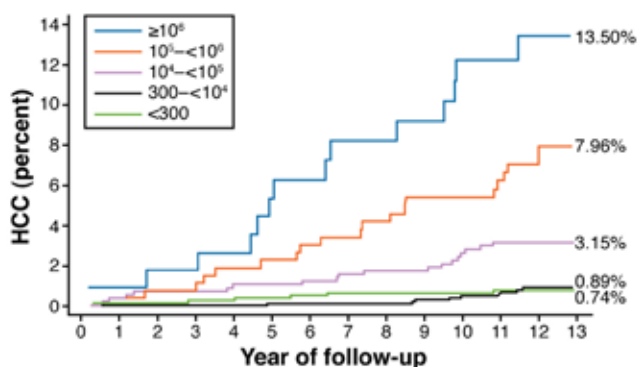


Figure 4 An association between baseline serum level of hepatitis B virus (HBV) DNA and future incidence of hepatocellular carcinoma (HCC). [Modified from Ref (27). Taken from El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264-73.e1.].

greatest difference occurred with $>100,000$ copies/mL (12,17). The cumulative incidence of HCC ranged from 1.3% with undetectable levels of HBV-DNA to 14.9% with $>100,000$ copies/mL. Additionally, in a study with follow up of 11 years, the relative risk of mortality from HCC was not significant for low viral load persons (HBV DNA less than 100,000 copies/mL) versus 10.7 with high viral load (HBV DNA $>100,000$ copies/mL) (30). It is unclear if these observations can be carried over in the Western world where the majority of hepatitis B viral infections occur horizontally. This correlation may not occur in infected persons <30 yrs who may be immune tolerant.

Alcohol consumption increases the risk of HCC in hepatitis B patients. Moderate drinking (≥ 3 drinks per week for >15 years) increases the odds ratio of HCC 3 to 4 fold (31). HBV-HCC occurred approximately ten years younger in chronic alcohol users (32,33).

Antiviral treatment reducing the levels of hepatitis B viral DNA can affect HCC occurrence. The cumulative HCC incidence at five years was reduced to 3.7% in an entecavir treated group versus 13.7% in controls. The reduction in HCC was greatest in those patients at high-risk for HCC especially in those with cirrhosis. Entecavir is superior to lamivudine in reducing the incidence of HCC (34).

Hepatitis C

The risk of HCC is increased 17-20 fold in HCV infected persons versus HCV negative controls (35). HCC mostly develops in cirrhotic individuals although in the HALT-C trial

8% occurred in patients with advanced fibrosis (36). Once cirrhosis occurs, the incidence of HCC is 1-4% per year.

The global incidence of hepatitis C is approximately 2% (37). In the U.S., between 4.1 and 5 million persons have antibodies to HCV and 3.2 to 3.4 million persons are chronically infected (38). The “biologic clock” (infection to cirrhosis to HCC) for hepatitis C is dependent on the time of infection. The average time from inoculation of HCV virus to the development of cirrhosis is 24 years and to the development of HCC 29 years. In Japan, most infections occurred in the 1920s and 1940s from a contaminated blood supply while in North America most infections occurred between 1960s and 1970s, largely as a result of intravenous drug experimentation. Thus, the incidence of HCC has peaked in Japan and is declining. In the U.S. the incidence is increasing and is expected to peak within the next five years (39,40). HCV was present in the blood supplies in North America until the development of screening tests in 1990 resulted in a dramatic decline in this infection route. HCC incident rates of 1 per 1,000 persons/year have been linked to recipients of HCV contaminated blood or blood products. Unlike hepatitis B, HCC risk association with viral factors such as genotype and viral load are less important than host factors such as time of acquisition, male gender, alcohol intake, metabolic syndrome, diabetes or co-infection with HIV/HBV. Co-infection with HBV dramatically increases occurrence of HCC with an odds ratio of 165 versus 17 for hepatitis C and 23 for HBV alone (41). The consumption of heavy alcohol (>50 g/day) results in increased incidence and earlier development of HCC. This synergistic increase is between 1.7 and 2.9 fold when compared to HCV-HCC alone (42).

Treatment resulting in a sustained viral response (SVR) results in a reduction of the incidence of HCC. A SVR is associated with 54% reduction in all-cause mortality (43). The reduction in HCC with a SVR occurs whether or not the patient has advanced fibrosis or cirrhosis. In persons at all stages of liver disease HCC occurred in 1.5% responding to treatment compared to 6.2% who did not respond. In patients with advanced liver disease the reduction of risk was similar but HCC occurred in 4.2% of SVR responders in contrast to 17.8% of nonresponders.

Importantly, even with the achievement of a SVR a risk for the development of HCC remains.

Nonalcoholic fatty liver disease (NAFLD)

In developed countries, the most common form of liver

disease is NAFLD (44). Being overweight and obesity is associated with a higher risk of HCC. Men with a body mass index over 35 kg/m² are four times more likely to die from liver cancer when compared to a control group with normal body mass index (18.5-24.9 kg/m²) (45). The relative risk of HCC is 117% for overweight subjects and 189% for obese patients (46). In the United States, 30% of the general population and 90% of the morbidly obese have fatty liver disease. The inflammatory component of NAFLD, nonalcoholic steatohepatitis (NASH), is estimated to be present in 5-7% of these patients (47). This may be an underestimate as reflected by a study in San Antonio, Texas which demonstrated NASH in 31% of patients who were found to have fatty liver by ultrasound (US) criteria (48).

Type II diabetes, often a component of fatty liver and the metabolic syndrome increases the risk of hepatocellular cancer threefold (49). Type II diabetes is associated with a hazard rate ratio of 2.16 for HCC (50). NAFLD is present in 74% of type II diabetics on liver biopsy. In a large healthcare database study between 2002 and 2008, HCC-NAFLD/NASH was found to be the most common underlying etiologic risk factor (59%), followed by diabetes (36%) and HCV infection (22%) (51). A European study analyzing HCC cases identified steatohepatitis as the leading etiology in 24% compared to chronic HCV in 23.3%, chronic HBV 19.3%, and alcoholic liver disease 12.7% (52).

The majority of HCC-NAFLD occurs in men (53). Compared to women, men develop HCC with less fibrosis and cirrhosis. The mean age at presentation is 70 years. The risk for HCC in NAFLD is less than that of hepatitis C. The cumulative U.S. incidence of HCC in NASH patients has been shown to be 2.6% compared to 4.0% with HCV. In Japan, the cumulative incidence was 11.3% for HCV versus 30.5% for NAFLD related cirrhosis.

HCC has increasingly been reported in the non-cirrhotic NAFLD. Concurrent metabolic syndrome and steatohepatitis has been found as risk factors in these patients. Non cirrhotic HCC was reported in 116 NAFLD patients from 2004 to 2012 representing one third of all cases. In a Japanese cohort which included 87 cases of HCC nearly half were found not to have cirrhosis. HCC has also been reported in NAFLD patients with neither steatohepatitis nor fibrosis.

A large proportion of cryptogenic cirrhosis is secondary to NAFLD (54-56). This is supported by a significant prevalence of diabetes and obesity in these patients. Patients with cryptogenic cirrhosis frequently develop NAFLD and

NASH post transplantation. Cryptogenic cirrhosis accounts for up to one quarter of HCC cases. Retrospective reviews have correlated the occurrence of diabetes, insulin resistance and dyslipidemia, elements of the metabolic syndrome and NAFLD, in many of these patients.

Diabetes

Diabetes is an independent risk factor for HCC (57,58). Diabetics have been shown to have between a 1.8 and 4 fold increased risk. Although closely associated with obesity and NAFLD, the risk of HCC remains after excluding patients with hepatitis C, hepatitis B, alcohol use and fatty liver disease. A graded dose response between fasting blood glucose and HCC risk has been reported that was independent of BMI (59). The risk is equally present in males and females. This association has been shown to be stronger in studies with a follow up period of >6 years. This increased risk is most evident in type II diabetics.

Dietary factors

Alcohol

Alcohol abuse in the United States occurs in more than 18 million people. The prevalence rate is five times higher than hepatitis C (60). In Europe, alcohol abuse accounts for 40-50% of all HCC cases (61). Alcohol consumption in 11-15-year-old has increased by two thirds since 1980 in the United Kingdom.

HCC risk in alcoholics is mostly associated with cirrhosis. Once decompensated cirrhosis develops risk is approximately 1%/yr. The risk increases with daily alcohol intake. An Italian study showed the risk was negligible for those who drink <40 g/d (one drink =12-14 grams). However, risk increases 1.5 (0.7-2.9) times for ingesting between 40-80 g/d and 7.3 (4.0-13.1) for those drinking > 80 g/d (62). The risk of HCC increases above 1 when daily ethanol consumption exceeds 60 g per day, increasing in a linear fashion thereafter (62). In the U.S., patients reporting drinking any alcohol versus total abstinence had an adjusted odds ratio for HCC of 2.4. This rose to 4.5 for drinking > 80 g/day. Discontinuing alcohol once cirrhosis occurs does not seem to lower the incidence of HCC. Alcohol when combined with HBV and HCV acts synergistically increasing the incidence of HCC 2-4 fold (63).

Aflatoxin

Aflatoxins are naturally occurring compounds produced by

Aspergillum species (molds) that grow on grains, corn, peanuts, or soybeans stored in warm humid conditions (64). Aflatoxin B1 is a potent hepatocarcinogen producing neoplasms in rodents and primates. The risk of HCC is dependent on dose and duration of exposure. The metabolite AFB-1 binds to DNA and produces a mutation in the p53 tumor suppressor gene. Aflatoxin exposure is more prevalent in rural areas. It has a synergistic effect on hepatitis B and C induced liver cancer. The risk of liver cancer is 30 times greater with chronic HBV plus aflatoxin exposure than with aflatoxin exposure alone (65). Aflatoxin exposure contributes an estimated 4.6% to 28.2% of the annual HCC cases. The highest distribution is in Africa followed by Southeast Asia and the Western Pacific nations. It is estimated that in high exposure areas of HBV, reducing exposure to non-detectable levels could reduce HCC cases by 23% (66).

Positive dietary factors

Coffee drinking in several studies including a meta-analysis has shown to reduce incidence of HCC. Coffee drinking has been associated with decreased risk of elevated enzymes and of cirrhosis. It has been shown to reduce insulin levels as well as reduce the risk of diabetes type II. The risk reduction of HCC is 40% for any coffee consumption per day versus no coffee consumption. Interestingly there appears to be a dose response relationship with a 20% reduction with 1-2 cups a day and a 75% reduction with 5 or more cups per day (67-69).

Other metabolic and genetic diseases

Hemochromatosis, alpha-1-antitrypsin disease, Wilson's disease, tyrosinemia, citrullinemia, Type I and III glycogen storage disease, fructose intolerance, and porphyrias have an association with HCC.

Hereditary hemochromatosis (HH) is associated with increased risk of HCC (70-72). The risk has been estimated to be between 100 to 200 fold increased. This occurs predominantly in patients with cirrhosis although it may also occur in the absence of cirrhosis. Multiple studies have shown the rate of HCC in patients with HH is approximately 10% overall. HCC has also been found in other iron overload disorders. In thalassemia, HCC was reported as a late complication. However, many of those patients were also positive for hepatitis C. The majority of patients had high serum ferritin levels (>2,000).

African iron overload occurs in patients who consume noncommercial beer brewed in nongalvanized steel drums.

South Africa blacks were found to have a relative risk for HCC of 10.6 in those with iron overload (transferrin saturation >60%) compared with those with normal iron stores after adjusting for alcohol, viral hepatitis and aflatoxin B1 exposure. It is inconclusive if mild to moderate iron overload associated with hepatitis C, alcohol related liver disease or the carriage of HFE mutation increases the risk of HCC in patients with cirrhosis.

Alpha-1-antitrypsin disease patients homozygous for the Z mutation (PiZZ), are at increased risk for HCC even in the absence of cirrhosis. Carriers (PiZ) may have also be at risk (73,74).

Hereditary tyrosinemia is an autosomal recessive of disorder in the pediatric population which results in individuals excreting higher levels of succinylacetone into the urine and elevated tyrosine levels in the serum results in rapid development of cirrhosis and potential for HCC (75). Treatment for this disorder when started before the age of two may prevent the occurrence of HCC.

Citrullinemia another autosomal recessive of disorder presenting in young children is associated with inborn errors of the urea cycle has also been associated with HCC (76).

Tumor markers

Most HCCs when diagnosed are advanced in size/stage resulting in five-year survival rates less than 12% in the United States. When HCC is discovered early, resection in non-cirrhotic patients offers a 5-year survival rate of 70%. Transplantation within the Milan criteria (single nodule <5 cm or 3 nodules each <3 cm in diameter) offers a greater than 75% five-year survival (77). Radiofrequency ablation singularly offers a five-year survival rate in patients with early HCC for Child-Pugh A and B between 51-64% and 31-38% respectively (78-80). Unfortunately, only 30% of the tumors are discovered early enough to offer treatment with resection or transplantation. Tumor markers and surveillance in high risk populations permit earlier discovery of HCC and will improve survival. The most commonly used biomarkers at this time are Alpha-fetoprotein (AFP), AFP-L3, and Des-Gamma-Carboxy-Prothrombin (DCP). Many potentially new markers show promise, two of which are Osteopontin (OPN) and fatty acids.

Alpha-fetoprotein (AFP)

AFP, with a half-life of 5-7 days, is synthesized by embryonic liver cells, the vitelline sac, and fetal intestinal

tract in the first trimester of pregnancy. Serum levels rapidly decline in the first 12 months after birth. It is the most widely investigated biomarker for HCC diagnosis. The false negative rate may be as high as 40% in patients with early HCC (<2 cm) (81). Levels may remain normal in 15-20% of patients with advanced HCC. Only 10-20% of early-stage HCC patients have abnormal AFP. Fluctuating levels occur with flare-ups of viral hepatitis without HCC. AFP cut off value of 20 ng/mL demonstrates good sensitivity but low specificity. Levels >200 ng/mL provides high specificity but markedly less sensitivity. Cut-off values for AFP in various studies ranging from 7.7 to 112 ng/mL have yielded sensitivity to be 25% to 90% and specificity between 85% and 97% (82). Increasing levels of AFP correlate with the development of HCC in cirrhotic patients. Consistently elevated levels greater than 500 ng/mL are indicative of HCC. In Alaskan hepatitis B carriers, AFP testing allowed detection of tumors in an earlier more treatable stage (83).

AFP-L3

AFP can be divided into three glycoforms. The AFP-L3 fraction expressed as a percentage of AFP reportedly is highly specific for HCC when AFP levels are greater than 20 ng/mL. AFP-L3 is correlated with a shorter tumor doubling time, an infiltrative tumor growth pattern, vascular invasion, and intrahepatic metastasis (84).

A new hypersensitive (hs) AFP-L3 has shown superior sensitivity even at AFP levels <20 ng/mL improving early detection of small tumors less than 2 cm. A cutoff value of 7% has been shown to best discriminate between benign liver disease (85). HS-AFP-L3 has been shown to be elevated one year prior to the diagnosis of HCC in 34.3% of high risk patients. Survival rate with hs-AFP-L3 >7% at one year prior to the diagnosis has been shown to be significantly lower than those patients with <7% (86).

Des-Gamma-Carboxy-Prothrombin (DCP)

DCP is produced only by malignant hepatocytes resulting from an acquired post translational defect in vitamin K dependent carboxylase system. Although independent of vitamin K deficiency, administration of vitamin K can transiently suppress DCP production (87). Levels greater than 100 ng/mL are very suggestive of HCC. DCP normalizes with successful tumor resection and has been shown to correlate with tumor activity. DCP level has the best correlation with tumors greater than 3 cm (88).

DCP levels >125 mAU/mL yield the best sensitivity and specificity for differentiating HCC for chronic hepatitis and cirrhosis (89). It is more sensitive and specific than AFP for differentiating HCC from nonmalignant liver disease. High-sensitivity DCP can be used at a cutoff value of 40 mAU/mL, AFP at a cutoff of 20 ng/mL and AFP-L3 cutoff at 10% in combination gives the highest accuracy of 82.2% (sensitivity 82.1%, specificity 82.4%) (90). The combination use of AFP, DCP and AFP/AFP-L3 yields increased sensitivity in diagnosing HCC (91,92). For this reason, the Japan Society of Hepatology (JSH) recommends all three biomarkers AFP, AFP-L3 and DCP along with ultrasonography in their screening for HCC (93).

Other potential markers

Several new promising markers are in phase I/II/III studies. These include OPN, Glypican-3, Hepatocyte Growth Factor, Insulin-like growth factor, and vascular endothelial growth factor (94).

OPN with cut off values of 156 ng/mL and AFP cut-off at 20 ng/mL combined have a sensitivity of 95% and specificity of 96% for diagnosis of HCC (95). Furthermore OPN levels were elevated more than one year before diagnosis.

Screening/surveillance for HCC

Screening strategy for HCC is based on two factors, an average tumor doubling time of 3-5 months and a cost effectiveness threshold of an expected annual incidence exceeding 1.5% in cirrhosis and 0.2% in non-cirrhosis HBV patients (96). Intervention is determined to be cost effective if it does not exceed \$50,000 per year of life gained. It is considered effective if it results in an increase in longevity of 100 days. Using this model, screening for most etiologies of cirrhosis is cost effective (autoimmune hepatitis cirrhosis may dip below this). The best radiologic tool that fits into this model is US examination at six months intervals. Biannual US/AFP exceeds the threshold in some studies while biannual AFP/annual contrast CT slightly exceeds the threshold by \$1,750 (97). US has, in general, a sensitivity and specificity greater 60% and 90% respectively with a positive predictive value of 70% (98). The ability of US to detect a HCC nodule is dependent on their size. HCC nodules >5 cm result in detection rate of 92%. However, the detection rate decreases to 75% for 3.1-5.0 cm lesions, 20% for 2.1 to 3.0 cm lesions and 13.6% for 1-2 cm lesions (99). False positive AFP results leading to additional unnecessary

Table 2 Surveillance guidelines for screening for HCC**

All patients with cirrhosis (any age)
Child-Pugh A/B
Child-Pugh C awaiting transplantation
Patients with HBsAg
Asians: females >50 yrs, males >40 yrs
Africans/North American Black >20 yrs
Family history of HCC
Non-Asians/Blacks: females >50 yrs, males >40 yrs. With "active disease**"
*, HBV DNA >100,000 copies/mL and/or elevated ALT; **, Modified from AASLD Guidelines; HCC, hepatocellular carcinoma; HBV, hepatitis B virus.

tests can result in US/AFP not meeting threshold (96). US detection varies with the expertise of the person performing the examination and with the body habitus of the patient. Central obesity hampers the ability of US to detect small lesions (100). A dedicated technician may increase the detection rate of HCC. It has been shown in hepatitis B patients that US surveillance every six months improved survival (101). The five year HCC related mortality was lower in the screened group attributable to HCC detection at an earlier stage I (60% *vs.* 0%) allowing more patients to be treated with resection (47% *vs.* 8%). This is less clear in cirrhotic patients. The current AASLD guidelines recommend US every six months without AFP as the screening tool for HCC.

Who to screen (Table 2)

All cirrhotic patients should be screened with US for HCC. The exception to this would be the non-transplantable, decompensated (Child C) HCV cirrhosis patient whose life expectancy is too short to experience any survival effects of surveillance (102). Alcohol related cirrhosis may fall below these thresholds because of a lower incidence of HCC and the high (58%) non-HCC related mortality (103). Also, HCC screening with CT scan while awaiting liver transplantation has been shown to be associated with the greatest gain in life expectancy and is cost effective in this setting (104).

Non-cirrhotic patients who are hepatitis B carriers comprise a group of patients with individual recommendations based on cost effectiveness (incidence of HCC exceeding 0.2%). Asians are at greater risk for HCC than Caucasians (105,106). The risk of HCC in Asian male

HBV carriers exceeds the threshold starting at the age of 40 yrs (107). US should be performed in Asian men over the age of 40 and Asian women over the age of 50. Black African non-cirrhotic HBV carriers have a particularly increased risk of HCC at a younger age (108). For this reason, screening should begin at the time of diagnosis or when reaching 20 years old. It is unclear if this early onset can be transferrable to non-African blacks. The guidelines are also vague in Caucasians with non-cirrhotic hepatitis B and those with a family history (FH) of HCC.

The risk of HCC in Caucasians appears to be more related to the virus inflammatory activity in non-cirrhotic patients. Surveillance should be performed in these patients with active disease as reflected by an elevated ALT and or a high viral load (>20,000 IU/mL) (109). It can be started in men at 40 years of age and in women at 50 years of age.

HBV carriers with a FH of HCC have increased risk (110). This risk increases with age (23% with HCC at 70 *vs.* 8.9% without a FH) and the number of family members affected (risk 5.6 times with >2 family members). Risk is independent of hepatitis however the combination of HBV or HCV serum markers plus FH increases the risk >70 times. It is unclear if there is a relationship between the age of occurrence of HCC in a family member, index case, and the age at which the risk of HCC will occur in the offspring. The age at which to start surveillance in these individuals has not been defined by the guidelines.

The diagnostic algorithms (*Figure 5*) once a lesion is discovered on US vary between the separate societies. Asians societies use AFP, the Americans and Europeans do not. All use US as the first screening modality. In the Asian guidelines any lesion with characteristic MR/CT enhancement is considered diagnostic for HCC while the Europeans and Americans use the size of the lesion (>1 cm). In a recent review the sensitivity and specificity for HCC diagnosis was 60% and 90% for US, 68% and 93% in the multiphasic CT, 81% and 85% in dynamic MRI. MRI showed the highest specificity. The diagnostic sensitivity depended on the size of the tumor. CT and MRI was greater than 90% sensitive for tumors 2 cm or larger, 61-65% and 80-92% tumors between 1 and 2 cm, 10% and 34-71% in tumors less than 1 cm, respectively (111). The greatest difficulty with diagnosing HCC by the various radiologic studies lies in diagnosing tumors less than 2 cm and in particular those less than 1 cm. The differential diagnosis for lesions found in a cirrhotic liver less than 2 cm is broad and includes fibrosis, regenerative nodules, cirrhotic nodules and dysplastic nodules. Lesions less than

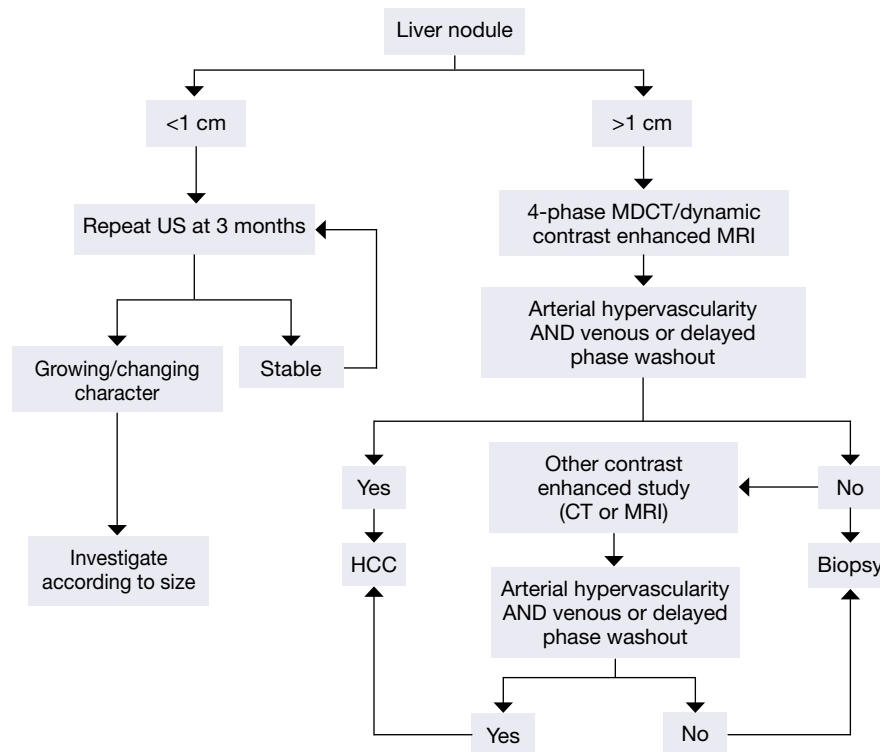


Figure 5 AASLD guidelines: diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound. [Modified from Ref (96)].

1 cm can be confused with arterial portal shunting. Variations can exist between areas within the liver itself. Arterial vascularization in the HCC tumor is an essential key to its diagnosis on imaging studies. Arterial enhancement occurs when a dysplastic nodule becomes a frank HCC (112). MRI is better than CT at visualizing very early vascular lesions. However, well differentiated HCC may not have significant arterial enhancement in early contrast phases and may in fact have some residual hepatocyte function. This has been overcome with a new contrast agent, gadoxetic acid (Eovist in the United States, Primovist in Europe). This agent used in a delayed hepatobiliary phase (20-minute delay) results in enhancement of functioning hepatocytes that appear brighter in contrast to nonfunctioning hepatocytes i.e., HCC. In comparison studies with MRI utilizing this contrast agent to CT multi detector scans, lesions less than 2 cm were significantly more often found with MRI. Lesions 1-2 cm detection rates were 71-87% with MRI *vs.* 65.7-78.7% with CTMD in one comparison study and all lesion detection rates were 82-85% versus 69-71% in an additional two comparison studies (113-115).

When atypical findings occur from a single imaging study the AASLD recommendations encourage the use of a second imaging modality for further assessment. If atypical findings are again found on the sequential scan biopsy is recommended. In these atypical lesions, biopsy improves specificity of imaging to 100% (116).

Biopsy of lesions less than 1 cm can be challenging. Therefore recall, repeating imaging studies, in close interval follow-up is essential. A three month interval is recommended. A longer interval, six-months, may be sufficient especially when the lesion is <5 mm noted to be subcapsular in location, ill-defined or wedge-shaped and thus more likely representing a vascular shunt. However if the lesion is noted to be round or oval, intraparenchymal or in a dominant mass a three month recall interval should be performed (117). Lesions that do not regress should be followed for two years before they are considered benign.

Screening and the guidelines: real world reality

It is important to understand that the various guidelines

adopted by different societies are not dictums but suggestions. They should be followed as best as possible but sometimes reality dictates otherwise.

For surveillance to work we first need to know that the patient has cirrhosis. In a recent review in a Marketscan claims database of 729,018 patients with at least one claim for NAFLD/NASH/HCV over one quarter of the patients diagnosed with HCC had no knowledge of liver disease prior to their diagnosis (118). Amazingly, of the patients known to have liver disease, only 20.1% of patients with NASH/cirrhosis and 22.3% of those with HCV/cirrhosis were undergoing regular HCC screening.

In a retrospective analysis (HALT-C), even when patients were closely followed by expert hepatologists at academic centers one third of the patients had inconsistent HCC surveillance (119). Only 20% of the patients that developed HCC were found at a very early stage (TNM stage T1) and over one fourth of the tumors were found beyond the Milan criteria. Patients beyond stage T1 were significantly more likely to have experienced absence of screening or follow-up. Additionally, the most common reason for surveillance failure (70%) in tumors beyond the Milan criteria was absence of detection by US and AFP. This underscores the importance of the imaging study chosen and establishing an adequate patient recall program. It is also imperative to make the patient understand the importance of screening.

In our center, we conduct surveillance for HCC utilizing US alternating with MRI scan at six-month intervals in any patient whose BMI is >30. Otherwise, US at six-month intervals is performed. We utilize AFP at six-month intervals. AFP-L3 and DCP are ordered with AFP in listed and in potential transplant patients. We tell patients to use their birthday as a point of reference in time to remind him/her of the need for surveillance (birthday and six months later).

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Footnote

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Novel biomarkers for hepatocellular carcinoma surveillance: has the future arrived?

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Abstract: Hepatocellular carcinoma (HCC) remains a major cause of mortality in patients with chronic liver disease worldwide. Early detection of HCC is critical to providing effective treatment and can have a significant impact on survival. In addition, effective surveillance following hepatic resection or locoregional ablative therapy can identify early recurrence and optimize long-term outcomes. Currently available serum tumor markers, including alpha-fetoprotein (AFP), are characterized by low sensitivity in the detection of HCC. Advances in genomic, proteomic, metabolomic, and glycomic profiling may provide a means to identify unique molecular signatures and characterization of complex processes associated with HCC incidence and recurrence. The development of highly sensitive and specific serum biomarkers for HCC may greatly enhance early detection rates, risk assessment in treatment candidates, and identification of potential new targets for anticancer therapy.

Keywords: Biomarker; hepatocellular carcinoma (HCC); glycomics; surveillance; tumor marker

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Hepatocellular carcinoma (HCC) continues to be a major cause of cancer-related mortality and morbidity (1,2). The vast majority of HCC cases occur in those with chronic liver disease, particularly chronic hepatitis B and chronic hepatitis C, which account for up to 85% of HCC cases worldwide (3). Early detection of HCC through surveillance methods has a major impact on patient outcomes, including increased survival (4,5). Efforts to identify HCC in individuals at risk at an early stage are critical to providing highly effective treatment, including primary curative hepatectomy, locoregional ablative therapy, or liver transplantation.

Limitations of current biomarkers

The utilization of serum tumor markers has played a major role in not only surveillance strategies in high-risk populations and achieving a diagnosis of HCC, but also in risk stratification and prediction of recurrence following initial therapy. However, the most widely used tumor

marker for HCC, alpha-fetoprotein (AFP), has fallen short in its ability to accurately diagnose HCC, discriminate between high and low risk individuals, and predict high-risk histopathologic features such as microvascular invasion and tumor differentiation. Consequently, AFP has been excluded in some guidelines on HCC surveillance as well as in the diagnostic assessment of hepatic nodules found on surveillance imaging (6).

A major limitation associated with serum AFP is its low sensitivity. Large-scale prospective data have revealed that over 45% of patients with HCC may have normal serum AFP levels (7). Multiple case-control and prospective cohort studies have described sensitivities of 41% to 65% and specificities of 80% to 94% for serum AFP levels >20 ng/mL (Table 1) (8). At increasing levels of serum AFP, the sensitivity for detection of HCC declines significantly. Additional limiting factors associated with AFP assessment include variation in serum AFP levels with aminotransferase levels, grade of necroinflammatory activity on liver biopsy, etiology of chronic liver disease, patient ethnicity, and

Table 1 Range of performance characteristics associated with common biomarkers used in the diagnosis of hepatocellular carcinoma (8,9)

Tumor biomarker	Sensitivity [range] (%)	Specificity [range] (%)
Alpha-fetoprotein		
>20 ng/mL	[41-65]	[80-94]
>200 ng/mL	[20-45]	[99-100]
>400 ng/mL	<20	[99-100]
<i>Lens culinaris</i> agglutinin-reactive alpha-fetoprotein		
Elevated serum AFP [†]	[37-75]	[83-94]
Low serum AFP (≤ 20 ng/mL) [‡]	[12-21]	[89-98]
Des- γ -carboxyprothrombin/PIVKA II [§]	[41-89]	[70-100]

[†], AFP-L3 cutoff values range from 10% to 35%; [‡], AFP-L3 cutoff value at 10%; [§], DCP cutoff values range from 60 to 150 mAU/mL. AFP, alpha-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive alpha-fetoprotein; DCP, Des- γ -carboxyprothrombin; PIVKA II, prothrombin induced by vitamin K absence II.

nodule size.

Several serum markers for HCC have now been identified in addition to AFP; however, data are limited and many have yet to be widely accepted in clinical practice. A fucosylated isoform of AFP reactive to *Lens culinaris* agglutinin, known as AFP-L3, was initially discovered to be significantly increased in patients with HCC compared with patients with elevated AFP in the absence of HCC (10). Several prospective studies have reported a high sensitivity and specificity associated with AFP-L3 as a diagnostic tool for HCC; however, this marker can only be used in patients with elevated baseline AFP levels. In patients with low AFP levels (≤ 20 ng/mL), the sensitivity of AFP-L3 can decline significantly (9). Prothrombin induced by vitamin K absence II (PIVKA II), known as des- γ -carboxyprothrombin (DCP), is an abnormal prothrombin molecule also increased in the setting of HCC. Prospective data have reported greater specificity associated with DCP in comparison with AFP, yet the sensitivity of DCP may be diminished. However, the performance characteristics of DCP appear to vary based on the etiology of liver disease, in which its sensitivity may increase in cases with underlying chronic viral hepatitis (11). A large multicenter case-control study evaluating the role of AFP, AFP-L3, and DCP in HCC surveillance found AFP to have the highest sensitivity, although data suggest that a combination of tumor markers may be more effective (11).

Additional serum and plasma biomarkers found to be potential screening tools in the early detection of HCC have included glypican-3 (GPC-3), osteopontin, golgi protein 73 (GP73), microRNA (miRNA), α -1-fucosidase, human telomerase reverse transcriptase, squamous cell

carcinoma antigen, and transforming growth factor- β 1. GPC-3 is a cell-surface proteoglycan overexpressed in HCC cells and may regulate tumor growth. Although GPC-3 appears to have a high specificity, it has a low sensitivity similar to AFP (12). Likewise, GP73 and miRNAs, such as miR-21, have demonstrated only a slight improvement in performance compared with serum AFP (13). Osteopontin is a glycoprotein expressed in HCC cells, and although it has a higher sensitivity than AFP in the detection of HCC, its specificity remains low and may require a combination with AFP in order to optimize performance (14).

Genome-wide association studies

As the ability to detect genomic variation between individuals has advanced, multiple single nucleotide polymorphisms (SNPs) associated with HCC risk have been identified through various studies involving a wide range of patient populations. Although questions remain regarding the applicability and reproducibility of genomic profiling across different patient groups, some recent reports have identified SNPs that appear to demonstrate a consistent association with risk of HCC (15). However, genomic profiling for assessment of risk of HCC may be limited by a high degree of variation in gene expression based on patient ethnicity and underlying chronic liver disease (16). Further large-scale genomic studies may be required to develop gene expression profiles that can reliably predict risk of HCC. Ultimately an individualized approach based on liver disease etiology and patient ethnicity or a combination of genomic profiling with other biomarkers may be needed to

Table 2 Diagnostic and prognostic value of serum *N*-glycans following primary curative hepatectomy for hepatocellular carcinoma (22)

Performance characteristic [†]	G2890	G3560
Sensitivity	82.7%	71.3%
Specificity	92.3%	88.5%
ROC-AUC	0.91	0.85
Overall survival (HR, 95% CI)	–	2.5 (1.6-3.9)
Disease-free survival (HR, 95% CI)	1.4 (1.1-1.9)	–

[†], sensitivity, specificity, and ROC-AUC data based on diagnosis of HCC vs. controls; overall and disease-free survival data obtained through multivariate analysis. AUC, area under the curve; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; ROC, receiver operating characteristic.

achieve acceptable consistency in identifying individuals at increased risk of HCC incidence or recurrence.

Proteomic and metabolomic analysis

Advancements in analytical techniques involving surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS), advanced chromatography, and nuclear magnetic resonance spectroscopy have introduced methods of identifying protein and metabolite expression associated with HCC. An array of proteomic studies have now identified multiple serum protein fragments with differential expression in the setting of HCC, many of which could serve as new biomarkers for HCC and may be instrumental in risk assessment, early detection, and surveillance. A limitation of proteomics currently lies in the lack of agreement among various studies in reporting changes in protein expression associated with HCC; however, a meta-analysis of proteomic profiling for HCC noted heat-shock 70-kDa protein (HSP70) and fructose-1,6-bisphosphatase 1 (FBPase) among the most consistently reported proteins with upregulation and downregulation, respectively, in the setting of HCC (17). Likewise, metabolomic studies evaluating changes in lipid and water soluble metabolites found in the blood or urine have paved the way towards identifying a wider array of potential biomarkers for HCC. Methods involving a combination of gene expression and metabolomics, or a combination of different metabolomic platforms, may be required to define markers with highest sensitivity and specificity in the detection of HCC (18-20).

Glycomics and beyond

An area of great interest in biomarker discovery for cancer

detection, including HCC, is glycomics. *N*-glycans are complex polysaccharides bound to biomolecules through *N*-glycosylation and are found throughout a wide range of biological processes including cell-cell interactions, protein folding, and receptor binding. In particular, specific *N*-glycosylation patterns may be associated with cancer development (21). Identifying these changes in glycosylation may provide a means to accurately detect HCC tumorigenesis at an early time point.

One recent study published in *Hepatology* by Kamiyama and colleagues evaluated *N*-glycosylation alterations in 369 patients with HCC who underwent primary curative hepatectomy compared with 26 controls identified as healthy living related liver transplant donors (22). A novel high-throughput glycoblotting method was utilized for glycomic profiling to identify 67 *N*-glycans associated with HCC, of which 14 *N*-glycans had a greater potential to discriminate between individuals with HCC and controls, as defined by receiver operating characteristic analysis. Two serum *N*-glycans, G3560 and G2890, were identified as significant predictors of overall survival and disease-free survival, respectively, over a median follow up of 5 years (*Table 2*). Both *N*-glycans also strongly correlated with other known prognostic markers, including DCP, number and size of tumors, microscopic vascular invasion, and macroscopic vascular invasion.

As demonstrated in this study, glycomic analyses could lead to discovery of alterations in *N*-glycan profiles that are highly specific to HCC. These data are encouraging and suggest that glycomic biomarkers could play a role in early detection of HCC with a high sensitivity and specificity as well as provide a measure of risk assessment in those with HCC who undergo curative therapy. However, similar to other biomarkers, there may be limitations in glycomic studies associated with variation in study

populations. Further investigation will be required to establish reproducibility of these findings and determine its applicability to a wider range of patient groups and liver disease etiologies.

Although challenges remain, a continued effort to identify novel biomarkers utilizing advanced proteomic, metabolomic, and glycomic methodology alongside genomic profiling and existing tumor markers such as AFP will greatly enhance our ability to detect HCC. In light of the complex interplay of cancer pathogenesis, underlying chronic liver disease, and variation among populations at risk of HCC, it is likely that a multimodal approach may be required to develop unique molecular signatures specific to HCC that can identify early patterns corresponding with incidence and recurrence. In addition, this line of research may also reveal further insight into HCC pathogenesis and identify potential therapeutic targets. Although it appears that the future has arrived, we have yet to see how these advances may impact patient outcomes on a larger scale.

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Footnote

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DKK1 as a serum biomarker for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis secondary to chronic alcoholism (1). Etiological factors for HCC vary widely depending on geographic location. In regions where Hepatitis B (HBV) is endemic, such as the eastern hemisphere, this is uniformly the most common cause (2). It is estimated that chronic HBV and hepatitis C virus (HCV) infections account for an estimated 78% of global HCC cases (3).

It has been widely established that the early detection of HCC enables more treatment options and translates to improved survival (4). Current American Association for the Study of Liver Diseases (AASLD) guidelines recommends the use of ultrasound for screening (5). Markers such as α -Fetoprotein (AFP) has long been used as a biomarker for HCC however often levels are related to vascular invasion and tumor burden and therefore can manifest late in presentation or sometimes not at all. The presence of AFP is not entirely specific to HCC and is often seen in situations of chronic benign liver disease and furthermore the most sensitive cut-off value by ROC analysis has been a topic of great debate. The need for a more sensitive and accurate screening tool in HCC has led to the emergence of various tumor biomarkers including microRNAs, osteopontin, & intermedin to name a few (6-9).

In a recent issue of *The Lancet Oncology*, Shen *et al.* designed a large-scale, multicenter validation study to assess the diagnostic accuracy of Dickkopf-1 (DKK1) as a serum protein marker for HCC (10). The authors have previously shown that DKK1 is overexpressed in HCC tissue but is not detectable in corresponding non-cancerous liver tissue, making this an attractive screening tool candidate (11,12). In

their current analysis the authors enrolled 1,284 participants including a test cohort of 424 HCC patients and 407 controls (213 healthy controls, 98 with chronic HBV, and 96 with liver cirrhosis). They compared results with a validation cohort (N=453) at a different institution.

Methodologically the authors analyzed serum DKK1 levels by receiver operating characteristics (ROC) to determine adequate cut-off values to determine validity of this as a screening adjunct. ROC curves showed the optimum diagnostic cutoff was 2.153 ng/mL [area under curve (AUC) 0.848 (95% CI, 0.820-0.875), sensitivity 69.1%, and specificity 90.6% in the test cohort; 0.862 (0.825-0.899), 71.3%, and 87.2% in the validation cohort]. They elegantly validate their findings which show that DKK1 alone or in combination with AFP was better than AFP alone. Previous cross sectional ROC studies of AFP as a screening tool (at various cut-off values) have shown sensitivities between 25-65% and specificities between 79-95% (13). Although impressive in sample size Shen *et al.*, seem to echo prior results rather than offer a more accurate and practical alternative.

Where DKK1 may have a substantial role is in patients where AFP levels are negative or equivocal such as the case in chronic liver disease. The authors addressed this by examining AFP-negative patients and those with early HCC. They convincingly show that raised concentrations of DKK1 in serum could differentiate HCC from chronic HBV infection and cirrhosis, and that DKK1 and AFP together improved diagnostic accuracy for HCC versus all controls compared with either test alone.

What the authors fail to address is how specific is DKK1 to HCC? DKK1, a secreted protein, is known as a negative regulator of the Wnt signaling pathway. DKK-1 is reported

to be over expressed in many malignant tissues including breast cancer, lung cancer, esophageal carcinomas, ovarian and gastric cancer and previous groups have reported its potential use as a biomarker (14). (Not the main weakness of AFP) This lack of specificity detracts from the overall benefit of using DKK1 as a serum biomarker and mirrors some of the same issues that plague AFP in the first place.

In summary the use of DKK1 as a serum biomarker for the presence of HCC seems plausible based on work by Shen *et al.*, but it is unclear whether this has an advantage over well established markers of similar accuracy. The authors stated interpretation that DKK1 *could* complement measurement of AFP in the diagnosis of HCC and improve identification of patients with AFP-negative HCC and distinguish HCC from non-malignant chronic liver diseases is not challenged. What remains unclear is the exact role DKK1 will play as an adjunct, in what populations, and with what end-points in mind. Looking forward further studies should continue to examine and validate this promising screening tool, perhaps in western populations with analysis of its effect on long-term survival. This would be in line with universally accepted guidelines for the development of appropriate screening markers in oncology.

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Midkine as a new diagnostic tool in hepatocellular carcinoma

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Abstract: In the field of hepatocellular carcinoma (HCC), new biomarkers are needed in order to refine diagnosis of small tumors accessible to curative treatments. However, most of biomarkers (AFP, AFPL3, DCP, PIVKA-II, etc.) have failed to show any additional value for the diagnostic of early HCC. A recent study published in *Clinical Cancer Research* by Zhu WW *et al.* has identified serum midkine as an interesting diagnostic tool for HCC. Despite some limitations, this study has paved the way for a potential use of serum midkine in clinical care.

Keywords: Hepatocellular carcinoma (HCC); diagnosis; midkine; biomarker

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Despite several advances in both curative and palliative treatment, hepatocellular carcinoma (HCC) remains a dreadful disease with a dismal prognosis (1). Along this line, the need for new biomarkers is crucial for improving screening, diagnosis and treatment of HCC patients (2,3). One of the unresolved issues is that of diagnosing early HCC in order to inaugurate curative treatment and consequently increase patient survival. Diagnosis of HCC on cirrhosis may be difficult when confronted with small nodules of less than 2 cm. Diagnosis of small nodules of less than 1 cm is virtually impossible, and those of 1 to 2 cm often difficult. In this particular clinical setting, AFP is useless; its sensitivity is insufficient using the usual cut-off (2). In addition, from a diagnostic point of view, specificity must be high in order to avoid false-positive results and overdiagnosis. Several new biomarkers have shown initial promising results (lectin-bound alpha-fetoprotein AFP L3, des-gamma carboxyprothrombin DCP, prothrombin induced by the absence of vitamin K or antagonist-II PIVKA-II), but have failed to perform satisfactorily, at least in western countries (4). In the clinical setting of western scientific societies, AFP have, for the most part, been rejected for screening of cirrhotic patients for HCC and, at present, only ultrasonography every six

months is recommended (5). In general, AFP is proposed only as a prognostic biomarker, and major efforts are required to identify new and robust diagnostic biomarkers. A new candidate biomarker, midkine, has emerged from a gene expression study of HCC (6) and has been extensively examined in a study recently published by Zhu WW *et al.* in *Clinical Cancer Research* (7). Midkine is a heparin-binding growth factor expressed during early embryogenesis (8). In adults, midkine is expressed only at very low levels in the kidney. However, midkine is involved in the inflammatory response, in wound repair and also in carcinogenesis (9). Midkine is overexpressed in several types of cancer, including gastric, pancreatic and colorectal cancer (10,11). Midkine acts as a ligand and uses several transmembrane receptors—ALK, LRP1, NGC or NOTCH2—to transduce the signal into the cell (9). In vitro studies suggested a role for midkine in proliferation and protection of cancer cells from drugs and autophagy, in addition to a role in neo-angiogenesis (8). A previous study by the team of XW Wang using microarray identified several genes, including GPC3, PEG10, SERPIN1, QP-C and MDK (coding for the midkine protein) as being specifically overexpressed in HCC compared to non-cancerous hepatic tissues (6). Following that study, a recent paper published by Zhu WW

et al. in *Clinical Cancer Research* assessed the diagnostic value of serum midkine in HCC in Chinese patient cohorts (7). First, they confirmed an increase in midkine expression in hepatocellular cell lines and in a set of HCC analyzed by immunohistochemistry. Interestingly, the serum level of midkine was correlated with the corresponding tumor level. Next, they found that the serum level of midkine was increased in patients with HCC compared to healthy patients, patients with cirrhosis, patients with benign liver tumor and patients with gastrointestinal cancer. One strength of the study lies in the validation of midkine diagnostic value and its related cut-off (0.654 ng/mL) in a second set of patients. In contrast to AFP, midkine was not significantly associated with advanced HCC or prognosis. This suggests that midkine could be used for diagnosis of early HCC. Supporting this hypothesis, the authors reported a sensitivity of 86% with a specificity of 90% in BCLC 0/A. Interestingly, serum midkine retains its diagnostic performance in AFP-negative HCC. Despite this impressive performance, some important points should be verified before translation into clinical practice. First, biomarkers should be prospectively and externally validated by another team to avoid overstatement of the discovery team. Next, most HCC included in this study developed in patients infected by chronic hepatitis B. Validation in other underlying liver diseases, including alcohol, NASH and hepatitis C, should be mandatory. Previous biomarkers (including PIV3KA, AFPL3, DCP, etc.) failed the validation step in western countries (4). This may reflect a differing carcinogenic process in non-HBV etiology. Moreover, several new diagnostic biomarkers have been recently identified by other teams, including serum DKK1, serum osteopontin and a combination of plasma microRNA (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a and miR-801) (12-14). The performance of serum midkine in the diagnosis of HCC should be compared to these new biomarkers. Finally, one of the major issues is the usefulness of this biomarker in a clinical setting. The authors reported high sensitivity and specificity for diagnosis of BCLC 0/A HCC. However, diagnosis using non-invasive criteria of BCLC A (>2 cm) HCC is not difficult and the usefulness of a diagnostic biomarker in this setting is limited. The main diagnostic problem remains that of BCLC 0 HCC smaller than 2 cm, and the usefulness of a new biomarker should be tested in that particular clinical setting. In their study, Zhu WW *et al.* did not validate the diagnostic value of midkine in BCLC 0 HCC in their second set of patients (7). Moreover, we are unaware of its potential utility for small nodules of

indeterminate origin, less than 2 cm and uncharacterized at imaging. Despite this limitation, the study of Zhu WW *et al.* has identified a new serum biomarker, midkine, that gives an attractive diagnostic performance for HCC (7). Additional studies are warranted in order to confirm the robustness of this data and to elucidate the potential role of serum midkine in HCC diagnosis. Consequently, there remains a long and winding road before midkine can be endorsed as a diagnostic biomarker in daily practice.

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TIE2-expressing monocytes as a diagnostic marker for hepatocellular carcinoma correlates with angiogenesis

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Abstract: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. In the past few years, the mechanisms of hepato-carcinogenesis have been elucidated and the involvement of a number of pathways, including angiogenesis, aberrant signal transduction, and dysregulated cell cycle control have been demonstrated. Myeloid lineage cells, such as macrophages and monocytes, have been reported to regulate angiogenesis in mouse models. TIE2, a receptor of angiopoietins, conveys pro-angiogenic signals and identifies a monocyte/macrophage subset with pro-angiogenic activity. Recently, one study suggests that TIE2-expressing monocyte/macrophage (TEMs) frequency can be used as a diagnostic marker for HCC.

Keywords: Hepatocellular carcinoma (HCC); markers; TIE2-expressing monocyte/macrophage (TEMs)

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Hepatocellular carcinoma (HCC) is a relevant health problem, being the sixth most common cancer worldwide in terms of incidence with 626,000 new cases per year, accounting for 5.7% of all new cancer cases (1). Due to the poor prognosis of the disease, the number of deaths per year is almost the same as new cases [598,000], making HCC the third most common cause of cancer-related death (1).

Prognosis and feasibility of treatments for HCC patients largely depend not only on tumor characteristics, but also on the severity of the underlying chronic liver disease that affects the majority of cases (2,3). Prognosis is relatively better for the subset of patients eligible for surgery (tumor resection or orthotopic liver transplantation) or for local ablation strategies with potentially curative aim (e.g., percutaneous ethanol injection or radiofrequency ablation). Outcome is significantly worse for those patients who can be treated only with palliative loco-regional treatments, such as transcatheter arterial chemo-embolization, or who are affected by advanced disease. Unfortunately, curative strategies are currently limited to a minority of patients, those

who present at diagnosis with small nodules, disease confined to the liver, good performance status and well preserved liver function. The proportion of patients presenting with these characteristics is currently no more than about 30-40% (4). In the experience of the Cancer of the Liver Italian Program (CLIP) group, in a series of 650 patients diagnosed in the years 1994-1999, 59% of patients at diagnosis were not treatable by surgery or percutaneous ablation (5). However, the proportion of small, early tumors is expected to significantly increase in the next years, together with the diffusion of surveillance procedures of high-risk patients, allowing tumor diagnosis at an earlier stage (4).

However, early stage HCC is difficult to detect by non invasive imaging, and AFP as "surveillance biomarker" has been dropped in current guidelines because of low sensitivity and specificity (6).

In a recent issue of hepatology, Matsubara *et al.* (7) reported on the significance of circulating TIE2-expressing monocytes (TEMs) as biomarkers for the detections of both early- and late-stage HCC.

In their study, the authors analyzed the occurrence and kinetics of TEMs in 168 HCV-infected patients including 89 with HCC, examining the frequency of TEMs, defined as CD14+CD16+TIE2+, in the peripheral blood and liver.

They found that the frequency of circulating TEMs was significantly higher in HCC patients than non-HCC patients and being higher in the liver than in the blood. Interesting the authors serially examined the frequency of TEMs in HCC patients who underwent RFA therapy or tumor resection and found that in patients without HCC recurrence, the frequency of TEMs decreased after successful HCC ablation or resection, instead in patients with subsequent HCC recurrence, TEMs increased before the apparent radiological identification of HCC, therefore, TEM frequency dynamically changes in patients in correlation with the presence or recurrence of HCC.

To assess the clinical significance of TEMs as tumor biomarkers, the authors compared various clinical parameters in patients with high or low TEM frequency and found that elevated TEM frequency in the peripheral blood is associated with a deterioration of liver function in HCC patients and suggesting that the assessment of TEMs frequency in the blood holds prognostic value.

Matsubara *et al.* also identified TEMs in HCC specimens and observed that these cells preferentially localize in perivascular tumor areas, in agreement with findings in mouse models of cancer (8). Furthermore, it was found that higher TEM infiltration correlated with increased microvessel density in the tumors, possibly suggesting that HCC-infiltrating TEMs are proangiogenic.

These new findings reported by Matsubara *et al.* provide further evidence that BM-derived cells may serve as biomarkers for HCC, also the data suggest that these cells could be involved in the pathogenesis of HCC and have the potential to regulate HCC angiogenesis and progression, possibly by releasing proangiogenic growth factors (9).

Indeed, detecting small HCCs during screening procedures will translate into survival benefits but further studies should be conducted to confirm the role of this biomarker before such prognostic marker can be used in clinical practice.

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Serum biomarkers for early diagnosis of hepatocellular carcinoma

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Abstract: Globally, many guidelines for hepatocellular carcinoma (HCC) treatment recommend HCC screening and surveillance. Serum biomarkers are striking potential tools to screen for and diagnose HCC early thanks to the non-invasive, objective, and reproducible assessments they can potentially enable. α -fetoprotein (AFP) is the biomarker most widely used to test for HCC, but the sensitivity and specificity of AFP vary widely, and total AFP is not always specific, especially when HCC is in its early stages. Recent years, research into multiple serum biomarkers to detect HCC early has garnered attention around the world. Multiple reports have found that combined testing with des- γ -carboxyprothrombin (DCP) and AFP has a sensitivity of 47.5-94.0% and a specificity of 53.3-98.5% in detecting HCC early. Most recently, using new reliable serum biomarkers, such as Dickkopf-1 (DKK1) and Midkine (MDK), to complement AFP as a new trend is expected to be used to facilitate screening for and diagnosing HCC at an earlier stage. However, more such studies are needed before they can be included as valid biomarkers in programs to screen for HCC and in strategies to diagnose patients who present with liver masses.

Keywords: Liver cancer; early detection; tumor marker; sensitivity; specificity

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Hepatocellular carcinoma (HCC) is the major histologic subtype of liver cancer, which is largely a problem of the less developed regions where 83% (50% in China alone) of the estimated 782,000 new liver cancer cases worldwide occurred in 2012 (1). HCC is the fifth most common cancer in men and is most prevalent in Eastern and South-Eastern Asia (31.9/100,000 and 22.2/100,000, respectively), it is the second most common cause of death from cancer worldwide and is estimated to be responsible for nearly 746,000 deaths in 2012 (1). Currently, surgical resection and liver transplantation offer the best potential for treating HCC but are only feasible when tumors are detected early (2,3). The overall 5-year survival rate for patients with HCC is about 40%, but liver resection of early HCC could result in a 5-year survival rate of 60-70% (4). Screening programs in many Asian countries have improved the early detection of HCC and have had a positive impact on survival, but most Asian patients with HCC still present with advanced stage disease (5,6). Thus, a well-considered strategy to screen for and diagnose HCC at an earlier stage is urgently needed

when curable interventions can be offered to achieve long-term disease-free survival for patients (7).

Globally, many guidelines for HCC treatment recommend HCC screening and surveillance, including the guidelines established by the American Association for the Study of Liver Disease (AASLD), the National Comprehensive Cancer Network (NCCN), and the Asian Pacific Association for the Study of the Liver (APASL) (8). In general, imaging tools have been widely used in the US and Europe while serum biomarkers are widely used in HCC screening and diagnosis in Asia. Diagnostic imaging techniques include ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). According to a systematic review, ultrasonography has a sensitivity of 60% and a specificity of 97%, CT has a sensitivity of 68% and a specificity of 93%, and MRI has a sensitivity of 81% and a specificity of 85% (9). Ultrasound is the most common imaging tool used to screen for HCC thanks to its features such as simplicity, low cost, minimal invasiveness, and the fact that it allows real-time observation. However, successful

ultrasound detection relies on the expertise of the physician, the availability of ultrasound equipment, and the echo texture of the liver. Thus, evaluating the actual sensitivity and specificity of ultrasound detection is difficult because of the lack of standards (10,11).

Serum biomarkers are striking potential tools to screen for and diagnose HCC early thanks to the non-invasive, objective, and reproducible assessments they can potentially enable. α -fetoprotein (AFP) is the biomarker most widely used to test for HCC, but the sensitivity and specificity of AFP vary widely, and total AFP is not always specific, especially when HCC is in its early stages. AFP has been found to have a sensitivity of 41-65% and a specificity of 80-90% when detecting HCC given an AFP cut-off of 20 ng/mL (12). However, up to 50% of patients with HCC have an AFP level below 20 ng/mL (13), and elevated levels of AFP can also be found in patients with non-malignant chronic liver disease, including 15-58% with chronic hepatitis and 11-47% with liver cirrhosis (12,14). Thus, AFP cannot be used as a sole tool to screen for and diagnose HCC. New reliable serum biomarkers need to be identified soon to complement AFP in order to improve clinical outcomes for patients.

Two other serum biomarkers besides AFP—the *lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) and des- γ -carboxyprothrombin (DCP, also known as prothrombin-induced by vitamin K absence-II, PIVKA-II)—have been studied around the world to explore their clinical usefulness in screening for and diagnosing HCC. According to HCC Guidelines in Japan, ultrasonography and measurement of AFP, AFP-L3, or DCP should be performed every 3-4 months in the highest-risk group (HBV- or HCV-related liver cirrhosis patients) and every six months in the high-risk group (patients with HBV- or HCV-related chronic liver disease or liver cirrhosis due to other causes) (15,16). Currently, AFP, AFP-L3, and DCP are used widely and routinely as a tool to screen for HCC in Japan, and these tests are covered by Japan's national health insurance as serum biomarkers to screen for HCC in clinical settings. Due to the routine practice of screening for HCC among high-risk patients, HCC nodules have been detected in the early stage in more than 60% of patients in Japan (17).

Since Liebman *et al.* first reported DCP in the plasma of 90% of patients with HCC in 1984 (18), substantial evidence has been assembled through numerous clinical trials, and studies have demonstrated the clinical usefulness of serum DCP levels to screen for and diagnose HCC. Multiple reports have found that combined testing with DCP and AFP has a sensitivity of 47.5-94.0% and a specificity of 53.3-

98.5% in detecting HCC early (5).

Recent years have also seen many studies on the clinical usefulness of other serum biomarkers in detecting HCC early, including Golgi protein-73 (GP73), glypican-3 (GPC3) and gamma-glutamyltransferase (GGTII). Most recently, research on Dickkopf-1 (DKK1) and Midkine (MDK) as diagnostic serum biomarkers has garnered interest.

In *Lancet Oncology*, Shen *et al.* published a retrospective, cross-sectional study in 2012 that assessed whether measurement of DKK1 concentrations in serum could enhance its accuracy at diagnosing HCC. Shen *et al.* used receiver operating characteristic analysis to calculate the optimum cut-off concentration in a test cohort of 424 patients with HCC and 407 controls without HCC (213 were healthy, 98 had chronic HBV infection, and 96 had liver cirrhosis) (19). They found that serum levels of DKK1 were significantly higher in patients with HCC than in all of the controls; that DKK1 was highly accurate at diagnosing AFP-negative patients with HCC, including patients with early-stage HCC; and that measurement of DKK1 and AFP together improved the accuracy with which HCC was diagnosed in comparison to any test alone. These findings add a new piece to the puzzle of diagnosing HCC and they open the door for further investigation of this promising tumor biomarker in independent, prospective studies (20).

In *Clinical Cancer Research*, Zhu *et al.* published a study in 2013 involving three independent cohorts with a total of 933 participants (388 patients with HCC and 545 different controls). Zhu *et al.* evaluated the value of serum MDK as a diagnostic biomarker of HCC, and particularly for patients who were negative for AFP and who had HCC in an early stage (21). They found that MDK levels were significantly elevated in HCC tissues as well as in serum samples; that serum MDK had a markedly higher sensitivity than AFP (86.9% *vs.* 51.9%) at diagnosing HCC but similar specificities (83.9% *vs.* 86.3%); that MDK has a significantly higher sensitivity than AFP (80% *vs.* 40%) even at diagnosing very early-stage HCC; that its sensitivity could be as high as 89.2% when diagnosing cases of AFP-negative HCC; and that serum MDK levels decreased significantly in patients with HCC after curative resection and rose again when the cancer recurred.

These two studies suggested that the novel serum biomarkers DKK1 and MDK can augment the measurement of AFP when diagnosing HCC, and particularly when diagnosing patients who are negative for AFP and/or who have HCC in an early stage. However, these studies were small in scale and involved few patients. According to the guidelines on

phases of evaluating an early detection biomarker for cancer developed by the National Cancer Institute's Early Detection Research Network (22), more prospective, randomized controlled trials need to be conducted at multiple centers to provide further validation using a larger cohort of serum HCC samples with hepatitis B and hepatitis C infectious liver disease, nonalcoholic fatty liver disease (NAFLD), and alcohol-induced liver disease (ALD).

In conclusion, research into multiple serum biomarkers to detect HCC early has garnered attention around the world. Using new reliable serum biomarkers, such as DKK1 and MDK, to complement AFP as a new trend is expected to be used to facilitate screening for and diagnosing HCC at an earlier stage. However, more studies of serum DKK1 and MDK are needed before they can be included as valid biomarkers in programs to screen for HCC and in strategies to diagnose patients who present with liver masses.

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Surgical resection for hepatocellular carcinoma

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Abstract: The incidence of hepatocellular carcinoma (HCC) is growing in the United States due to increasing rates of cirrhosis from viral hepatitis, alcohol, and fatty liver disease. The elevated incidence, along with the associated high mortality rate for patients with this diagnosis, highlights the importance of an understanding of the optimal management of HCC. Surgical resection and liver transplantation offer the only options for long-term cure. However, without careful patient selection, meticulous intraoperative technique and perioperative management, liver resection in patients with underlying cirrhosis is associated with a significant risk of postoperative morbidity and/or mortality. This article will describe key considerations in patient selection and recent improvements in surgical technique and peri-operative management that have increased the safety of liver resection in patients with HCC, particularly those with underlying cirrhosis.

Keywords: Surgical resection; hepatocellular carcinoma (HCC); liver transplantati; intraoperative technique; perioperative management; liver resection

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Background

Worldwide, hepatocellular carcinoma (HCC) is the 6th most common cancer and has the 3rd highest mortality of any cancer (1). While the burden of HCC is highest in developing countries, the incidence is rising in the United States and is expected to continue to rise for the next two decades (2-4). Approximately one-third of patients with cirrhosis due to hepatitis C will eventually develop HCC (5). Obesity also appears to be an emerging significant risk factor for the development of HCC and interacts synergistically with both alcohol and tobacco use to further increase the risk (6,7). For patients affected by this often devastating disease, surgical therapy represents the only hope for cure.

Over the last 20 years, significant advances in both surgical technique and peri-operative care have resulted in improvements in morbidity and mortality rates after major liver resection. Despite these advances, a recent analysis of the SEER-Medicare database suggests that surgical therapy remains widely under-utilized in this patient population (8). Educating the healthcare community about the role of surgical therapy in the management of patients with HCC is likely the most effective means of increasing

its utilization, and by extension, improving life expectancy for these patients.

Methods

Articles for this review were chosen by performing a PubMed search for relevant English language articles using keywords including HCC, surgery, hepatectomy, and related topics. Preference was given to randomized controlled trials for topics for which those were available. For topics for which no randomized controlled trials were available, the methodology of available articles was reviewed to determine the quality of evidence. Preference was given to those studies with prospective data collection and then to carefully conducted large retrospective studies.

Pre-operative assessment of resectability

While determining which patients are appropriate candidates for surgical resection can be challenging for many malignancies, this task can be especially difficult in the case of patients with HCC because the majority of them

have some degree of compromised liver function that may represent a contraindication to an otherwise anatomically feasible resection. For this reason, a careful pre-operative assessment is critical for these patients and must include an evaluation of medical comorbidities, tumor location, baseline liver function and tumor biology.

The same medical comorbidities that would render a patient unsuitable for major abdominal surgery are applicable in patients being considering for hepatectomy for HCC. Determination of the anatomic resectability of an HCC requires careful consideration of technical factors (9). In general, liver tumors are technically resectable if they can be removed with negative margins while preserving a liver remnant with adequate hepatic arterial and portal venous inflow, venous outflow, biliary drainage, and sufficient parenchyma to support critical liver functions (10). While this axiom holds true for HCC, determination of what constitutes 'sufficient remnant parenchyma' necessitates an understanding of the patient's baseline liver function.

The incidence of death from postoperative liver failure after right hepatectomy has been shown to be significantly higher in patients with fibrosis or cirrhosis compared to patients with normal background liver parenchyma (11). Prior studies have also shown that for patients with normal livers a functional liver remnant of 20% of standardized liver volume is adequate to avoid postoperative liver-related mortality (12,13), but for patients with cirrhosis, a 40% remnant is generally accepted as the lower limit of what is necessary for a safe resection (14,15). Although these percentage point thresholds are useful as guidelines, they are not a direct reflection of liver function. In some areas, ICG retention testing is available as a direct measure of liver function. In the absence of this test, patients with marginal functional liver remnant are recommended to have preoperative portal vein embolization performed, as this allows the surgeon to test the regenerative capacity of the liver prior to operative intervention.

In cirrhotic patients being evaluated for possible liver resection, the presence of portal hypertension is one of the strongest predictors of poor outcome (16,17). Frequently, patients with advanced cirrhosis and portal hypertension will describe a history of hepatic encephalopathy, gastrointestinal bleeding, easy bruisability, and ascites. These signs and symptoms should be sought in all cirrhotic patients and combined with the prothrombin time and serum albumin to determine a Childs-Turcotte-Pugh score (18). Portal hypertension is also characterized by a hepatic venous pressure gradient ≥ 10 mmHg, the presence of esophageal varices

or splenomegaly and thrombocytopenia (platelet count $< 100,000/\text{mm}^3$). Preoperative imaging should be carefully evaluated for the presence of varices and/or splenomegaly and in patients at high risk of portal hypertension, direct measurement of the hepatic venous pressure gradient should be considered (19).

The Model for End-Stage Liver Disease (MELD) score was originally developed as a tool to predict the survival of cirrhotic patients after transjugular intrahepatic portosystemic shunt placement, but was subsequently shown to be predictive of survival in patients with cirrhosis and has been adopted as a means of prioritizing patients for liver transplantation (20). It is calculated by the formula: $9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{INR}) + 6.43$ and, therefore, does not rely on any tumor characteristics for predicting prognosis. Despite this limitation, its powerful stratification of severity of liver disease makes it useful for the majority of patients with HCC. One of the first studies correlating MELD score with postoperative outcomes after resection of HCC in patients with cirrhosis was from the Mayo Clinic. This study showed that liver resection patients with MELD scores of 9 and higher had significantly higher perioperative mortality (29% *vs.* 0% for patients with lower MELD scores) and significantly lower 5-year survival rates (21). Another more recent retrospectively study of MELD scores in patients with HCC who underwent liver resection corroborated a MELD cutoff of 9 as an independent predictor of higher perioperative mortality and lower 3-year postoperative survival (22).

Several oncologic factors should also be considered when evaluating a patient's appropriateness for resection of an HCC. In many cases, the first challenge may lie in determining whether a suspicious lesion in a patient with chronic liver disease truly represents a cancer or just a regenerating nodule. For cirrhotic patients with suspicious lesions measuring 1-2 cm, the EASL-EORTC clinical practice guidelines for the management of HCC support either pathologic confirmation with biopsy or the presence of arterial phase contrast uptake with venous phase contrast washout (i.e., the radiological hallmark) on two concordant imaging techniques as diagnostic criteria (16,23). Once a diagnosis of HCC has been established, the next factor that should be evaluated is whether any extrahepatic disease is present. Both of these factors can be accurately assessed with magnetic resonance imaging (MRI) and/or computed tomography (CT) (17).

Regarding evaluation of intrahepatic disease burden, the joint consensus statement from the Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract recommends MRI as the preferred preoperative imaging for HCC because of its performance characteristics (17). Accurate preoperative imaging is essential for determining the number and location of tumors as well as the relationship of the tumor(s) to the major vascular structures within the liver. As a final assessment of resectability, intraoperative ultrasound (IOUS) should be utilized to confirm the number and location of the tumor(s) as well as the anatomy of the major vascular structures within the liver immediately prior to resection.

Staging

Clinical staging systems rely on non-pathologic tumor and/or patient characteristics. These systems aim to stratify patients by anticipated survival and suitability for different treatment modalities and are applicable for all patients with HCC, regardless of the extent of disease (18). Among the clinical staging systems for HCC, only the Barcelona Clinic Liver Cancer (BCLC) staging system has been widely tested, externally validated (19,24,25), and recommends appropriate treatment strategies for specific prognostic classifications (16,26). For these reasons, the EASL-EORTC Guidelines for the management of HCC recommend it as the preferred clinical staging system. The BCLC system classifies patients into 5 stages (0, A, B, C, and D) based on tumor-related variables (number, size, presence of vascular invasion, involvement of lymph nodes, and presence of metastases), liver function (Child-Pugh score), and patient functional status (ECOG) (27). Patients classified as stage 0 are Child-Pugh A with an ECOG of 0 and have a single tumor <2 cm in size. Such patients are appropriate candidates for liver resection. Stage A patients are Child-Pugh A or B with a performance status of 0 and have 1-3 tumors, all ≤ 3 cm. These patients are candidates for resection, liver transplantation, or ablative therapies. Together these two groups of patients have an expected median overall survival of 60 months or longer (27). Stage B patients are also Child-Pugh A-B with a performance status of 0, but have multinodular tumors and so are not candidates for curative therapy and have an expected median overall survival of about 20 months. Patients in this class are most frequently treated with chemoembolization. Patients who are stage C are also Child-Pugh A-B, but have a lower performance

status of 1-2 and have portal vein invasion, positive lymph nodes, or metastatic disease and thus, have an expected median overall survival of only 11 months. Such patients would be considered for treatment with sorafenib (27). Stage D patients are terminal patients with a performance status >2 and Child-Pugh C, have a limited survival <3 months, and should be treated with best supportive care (27).

Preoperative preparation

Portal vein embolization

Portal vein embolization (PVE) is an important adjunct procedure in patients requiring major hepatectomy that provides an assessment of the ability of the future liver remnant to hypertrophy after hepatectomy. This ability closely correlates with avoidance of liver failure after hepatectomy in cirrhotic and noncirrhotic patients (28). A prospective clinical trial of PVE prior to right hepatectomy stratified patients by those with normal livers and those with chronic liver disease (29). All the patients in this study with chronic liver disease were undergoing hepatectomy for treatment of HCC. The authors found that while patients with chronic liver disease were slightly less likely to experience hypertrophy after PVE (86% *vs.* 100% of patients with normal livers) and had a lower median absolute increase in functional liver remnant percentage (9% \pm 3% *vs.* 16% \pm 7% for patients with normal livers), the use of portal vein embolization in patients with fibrosis due to chronic liver disease significantly lowered the rate of postoperative complications, improved postoperative liver function tests, and shortened intensive care unit and hospital lengths of stay (29). This study established that PVE was feasible, safe, and beneficial in patients with HCC and severe fibrosis/cirrhosis. The authors also hypothesized that a lack of hypertrophy in the future liver remnant after PVE was a sign that the underlying liver parenchyma lacked the ability to regenerate and so should be considered a contraindication to major hepatectomy (29), a theory that has since become widely accepted (14,28). Subsequent retrospective studies have corroborated the safety of PVE in patients with HCC and cirrhosis and have also found equivalent overall and disease-free survival rates for patients undergoing lesser hepatectomy for HCC without pre-operative PVE as for those requiring PVE for major hepatectomy (30,31). Patients with HCC and advanced forms of chronic liver disease may have physiologic and anatomic factors that represent a contraindication to use of PVE, including portal

vein invasion, portal vein thrombosis, tumor extension into the functional liver remnant, uncorrectable coagulopathy, renal failure, and portal hypertension (28). In most cases, these same features contraindicate any resectional therapies and serve as guideposts for the dangers of local therapy of any type.

TACE + PVE

Concerns have been raised about a compensatory increase in hepatic arterial blood flow within the embolized liver of patients with chronic liver disease who undergo PVE, a physiologic change which might either limit the hypertrophy of the future liver remnant or result in increased blood flow to the tumor, potentially speeding growth (32). Combining PVE with transcatheter arterial chemoembolization (TACE) has been suggested as an approach to address these concerns. The use of this combination of procedures for patients with HCC and cirrhosis has been reported in retrospective studies, two of which have compared results after the combined procedure with those after PVE alone and have shown a higher mean increase in the percentage of the future liver remnant volume, a lower incidence of postoperative liver failure, higher rates of complete tumor necrosis, and higher recurrence-free and overall survival rates for the patients treated with the combined procedure versus those treated with PVE alone (32,33). Although the efficacy of the dual procedure has yet to be proven in prospective trials, the results from these studies suggest this approach warrants continued consideration.

Technical considerations

Open resection

Non-anatomic vs. anatomic resections

HCC tumors have a propensity for local portal vein invasion with extension toward the main portal vein, indicating that anatomic resection of the segmental, sectional, and lobar vascular structures, depending on the site and size of the tumor, may improve outcomes. A Japanese study compared results for 207 patients undergoing either anatomic (based on vascular pedicles) or non-anatomic resections for HCC and found that anatomic resection was an independent predictor of improved recurrence-free survival (34). A smaller French study reported similar results with the anatomic resection group having significantly improved

disease-free survival rates (35). For this reason, anatomic resections are recommended in the EASL HCC guidelines as the preferred approach provided that adequate remnant liver volume can be preserved (16).

Margins

Micrometastases are frequently found within the region surrounding HCCs, providing support for the use of wide resection margins for these tumors (36). The aim of adequately treating micrometastatic disease, however, must be balanced against the need to preserve a maximal volume of functional liver parenchyma to minimize the risk of postoperative liver insufficiency (particularly in patients with underlying cirrhosis) and to preserve options for future treatment of recurrent disease. In an effort to balance these competing aims, a prospective randomized controlled trial was undertaken to compare 1 vs. 2 cm margins for patients with solitary resectable HCCs (37). This trial, in which anatomic resections were performed in the majority of patients, found that 2 cm gross resection margins were associated with improved overall survival rates and that assignment to the wide margin group was an independent predictor of lower risk of death in multivariate analysis. In addition, higher recurrence-free survival rates were seen in the patients in the wide margin group, as were lower rates of recurrences at the resection margins and lower rates of multifocal recurrences. Multivariate analysis of factors associated with tumor recurrence showed that the only two independent predictors were the presence of micrometases and the width of the final resection margin. Patients in the wide margin group also had significantly higher 1- and 2-year survival rates after tumor recurrence (37). These results provide compelling evidence favoring the use of anatomic resections with 2 cm margins, when feasible, for patients with solitary HCCs.

Low central venous pressure (CVP) anesthesia

Recognition of the relationship between CVP and blood loss during parenchymal division has been one of the key factors contributing to the improvement in the safety of liver resections in recent years. A prospective study from Australia examined the relationship between CVP and blood loss during hepatectomy (38). This study found that patients with a mean CVP during parenchymal transection of 5 cm H₂O or less had a median blood loss of 200 versus 1,000 mL in patients with a CVP higher than 5 (P=0.0001) and a 5% transfusion rate versus a 48% transfusion rate. Maintenance of a low CVP can typically be accomplished

by fluid restriction, but in cases where this strategy is inadequate, use of vasodilators or diuretics may also be effective.

(Vascular inflow occlusion) Pringle maneuver

The use of the Pringle maneuver (hepatic artery and portal vein clamping) as a method of minimizing blood loss during hepatectomy has been evaluated in a randomized controlled trial (39). This trial showed that intermittent use of the Pringle maneuver (20 minutes of clamp time followed by a 5-minute clamp-free period) decreased the blood loss per cm² of transection surface, reduced the transection time and resulted in lower early postoperative serum bilirubin levels and higher postoperative transferrin levels in cirrhotic patients without significantly changing the morbidity or mortality rates or the 15-minute ICG-retention rate on postoperative day#8. This finding is significant because other studies have shown that increased intraoperative blood loss is an independent predictor of postoperative morbidity after hepatectomy and correlates with shorter overall and recurrence-free survival for patients with HCC (40,41).

Cross clamping of the infrahepatic vena cava is another means of decreasing blood loss during parenchymal transection. This technique has been compared to a strategy of maintaining a low CVP by using anesthetic techniques (fluid restriction, diuretic administration, use of vasodilators) in a randomized controlled trial without routine use of portal triad occlusion (42). This trial found that infrahepatic vena cava clamping was associated with significantly lower total intraoperative blood loss, lower blood loss during parenchymal transection, and less intraoperative hemodynamic instability than anesthetic interventions to maintain a low CVP. The group of patients in whom vena cava clamping was utilized, however, also had a significantly higher rate of pulmonary embolism, which limited the authors' enthusiasm for routine implementation of this strategy (42). A second randomized trial also compared these two strategies in combination with portal triad occlusion (43). This trial also found that vena cava clamping reduced blood loss during parenchymal transection and resulted in fewer hemodynamic changes, but in contrast to the earlier trial, also found that it was associated with a more rapid improvement in postoperative bilirubin levels. This trial reported similar rates of complications in the two groups without specific mention of whether any patients suffered a pulmonary embolism. In addition, it specifically examined results in the subgroup of patients with moderate to severe cirrhosis and found that the effect on blood loss

during parenchymal transection was also significant for this high-risk subgroup (43). Combined, these data indicate that judicious use of perihepatic vascular control maneuvers can improve outcomes in cirrhotic liver resection patients by limiting blood loss.

Laparoscopic resection

While no randomized controlled trial has compared laparoscopic versus open approaches to resection in patients with HCC, four meta-analyses of nonrandomized studies have examined both short-term postoperative and longer-term oncologic outcomes after laparoscopic and open liver resection for this group of patients (44-47). Each of these meta-analyses found that laparoscopic resection was associated with significantly less blood loss, lower transfusion requirements, lower overall morbidity, and shorter length of hospital stay without a significant difference in length of operation, surgical margin status, or tumor recurrence rates. The two meta-analyses which examined postoperative mortality also found no significant difference after laparoscopic versus open resection (44,45). Specific types of postoperative complications were also examined in two of the studies, with both finding that laparoscopic resections were associated with significantly lower rates of pulmonary complications, ascites, and lower rates of liver failure, although this reached significance in only one of the two studies (44,45). While these results provide compelling evidence that laparoscopic resection is safe for patients with HCC and likely improves short-term postoperative outcomes, it should be kept in mind that the studies included in these meta-analyses included few major hepatectomies and few tumors in segments VII and VIII, so caution should be taken in applying these results to more challenging liver resections.

Radiofrequency ablation (RFA)

The use of percutaneous RFA for treatment of solitary HCCs ≤ 5 cm has been compared to surgical resection in a prospective randomized controlled trial (48). In this trial, ultrasound was utilized to confirm that ablation achieved a hyperechoic treatment zone that was larger than the target HCC. With this meticulous RFA technique, 1-, 2-, 3-, and 4-year overall and disease-free survival rates were achieved that were equivalent to those after resection. A second randomized controlled trial compared percutaneous RFA to hepatectomy for HCCs within the Milan criteria (solitary

tumor <5 cm or up to 3 tumors all <3 cm) (49). In contrast to the earlier trial, this study found lower rates of 1-, 2-, 3-, 4-, and 5-year overall and recurrence-free survival for the patients treated with RFA. A third randomized controlled trial compared RFA and resection for HCCs up to 4 cm in diameter with one or two tumors and found that the difference in overall and recurrence-free survival between the two groups was not statistically significant (50). While the existing data are inconclusive as to whether results after RFA for small HCCs are as good as those after resection, they do suggest that RFA is a reasonable treatment strategy for such tumors, particularly in patients who may be at higher risk after resection or who prefer not to undergo a major operation.

Management of patients with major vascular invasion

Portal vein thrombosis and major vascular invasion have been shown to be robust prognostic factors for increased mortality in patients with cirrhosis and HCC (51,52). Even after resection the 5-year survival rates of patients with macroscopic invasion of the 1st order branches or main portal or hepatic vein trunks are only about 10-12% (53,54). In addition, reported median survival rates for these patients after treatment with transarterial chemoembolization, chemotherapy, or radiation rarely exceed 12 months, likely because of the high incidence of rapid development of extrahepatic metastatic disease after major vascular invasion/tumor thrombus (55). The most promising results for patients with major vascular invasion have been reported in a retrospective study of patients treated with preoperative transcatheter arterial chemoembolization followed by hepatectomy (56). In this study, the 18 patients who received both therapies had an 82% 1-year and 42% 3- and 5-year overall survival rates. While these results have yet to be confirmed in a large, prospective trial, at present, this combined therapy seems to be a reasonable approach, when technically feasible, for this high-risk group of patients.

Resection vs. transplantation

Although surgical resection has never been directly compared to liver transplantation for HCC in a randomized clinical trial, a 1999 study from the BCLC attempted to answer the question of which provides superior survival with a retrospective intention-to-treat analysis comparing patients who underwent resection with those who were

listed for liver transplantation (57). The results of this study showed similar 1-, 3-, and 5-year intention-to-treat survival rates for both groups, but they also showed that in later years of the study, when rates of drop out on the transplant waiting list were higher, intention-to-treat survival rates decreased for the transplant group. Although the results of this study are difficult to interpret because nearly all the patients in the resection group were Child's A, compared to less than 1/3 of the patients in the transplant group and the authors acknowledge that patients who were felt to be unsuitable for resection (largely on the basis of elevated portal pressures) were referred for transplant evaluation, this study does highlight the importance of considering waitlist dropout rates when selecting transplantation as the preferred treatment strategy for a patient with HCC.

In another recent intent-to-treat retrospective analysis of resection *vs.* transplantation for solitary small HCCs, transplantation was found to result in improved outcomes for patients with tumors >2 and <5 cm (58). It should be taken into account, however, when interpreting these results that the waitlist time in the study was shorter than that expected at most U.S. transplant centers. In a subset analysis, the authors of this study found that even with a short waitlist time, patients with tumors ≤2 cm had equivalent survival rates after resection and transplant evaluation (58). Among patients who experienced recurrence of HCC after resection (the majority of whom had hepatitis C), only 22% were eligible for salvage transplantation. Others have proposed strategies for combining resection and transplantation for HCC such as immediately listing patients with high risk pathology for post-resection transplantation or using resection as a bridge therapy for patients likely to have a long waitlist time (59).

Complications

Although postoperative mortality after major hepatectomy has declined significantly with improvements in surgical and anesthetic techniques, complications after hepatectomy for HCC continue to occur in up to 50% of patients and have been shown to correlate with a lower overall survival rate (60,61). While patients undergoing hepatectomy for HCC are susceptible to the same cardiopulmonary, infectious and bleeding complications as patients undergoing other types of major general surgical procedures, they are also susceptible to specific liver-related complications, which are worthy of further discussion.

A recent retrospective study reported a 12.8% incidence

of bile leak following hepatectomy for HCC (62). This study identified repeat hepatectomy and prolonged operative time as independent risk factors for bile leak and showed that occult biliary strictures as a result of previous therapy for HCC and intraoperative hepatic duct injury during repeat hepatectomy were the main factors associated with bile leakage that required either percutaneous transhepatic biliary or endoscopic retrograde biliary drainage for definitive management.

Postoperative liver insufficiency is closely associated with high mortality rates following major liver resection (28). Many definitions of posthepatectomy liver failure have been used in the literature and although recently a standardized definition has been proposed, it has yet to significantly impact the literature, making it difficult to understand the true incidence of this complication (63). Nonetheless, it is critical to recognize that this entity is characterized by persistently high bilirubin levels and abnormal coagulation studies, is typically associated with large volume ascites, and it puts patients at high risk of subsequent episodes of sepsis, multisystem organ failure, and death (64). The most effective treatment for this often devastating complication is prevention through careful selection of patients for resection, particularly in the setting of underlying cirrhosis, and judicious use of PVE for patients requiring major hepatectomies for treatment of their tumors.

Subsequent followup

Survival after resection and risk factors for recurrence

Five-year overall survival rates of 40-50% have been reported in modern series of patients treated with hepatectomy for HCC (52,65). Most factors predicting poor overall survival are associated with poor tumor biology (high AFP levels, large tumor size, major vascular invasion, extrahepatic metastatic disease, and positive margins) (52). Patients who have undergone hepatectomy for HCC are at high risk of developing recurrent disease, with 40-80% of patients recurring within five years of resection (65,66). The most significant risk factor for recurrence in patients with HCC is the presence of underlying cirrhosis (67) and active hepatitis. For patients with cirrhosis, genetic alterations frequently exist that represent a field defect that puts the entire liver parenchyma at risk for development of cancer. In addition, the presence of satellite nodules and venous invasion in the primary tumor also increase a patient's risk of developing recurrent intrahepatic disease (68).

At a minimum, patients with a history of resected HCC should undergo surveillance with liver ultrasound and an alfafetoprotein level every six months.

Management of recurrence

Two different types of intrahepatic recurrences from HCC have been identified—those due to intrahepatic metastases and those due to multicentric occurrences (69). Intrahepatic metastases result from spread of the primary tumor to other parts of the liver, predominantly due to dissemination via the portal vein, whereas multicentric occurrences are *de novo* primary tumors arising within a high-risk parenchyma. As might be expected based on these different etiologies, the timing of recurrence and the prognosis following recurrence differs for the two types. Multiple studies have shown that survival after repeat resection of intrahepatic metastases is worse than after repeat resection for multicentric recurrences (69,70). One carefully conducted retrospective study of repeat hepatectomy for HCC found that the most reliable clinical factor for differentiating between intrahepatic metastases and multicentric recurrences was the time between the initial resection and the discovery of the recurrence, with 18 months being the cutoff point that most accurately differentiated the two types (70). Although management of recurrence should be individualized to patient circumstances, those patients with early recurrence after resection are generally recommended to have TACE, radioembolization or systemic therapy, while those with longer disease free intervals may benefit from repeat resection.

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Footnote

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Laparoscopic liver resection: basic skills for peripheral lesions

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Abstract: An evaluation of the literature demonstrates atypical wedge or single segment resections to be the most commonly performed laparoscopic liver procedures. Lesions that are both visible on the surface of segments 2-6 and $\leq 2-3$ cm can be resected by most surgeons holding a fundamental understanding of liver anatomy. These criteria are based on the anatomical circumstance that sectoral and segmental pedicles should not course through depths necessary to obtain negative margins for these sized and positioned lesions. Videos of laparoscopic liver resections referenced in PubMed demonstrate complex procedures that are rarely performed and assume an advanced skill set for laparoscopic dissection and transection of parenchyma and management of vascular and biliary structures. Herein is demonstrated basic skill for peripheral resections via two cases in one video, so that these procedures can be safely performed by surgeons with commonly available laparoscopic equipment.

Keywords: Hepatectomy; laparoscopy; minimally invasive; video-audio media

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Introduction

Integration of laparoscopic techniques in to hepatic surgery has been slower than in other surgical disciplines. Case-control studies have repeatedly demonstrated these techniques to be safe, have equivalent oncologic outcomes and offer many of the patient-centered benefits assumed when comparing laparoscopy with laparotomy (1,2). An evaluation of the literature demonstrates atypical (wedge) or single segment resections to be the most commonly performed procedures, and there is little doubt the number of such cases performed far outnumbers those in the literature (3). It is also fair to assume these procedures are frequently performed at non-specialized centers. By way of example, it is well recognized that laparoscopic colorectal surgery is practiced by general surgeons outside of tertiary institutions (4-6).

The 2008 Louisville Statement was initiated by the world's leading laparoscopic liver surgeons in order to set forth principles for the safe dissemination of these practices (7). According to the Statement, single lesions located in liver segments 2 to 6 that are ≤ 5 cm are candidate

lesions for laparoscopic resection at centers where there is combined expertise in liver and laparoscopic surgery. It was concluded that emphasis should be placed on avoidance of patient harm that is likely to come from inexperience rather than safety issues inherent in the procedures (7).

Recognizing laparoscopic liver surgery is currently dominated by wedge resections and likely often occurs outside of specialized centers, it behooves to disseminate safe technical practices and criteria for surgeons. Lesions that are both visible on the surface of segments 2-6 and $\leq 2-3$ cm can be resected by most surgeons holding a fundamental understanding of liver anatomy. These stricter criteria are based on the anatomical circumstance that sectoral and segmental pedicles should not course through depths necessary to obtain negative margins for these sized and positioned lesions. Larger or deeper lesions should be referred to specialists. Hepatocellular carcinoma, as opposed to metastatic lesions, should also be referred to specialized centers. This is because of the increased operative risks associated with underlying liver disease and portal hypertension, and evidence these lesions should be resected inclusive of the segmental pedicle to achieve better



Figure 1 Laparoscopic liver resection: basic skills for peripheral lesions. Available online: <http://www.thehbsn.org/article/view/3376/4197>

outcomes (8-10).

A PubMed search for the terms *laparoscopic liver* and *video* demonstrates many films of complex resections such as hemi- or extended hepatectomy, posterior segmental resection, or involving biliary reconstruction. Though instructive (and often elegant), these rarely performed laparoscopic procedures are not for the generalist and assume a skill set for laparoscopic dissection and transection of liver parenchyma and management of vascular and biliary structures (11). Herein is demonstrated basic skill for peripheral resections via two cases (*Figure 1*), so these procedures can be safely performed by surgeons with commonly available laparoscopic equipment, and a nominal learning curve.

Technical points

Operative planning should be based on recent triple phase cross sectional imaging that demonstrates lesion location in relation to the portal veins (i.e., pedicles) and hepatic veins. Review of images with a radiologist will be helpful. The surgeon must be able to visualize the lesion on cross-sectional imaging to be superficial if no laparoscopic ultrasound probe is available, and confirm a safe margin can be obtained without damaging the pedicles or encountering large hepatic vein tributaries before proceeding to the operating room. The patient should be classified as Child-Pugh A.

At least one 10-12 mm trocar is necessary for specimen extraction at the conclusion of the case, and a 10 mm 30° scope unquestionably allows for better visualization. Trocars should provide triangulation about the lesion to be

resected. Two-to-three 5 mm trocars and one 10-12 mm trocar is satisfactory, but a second 10-12 mm in place of a 5 mm trocar may be considered because it allows for urgent insertion of a locking clip applier or surgical sponge. Ligaments need only be transected if it will improve exposure. Preparation for a Pringle maneuver is rarely necessary for these resections, but is an important safety measure to be considered.

I prefer Harmonic shears for these resections (Ethicon Endo-Surgery, Inc., USA). The tapered active blade allows for dissection without significant parenchymal stretching or trauma. Dissection is further enhanced by vessels and ducts $\leq 2-3$ mm being coagulated on contact, so instrument activity does not require blade opposition. For coagulation of larger structures, exertion of pressure between blades for 3-5 s is required.

Resection margins are marked on the liver's surface using diathermy. The open jaws of a Harmonic Ace are 14 mm from edge-to-edge, and can be used as an *in vivo* measuring tape. Wide margins are not required for benign lesions, while a 10-mm margin is classically recommended for malignancies. The active blade of the Harmonic at a generator setting of 3 is used to penetrate, seal and transect the parenchyma. The jaw is slowly closed until the tissue gives way. The Harmonic is capable of sealing vessels ≤ 5 mm, and therefore any vascular or biliary structures encountered during the resections here proposed. Additional hemostasis is achieved with bipolar diathermy at generator settings of approximately 60 Watts. It may be useful to gently irrigate in order to keep the bipolar forceps from adhering to the eschar and disrupting hemostasis.

It is technically easier to resect a wedge of tissue with the base being the free edge of the liver than to core out a lesion. When a 360° coring out of a lesion is necessary, work circumferentially around the lesion with the Harmonic, progressively extending and measuring depth. Otherwise coning around the lesion and exposing the deep surface of the tumor is possible, or vascular and biliary structures can be inadvertently violated. Use of a suture is a helpful maneuver under these circumstances: a 4-0 suture is driven through the parenchyma without violating the gross tumor and used to lift the lesion away from the surrounding parenchyma to promote circumferential, consistent depth dissection. Tension should be just enough to move or elevate the lesion without tearing through the parenchyma, which will result in needless bleeding.

Regarding post-operative care, diets are advanced

immediately and patients can be discharged home the same or next day as long as hemodynamics and hemoglobin are stable 2 and 6-8 hours after the procedure.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The two patients presented here are not identifiable during the operation and both consented for their operations to be recorded for educational purposes.

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Laparoscopic resection for hepatocellular carcinoma: comparison between Middle Eastern and Western experience

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Background: Laparoscopic liver resection (LLR) is growing in popularity, but the short- and long-term outcome of patients undergoing LLR for hepatocellular carcinoma (HCC) has not yet been established.

Methods: A literature search was performed using PubMed, Scopus, and Web of Science (WoS) from cited English and Chinese publications. Clinical and survival parameters were extracted. The search was last conducted in October 2013. After application of selective criteria, 24 remaining original studies with more than 15 patients were analyzed.

Results: In the Western experience, mean operative time was between 150 to 300 minutes, and mean blood loss ranged from 55 to 452 mL. Transfusion was required in all series, ranging from 2.8% to 50%. The conversion rate ranged from 5% to 19.4%. Three cases of death were reported. General morbidity rate ranged from 1.5% to 25%. Specific complications were divided into hemorrhage (2.4% to 25%), ascites (3.7% to 15.3%), and biliary collection (0.6% to 5%). Liver insufficiency was reported in two cases. Mean hospital stay ranged from 5.4 to 15 days. In all case-matched studies, LLR was statistically associated with a shorter hospital stay. The 5-year overall survival rate ranged from 55% to 70%. No trocar-site recurrence was observed. The recurrence rate ranged from 21.4% to 50%. Comparative studies did not demonstrate any significant difference in terms of recurrence between LLR and open liver resection (OLR). In the Middle Eastern experience, mean operative time ranged from 147 to 325 minutes, and mean blood loss ranged from 88 to 808 mL. Transfusion was required, ranging from 1.8% to 19.2%. The conversion rate ranged from 1.8% to 18.6%, and four series reported no conversion. There was no mortality. The main specific complication was ascites (1.7% to 26.6%). A biliary collection was reported in only two series (10.7% and 13.3%), and only one case of postoperative liver insufficiency was reported. Mean hospital stay ranged from 4 to 11.5 days. Statistically, three comparative studies reported a shorter postoperative hospital stay following LLR versus OLR. The 5-year overall survival rate ranged from 50% to 76.6%. Comparative studies did not demonstrate any significant difference in terms of overall survival and recurrence rate between LLR and OLR. No trocar-site recurrence was reported. The recurrence rate ranged from 26.9% to 45.5%, and two series reported no recurrence.

Conclusions: Laparoscopic surgery should be considered an acceptable alternative for the treatment of HCC.

Keywords: Laparoscopic liver resection (LLR); hepatocellular carcinoma (HCC); outcome; survival; morbidity; review

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Currently, the treatment of HCC is multidisciplinary but surgery remains the gold standard. HCC can be treated by either liver resection or liver transplantation (LT). Resection can precede LT according to different strategies such as primary therapy, patient selection for LT based on tumor histology or as a bridge treatment before LT (1). In this context, the development of minimally invasive surgery has led to an increase in laparoscopic liver resection (LLR) for HCC in which the possibility of repeat surgery is normally accepted.

The LLR technique could be divided into three main categories based on the Louisville statement, i.e., pure laparoscopy, hand-assisted laparoscopy, and the hybrid technique (2). Pure laparoscopy involves the performance of the entire liver resection using laparoscopic ports only. The hand-assisted approach is defined as laparoscopy with the addition of a hand-port placed to facilitate the procedure, and the hybrid technique is when the operation is started laparoscopically to mobilize the liver, followed by a mini-laparotomy to complete parenchymal transection. Today, in patients with a solitary HCC <5 cm in the anterior segment, with no evidence of an extrahepatic tumor burden, in case of compensated liver disease with absence of significant portal hypertension, LLR is considered a safe and feasible treatment option (2,3). In addition, due to improved laparoscopic instruments and increasing surgical experience, the technical difficulty of LLR is slowly being overcome. Henceforth, series have reported LLR of lesions located in posterior superior segments with good results (4,5). A number of advantages have been recognized when comparing LLR to open liver resection (OLR) from case-matched analyses, including reductions in postoperative pain, less operative morbidity, and shorter length of hospital stay (6-10).

The purpose of this review is to provide a thoroughly detailed description of reported studies about LLR for HCC in the literature in recent years. Specific emphasis will be placed on the comparison between Middle Eastern and Western experience with regards to resection types, technical approaches, postoperative course, and outcomes.

Methods

A literature search was performed using PubMed, Scopus, and Web of Science (WoS) from cited English and Chinese

publications. Data collection was performed until October 2013. Search phrases were “laparoscopy”, “liver resection”, and “HCC”. Manual cross-referencing was performed for all titles and abstracts, and relevant references from selected papers were reviewed. Publications with fewer than 15 cases, case reports, abstracts, letters, editorials and expert opinions were not considered for the drafting of the study. Review articles and meta-analyses were considered for the study. When there was more than one publication from the same team and/or authors, only the last publication in chronological order was considered for the study. Should a publication be written in Chinese, a translation was carried out, as faithful as possible, with the help of translators as native speakers.

Tables have been drawn up based on the geographical origins of authors and divided into Middle Eastern and Western experience. The results of the meta-analysis were not included in the tables.

Three reviewers (TP, DS, PP) independently considered the eligibility of potential publications and archived the following parameters from each study, namely first author, study design, number of patients, laparoscopic liver technique (pure laparoscopic, laparoscopic hand-assisted, laparoscopic assisted open), patient characteristics (age, gender, presence of cirrhosis, Child-Pugh score), size and number of tumors, location of tumor, type of resection (i.e., minor resection: ≤ 2 segments, major resection: ≥ 3 segments), associated resections, conversion rate, operative outcomes (operative time, blood loss, number of patients requiring transfusion, number of units of packed red blood cells (PRBCs), use and duration of portal clamping), postoperative outcomes (hospital stay, mortality and morbidity [general and specific: hemorrhage, ascites, biliary collection, liver failure]), and oncologic results [surgical margins, overall survival (1-3-5 years) and percentage of recurrence].

Results

Studies included in the analysis

There were 593 relevant papers in the initial search. After eliminating case reports, abstracts, letters, duplicates and studies where it was impossible to recover the data of HCC only, 24 remaining original studies with more than 15 patients were analyzed. There were 11 studies from the Western world (11-21) including two multicenter series (12,18), and 13 studies from the Middle Eastern world (4,22-33), and 4 meta-analyses from Chinese institutions (6-9).

Table 1 Study design

Authors	Period of inclusion	Number of patients	Pure laparoscopy	Laparoscopic Hand-assisted	Hybrid technique
Truant S <i>et al.</i> (11)	2002-2009	36	36	0	0
Dagher I <i>et al.</i> * (12)	1998-2008	163	155 [95%]	8 [4.9%]	0
Tranchart H <i>et al.</i> (13)	February 1999-August 2008	42	42	0	0
Sarpel U <i>et al.</i> (14)	2004-2007	24	24	0	0
Belli G <i>et al.</i> (15)	2000-2008	65	60 [92.3%]	5 [7.6%]	0
Casaccia M <i>et al.</i> (16)	June 2005-February 2009	20	20	0	0
Aldrighetti L <i>et al.</i> (17)	September 2005-June 2009	16	16	0	0
Soubrane O <i>et al.</i> * (18)	1998-2010	351	351	0	0
Santanbrogio R <i>et al.</i> (19)	January 2007	22	22	0	0
Cherqui D <i>et al.</i> (20)	May 1998-December 2003	27	27	0	0
Vibert E <i>et al.</i> (21)	January 1995-December 2004	16	16	0	0

*, Multicentre experience.

Table 2 Study design

Authors	Period of inclusion	Number of patients	Pure laparoscopy	Laparoscopic Hand-assisted	Hybrid technique
Lai EC <i>et al.</i> (22)	January 1998-december 2007	25	3	21	0
Lee KF <i>et al.</i> (23)	June 2004-march 2010	33	33	0	0
Kobayashi S <i>et al.</i> (24)	1997-2011	56	24	3	29
Kaneko H <i>et al.</i> (25)	15 years	39	33	2	4
Shimada M <i>et al.</i> (26)	1994-2000	17	17	0	0
Teramoto K <i>et al.</i> (27)	May 1997-April 2003	33*	15	0	0
Cheung TT <i>et al.</i> (28)	October 2002-september 2009	32	26	6	0
Hu BS <i>et al.</i> (29)	January 2006-January 2011	30	30	0	0
Yoon YS <i>et al.</i> (4)	September 2003- November 2008	69	69	0	0
Chen HY <i>et al.</i> (30)**	1998-2006	116	116	0	0
Sasaki A <i>et al.</i> (31)	May 2007-April 2008	37	37	0	0
Kim HH <i>et al.</i> (32)	July 2005-December2009	26	26	0	0
Kanazawa A <i>et al.</i> (33)	2006-2010	28	23	2	5

*, including 18 thermal ablation; **, group I (G1) (≤ 2 segments) and group II (G2) (> 2 segments).

Western experience (Table 1)

All 11 publications were retrospective analyses: four retrospective case-matched studies comparing LLR *vs.* OLR (11,13,14,17), two multicenter series from the French experience performed between 1998 and 2010 (18), and a European experience which included the databases of three European academic liver surgical centers (12). The other five series originated from a monocentric experience with minimally invasive approaches of LR: one series reported LLR

in benign conditions and malignant tumors (21), and four series reported the feasibility of LLR in HCC (15,16,19,20).

Middle Eastern experience (Table 2)

All 13 publications were retrospective analyses: only four studies were designed to compare the results of LLR versus OLR (28,29) including two retrospective case-matched analyses (23,32). The other 9 publications were monocentric experiences.

Selection criteria and type of laparoscopic approaches

Western experience

In three studies (12,13,15), selection criteria for LLR were well-compensated Child-Pugh Class A/B cirrhosis, esophageal varices \leq grade 2, platelet count $\geq 80 \times 10^9/L$, small tumors less than 10 cm, without major vascular invasion, and ASA score not exceeding 3. Casaccia *et al.* (16) and Truant *et al.* (11) selected patients with platelet count $\geq 40 \times 10^9/L$, solitary lesion of ≤ 5 cm, and treatable via limited resection (< 3 segments). In contrast, Vibert *et al.* (21) considered a disease with fewer than three nodules and no invasion of the portal convergence irrespective of the lesion's diameter eligible for LLR. Aldrighetti *et al.* (17) and Santambrogio *et al.* (19) advocated the absence of previous major upper abdominal surgery as well as cardiac or respiratory failure.

In the Western surgical experience, only two series (12,15) reported the use of hand-assisted laparoscopy, with a percentage of total LLR of 92.3% and 95.1% respectively. No series reported any experience with the hybrid technique. All other experiences reported in the literature proposed a total laparoscopic approach associated with an incision to remove the surgical specimen.

Middle Eastern experience

In major series, lesions were ≤ 5 cm without any vascular invasion. For pure laparoscopic resection, Kobayashi *et al.* (24) reported a sufficient distance from major vascular branches, small tumors peripheral to the liver; for hand-assisted LLR, tumors located in the right posterior sector; and for hybrid resection, cancers not fulfilling any of the aforementioned criteria.

There were selective biological liver function tests such as albumin levels above 3.5 g/dL, bilirubin levels below 1.5 mg/dL, indocyanine green (ICG) retention at 15 min lower than 40%, and prothrombin time (PT) greater than 60% (26,33).

Five publications (38.4%) reported different techniques of LLR. In particular, Kobayashi *et al.* (24) compared hybrid with pure laparoscopic procedures as well as with open surgery. The hybrid procedure was applied to enlarge indications to minimally invasive surgery and represented about half of the cases in Kobayashi's series. The percentage of laparoscopic hand-assisted procedures ranged from 5.1% to 84%.

Patients and tumors' characteristics

Western experience (Table 3)

In all series, mean age was between 60 to 66 years with a

predominance of male patients. The ASA score was > 2 only in 30% of patients.

Fifty to one hundred percent of patients with cirrhosis presented a well-compensated chronic liver disease (Child-Pugh Class A). However, seven series reported patients with Child-Pugh Class B with a rate ranging from 3.2% to 22.7% (13,19). Only two series (12,18) reported their experience with Child-Pugh Class C patients.

LLR was recommended for lesions within 5 cm and with a mean size ranging from 2.7 to 6.5 cm. Vibert *et al.* (21) and Soubrane *et al.* (18) reported maximal tumor sizes of 18 and 17 cm respectively. The lesions were located only in anterior lateral segments more or less associated with segments VII and VIII in four studies (11,17,19,20). The most common type of LLR was a wedge resection or segmentectomy and left lateral sectionectomy. However, without considering multicenter studies, 13 major LLRs were performed (6%) (13,15,20). Radiofrequency ablation was associated for the treatment of intrahepatic lesions in three series (12,16,19).

Middle Eastern experience (Table 4)

Only five studies (38.4%) reported an ASA score which was > 2 in only 12.8% of cases.

Cirrhosis was present also from 50% to 100% of patients. Only two series did not describe the Child-Pugh status of the patients. Eight publications reported patients with Child-Pugh Class B cirrhosis ranging from 8.7% to 66.7%. In fact, Teramoto *et al.* (27) included 66.7% of Child-Pugh Class B patients with ICG retention rate at 15 minutes of $22.1 \pm 12.0\%$. Three series (4,25,30) reported their experience with Child-Pugh Class C patients. Chen *et al.* (30) reported patients with Child-Pugh Class B/C without distinguishing between the two different statuses.

Mean size of the tumor was less than 5 cm except for Hu *et al.* (29) who reported a mean tumor size greater than 6 cm. However, tumor size ranged from 0.6 to 9 cm. The lesions were located in all segments. Teramoto *et al.* (27) reported a thoracoscopic approach for posterior segments in five cases (S8=4, S7=1). Most of the resections were minor but 27 major LLRs (10.8%) were reported. The most common major liver resection was right hepatectomy. Only one central hepatectomy was performed by Yoon *et al.* (4).

Intraoperative and immediate postoperative outcomes

Western experience (Table 5)

Mean operative time was between 150 to 300 minutes. In the four case-matched studies (11,13,14,17), there was no

Table 3 Patients and tumors descriptions

Authors	Mean age years	Gender [M/F]	ASA >2 n [%]	Child-Pugh A-B-C n [%]	Cirrhosis n [%]	Mean size of the tumor cm [range]	Location of the tumor	Number of tumours	Type of resection n	Associated resections	Surgical margin mm [range]
Truant S <i>et al.</i> (11)	60.6±10.2	31/5	11 [30.6]	A: 32		2.9±1.2	Ant.segments	1.1±0.3	Minor	4 LC	9.5±2.8
Dagher I <i>et al.</i> * (12)	65 [24-84]	112/51	45 [27.6]	A: 111 B: 8 C: 1	120 [73.6]	3.6 [1-20]	All segments	NR	Minor: 147; major: 16	40 LC 14 other 12 RFA	12 [0-58]
Tranchart H <i>et al.</i> (13)	63.7±13.1	27/15	12 [28.5]	A: 30 B: 1	31 [73.8]	NR	NR	NR	Minor: 37; major: 5	NR	10.4±8.0
Sarpel U <i>et al.</i> (14)	63.8±10.3	15/9	NR	NR	9 [45]	4.2±2.1	NR	NR	NR	NR	NR
Belli G <i>et al.</i> (15)	63±6.8	38/27	13 [20]	A: 58 [89] B: 7	65 [100]	3.8±1.4	All segments	Single: 53; multiple: 12	Minor: 6; major: 59	NR	<10: 9 >10: 56
Casaccia M <i>et al.</i> (16)	66 [47-76]	12/8	NR	A: 17 B: 3	20 [100]	3.1 [0.9-5]	All.segments	>1	Minor: 19; major: 1	5 LC 3 other	15 [0-40]
Aldrighetti L <i>et al.</i> (17)	65±10	11/5	2 [12.9]	A: 9	9 [56]	4±2.2	Ant.segments + VII	NR	Minor: 16	5 LC	11±7.4
Soubrane O <i>et al.</i> * (18)	63 [30-90]	260/91	91 [31.4]	A: 275 B: 8 C: 1	NR	3.5 [0.5-17]	All segments	Single: 302; multiple: 49	Minor: 315; major: 36	NR	10 [0-78]
Santanbrogio R <i>et al.</i> (19)	61.4±8.3	13/9	NR	A: 17 B: 5	22 [100]	2.7±1.2	Ant.segments	NR	Minor: 22	3 RFA 1 alchoolic ablation	11.1±7.4
Cherqui D <i>et al.</i> (20)	63±9	22/5	NR	A: 20	20 [74]	3.3 [2-5]	Ant.segments + VIII	1	Minor: 26; major: 1	NR	11 [1-47]
Vibert E <i>et al.</i> (21)	NR	NR	NR	A: 7 B: 1	8 [50]	6.5 [0.8-18]	NR	Single: 15; multiple: 1	NR	NR	10 [1-50]

*, Multicentre experience; Ant. segments, II, III, IVb, V, VI; LC, laparoscopic cholecystectomy; RFA, radiofrequency ablation; NR, no reported.

Table 4 Patients and tumors descriptions

Authors	Mean age years	Gender [M/F]	ASA >2 n	Child-Pugh A-B-C n [%]	Cirrhosis n [%]	Mean size of the tumor cm [range]	Location of the tumor* segments	Number of tumours n [%]	Type of resection	Associated resections	Surgical margin cm [range]
Lai EC et al. (22)	59 [35-79]	18/7	1	A: 23 [92]	23 [92]	2.5 [1-7]	Ant. segments	NR	Minor: 24 Major: 1	NR	0.5 to 4
Lee KF et al. (23)	59 [36-85]	24/9	6	A: 33 [100]	28 [84.8]	2.5 [1.5-9]	Ant. segments	Single: 31; multiple: 2	Minor	NR	1.8 [0-4]
Kobayashi S et al. (24)	70 [37-86]	41/15	9	A: 48 [85.7] B: 8 [14.3]	NR	2 [1-9]	All segments	1 [1-3]	Minor	NR	NR
Kaneko H et al. (25)	59±8	NR	NR	A: 30 [76.9] B: 8 [21] C: 1 [2.5]	39 [50.6]	<4	All segments	NR	Minor: 38 Major: 1	NR	NR
Shimada M et al. (26)	62±9	15/2	NR	NR	76.5	2.6±0.9	Ant. segments	NR	Minor	3 splenectomy	0.8±0.7
Teramoto K et al. (27)	64±10	9/6	NR	A: 5 [33.3] B: 10 [66.7]	NR	1.9±0.6	All segments	NR	NR	NR	NR
Cheung TT et al. (28)	59.5 [39-79]	22/10	NR	A: 32 [100]	28 [87.5]	2.5 [1-10]	All segments	NR	Minor	NR	0.95 [0-3]
Hu BS et al. (29)	46±12	19/11	NR	A: 24 [80] B: 6 [20]	25 [83.3]	6.7±3.1	Ant. segments	NR	NR	NR	NR
Yoon YS et al. (4)	56.5±11.7	50/19	NR	A: 62 [89.8] B: 6 [8.7] C: 1 [1.5]	38 [55]	3.1±1.5	All segments	Single: 56 [81.5]; multiple: 12 [17.3]	Minor: 60 Major: 9	NR	1.5±1.6
Chen HY et al. (30)**	G1: 57±12.6 G2: 61.6±13.1	G1: 78/19 G2: 14:5	G1: 13 G2: 1	G1: A: 79 B/C: 18 G2: A: 19	NR	G1: 2.1±0.8 G2: 3.2±1.9	All segments	NR	Minor: 104 Major: 12	NR	≤1
Sasaki A et al. (31)	57.84±9.66	18/8	3	A: 23 [86] B: 4 [14]	27 [100]	2.5 [1.5-6]	All segments	NR	Minor	NR	0.7 [0-2.5]
Kim HH et al. (32)	69 [40-85]	16/12	NR	A: 20 [71.4] B: 8 [28.5]	28 [100]	2 [0.6-2.7]	All segments	Single: 18 [64.2]; multiple: 10 [35.7]	Minor: 22 Major: 4	NR	NR
Kanazawa A et al. (33)											

* , Ant. segments (I,III,IVb,V,VI); ** , group I (G1) (≤2 segments) and group II (G2) (>2 segments); NR, no reported.

Table 5 Surgical results

Authors	Conversion n [%]	Mean operative time min [range]	Mean blood loss mL [range]	Transfusion n [%] n [range]	PRBC units n [range]	Use of portal clamping n [%]	Mortality n [%] n [%]	Morbidity n [%]	Specific morbidity: n
Truant S <i>et al.</i> (11)	7 [19.4]	193±104	452±442	1 [2.8]	-	13 [36]	0	4 [11.7]	Ascites: 5
Dagher I <i>et al.</i> * (12)	15 [9.2]	180 [60-655]	250 [30-2,000]	16 [9.8]	2.5 [1-5]	43 [26.4]	2 [1.2]	17 [10.4]	Hemorrhage: 4; ascites: 14; biliary collection: 1
Tranchart H <i>et al.</i> (13)	2 [4.7]	233.1±92.7	364.3±435.7	4 [9.5]	3±0.7	0	1 [2.4]	4 [9.5]	Hemorrhage: 1; ascites: 3; biliary collection: 1
Sarpel U <i>et al.</i> (14)	4 [17]	161±37	NR	NR	NR	0	NR	NR	NR
Belli G <i>et al.</i> (15)	7 [10.7]	169±46	311±180	7 [10.7]	NR	2 [3]	1 [1.5]	1 [1.5]	Hemorrhage: 2; ascites: 10
Casaccia M <i>et al.</i> (16)	1 [5]	300 [120-560]	55 [20-1,400]	10 [50] ^o	1 [1-4]	1 [5]	0	0	Ascites: 2; biliary collection: 1
Aldrighetti L <i>et al.</i> (17)	1 [6.25]	150±57	258±186	4 [25]	NR	0	0	0	Hemorrhage: 4
Soubrane O <i>et al.</i> * (18)	45 [13]	180 [15-655]	NR	12 [3]	NR	85 [24]	7 [2] ^o	52 [14.8]	Ascites: 16; biliary collection: 7; hepatic failure: 5
Santanbrogio R <i>et al.</i> (19)	3 [13.6]	199±69	183±72	1 [4.5]	2	NR	0	0	Hemorrhage: 2
Cherqui D <i>et al.</i> (20)	7 [26]	240±75	338±182 [6 patients ≥1,000 mL]	3 [15]	2-5	27 [100]	0	7 [25]	Ascites: 1; hepatic failure: 1
Vibert E <i>et al.</i> (21)	NR	NR	NR	NR	NR	NR	1 [6.25]	NR	NR

* , Multicentre experience; PRBC, packed red blood cell units; ^o, 30-days mortality; NR, no reported.

difference between LLR and OLR. In the series with major hepatectomy, maximal operative time ranged from 325.7 to 655 minutes.

Mean blood loss ranged from 55 to 452 mL. In two series, blood loss >1,000 mL was reported (12,16). Transfusion was required in all series, ranging from 2.8% to 50%. In case-matched studies, one study (17) reported a lower blood loss in the LLR group as compared to the OLR group (258±186 versus 617±433 mL; P=0.008). In contrast, the two other studies did not determine any difference between LLR and OLR (11,14). More than 50% of the series reported the use of a Pringle maneuver during resection. Cherqui *et al.* (20) reported 100% of intermittent portal triad clamping.

The conversion rate ranged from 5% to 19.4%. The most frequent reasons for conversion were bleeding during parenchymal transection, technical difficulties in exposure, and adhesions. In the four case-matched series (11,13,14,17), there was no difference in terms of surgical margins between LLR and OLR. Three cases of death were reported: one liver failure (13), one severe respiratory distress syndrome (15), and one cerebral infarction (21). The global morbidity rate ranged from 1.5% to 25%. Specific complications were divided into hemorrhage (2.4% to 25%), ascites (3.7% to 15.3%), and biliary collection (0.6% to 5%). A liver insufficiency was reported in two cases (18,20). Mean hospital stay ranged from 5.4 to 15 days. In all case-matched studies, LLR was statistically associated with a shorter hospital stay.

Middle Eastern experience (Table 6)

Mean operative time ranged from 147 to 325 minutes. In the two case-matched studies, there was no difference between LLR and OLR. In the five series with major hepatectomy, maximal operative time ranged from 210 to 500 minutes.

Mean blood loss ranged from 88 to 808 mL. In six series, blood loss >1,000 mL was reported (12,16). Save from two studies (28,33), transfusion was required, ranging from 1.8% to 19.2%. The two case-matched studies did not report any difference between LLR and OLR (23,32). Only three series reported the use of a Pringle maneuver during parenchymal transection (22,26,33).

The conversion rate ranged from 1.8% to 18.6%, and no conversion was reported in four series (7,8,31,33). The most frequent reasons for conversion were uncontrolled bleeding, and inadequate margin or poor localization (4,27,30). In five series (38.5%), the surgical margin was not reported. There

was no mortality. There was no specific morbidity in five series (22,23,27,28,32). The main specific complication was ascites (1.7% to 26.6%). A biliary collection was reported in only two series (4,29) (10.7% and 13.3% respectively), and only one case of postoperative liver insufficiency was reported (26). Mean hospital stay ranged from 4 to 11.5 days. Three comparative studies statistically reported a shorter postoperative hospital stay following LLR versus OLR (23,28,32).

Long-term results: survival and recurrence

Western experience (Table 7)

The 5-year overall survival rate was reported in five studies and ranged from 55% to 70%. Trancart *et al.* (13) reported no difference between LLR and OLR with a 1-, 3-, and 5-year overall survival rate of 93.1%, 74.4%, and 59.5% versus 81.8%, 73%, and 47.4% (P=0.25) respectively. No trocar-site recurrence was observed. The recurrence rate ranged from 21.4% to 50%. Comparative studies did not demonstrate any significant difference in terms of recurrence between LLR and OLR (11,13,14,17).

Middle Eastern experience (Table 8)

The 5-year overall survival rate was reported in six studies and ranged from 50% to 76.6%. Comparative studies did not demonstrate any significant difference in terms of overall survival and recurrence rate between LLR and OLR. Chen *et al.* (30) differentiated two groups of patients according to the type of resection (minor or major): the 1, 3 and 5 years were 85.4%, 66.4%, and 59.4% in the minor resection group, and 94.7%, 74.2%, and 61.7% in the major resection group respectively, without significant difference. No trocar-site recurrence was reported. The recurrence rate ranged from 26.9% to 45.5%, and two series (26,29) reported no recurrence.

Discussion

LLR for HCC is safe and feasible. Additionally, using a progressive approach, excellent outcomes can be obtained in the setting of underlying cirrhosis. Since the first reported case (34), an increasing number of series was published, and especially so since year 2000. Eight studies (four Middle Eastern and four Western ones) compared the benefits of the LLR versus the OLR approach but, to the best of our knowledge, a prospective randomized study has not been published yet (Table 9). In these different

Table 6 Surgical results

Authors	Conversion n [%]	Mean operative time min [range]	Mean blood loss mL [range]	Transfusion n [%]	PRBC *units n [range]	Use of portal clamping n [%]	Mortality [%]	Morbidity n [%]	Specific morbidity: n [%]
Lai EC <i>et al.</i> (22)	1 [4]	150 [75-210]	200 [5-2,000]	2 [8]	NR	16 [58.8]	0	4 [16]	0
Lee KF <i>et al.</i> (23)	6 [18.2]	225 [100-120]	150 [10-1,610]	2 [6.1]	NR	0	0	2 [6.1]	0
Kobayashi S <i>et al.</i> (24)	1 [1.8]	202 [45-512]	150 [0-1,180]	1 [1.8]	NR	NR	NR	0	Ascites: 1
Kaneko H <i>et al.</i> (25)	2 [2.6]	182±38	380±210	NR	NR	NR	NR	0	Ascites: 2
Shimada M <i>et al.</i> (26)	NR	325 [214-430]	400 [188-1,050]	5.9	NR	Yes	0	0	Hepatic failure: 1
Teramoto K <i>et al.</i> (27)	2 [13.3]	214±63	296±341	NR	NR	NR	NR	4/15 [26.6]	0
Cheung TT <i>et al.</i> (28)	0	235.5 [70-450]	150 [100-1,460]	0	0	0	0	2 [6.3]	0
Hu BS <i>et al.</i> (29)	0	180±45	520±30	NR	NR	NR	0	0	Biliary collection: 4
Yoon YS <i>et al.</i> (4)	5 [7.2]	280.9±128.2	808.3±1011.7	23 [33.3]	NR	0	0	15 [21.7]**	Ascites: 4 [26.6]; biliary collection: 2
Chen HY <i>et al.</i> (30)**	6 [5.2]	G1: 152.4±336.3 G2: 175.8±57.4	G1: 101.6±324.4 G2: 329.2±338.0	G1: 5 [5.2] G2: 3 [15.8]	[§] G1: 36.1±148.7 [§] G2: 105.3±267.7	NR	G1: 0 G2: 0	G1: 6.2 G2: 5.2	Ascites: 2
Sasaki A <i>et al.</i> (31)	0	195 [91-355]	103 [1-917]	NR	NR	0	0	1 [2.7]	Ascites: 1
Kim HH <i>et al.</i> (32)	3 [10.3]	147.5 [45-500]	NR	5 [19.2]	0.35±0.75	0	0	1 [3.8]	0
Kanazawa A <i>et al.</i> (33)	0	228 [69-515]	88 [0-900]	0	0	Yes	0	3 [10.7]	Ascites: 3

PRBC, packed red blood cell units; [§], blood transfused in mL; **, group I (G1) (≤2 segments) and group II (G2) (>2 segments).

Table 7 Outcomes

Authors	Mean hospital stay days [range]	1-year survival [%]	3-years survival [%]	5-years survival [%]	Recurrence n [%]	Mean follow-up months
Truant S <i>et al.</i> (11)	6.5±2.7	NR	NR	70	16 [44.4]	35.7±27
Dagher I <i>et al.</i> * (12)	7 [2-76]	92.6	68.7	64.9	64 [39]	30.4
Tranchart H <i>et al.</i> (13)	6.7±5.9	93.1	74.4	59.5	10 [23.8]	29.7
Sarpel U <i>et al.</i> (14)	NR	NR	NR	NR	NR	NR
Belli G <i>et al.</i> (15)	8.2±2.6	95	70	55	31 [48]	29
Casaccia M <i>et al.</i> (16)	8 [5-16]	NR	NR	NR	10 [50]	26
Aldrighetti L <i>et al.</i> (17)	6.3±1.7	NR	NR	NR	6 [37.5]	22
Soubrane O <i>et al.</i> * (18)	7 [1-90]	NR	NR	65.7		21
Santanbrogio R <i>et al.</i> (19)	5.4±1	NR	NR	50, 4 years	5 [26.3]	11.5
Cherqui D <i>et al.</i> (20)	15±17.5	NR	93	NR	8 [30]	24
Vibert E <i>et al.</i> (21)	NR	85	66	NR	3 [21.4]	40

*, Multicentre experience; NR, no reported,

Table 8 Outcomes

Authors	Mean hospital stay days [range]	1-years survival [%]	3-years survival [%]	5-years survival [%]	Recurrence n [%]	Mean follow-up months
Lai EC <i>et al.</i> (22)	7 [4-11]	NR	60	NR	25 [36]	29
Lee KF <i>et al.</i> (23)	5 [2-15]	87.5	87.5	75	15 [45.5]	35.4
Kobayashi S <i>et al.</i> (24)	11.5 [7-28]	NR	100	NR	NR	19.2
Kaneko H <i>et al.</i> (25)	NR	NR	NR	NR	NR	NR
Shimada M <i>et al.</i> (26)	12±5	85	75	50	0	16.6
Teramoto K <i>et al.</i> (27)	12±7.2	100	80	–	6 [40]	23±21
Cheung TT <i>et al.</i> (28)	4 [2-16]	96.6	87.5	76.6	NR	NR
Hu BS <i>et al.</i> (29)	13±2.1	NR	NR	50	0	NR
Yoon YS <i>et al.</i> (4)	9.9±5.6	NR	90.4	NR	21 [30.4]	21.3
Chen HY <i>et al.</i> (30)**	NR	G1: 85.4 G2: 94.7	G1: 66.4 G2: 74.2	G1: 59.4 G2: 61.7	NR	94
Sasaki A <i>et al.</i> (31)	10 [6-37]	NR	73	53	13 [35]	36
Kim HH <i>et al.</i> (32)	11.08±4.96	NR	NR	NR	7 [26.9]	21.75
Kanazawa A <i>et al.</i> (33)	10 [6-25]	NR	NR	NR	NR	NR

**, group I (G1) (≤2 segments) and group II (G2) (>2 segments); NR, no reported.

Table 9 Summary of trends comparing data of Middle Eastern and Western experiences (no statistical analysis)

	Middle Eastern	Western
Technique	Hybrid technique	No hybrid technique; more pure laparoscopic approach
Patients	Severity of the cirrhosis (more Child B and C)	More patient with cirrhosis
Tumor		Slightly larger size
Procedure		More conversion; more portal clamping

comparative studies, LLR can achieve survival equal to open hepatectomy in patients with HCC but with the benefit of less blood loss, less transfusion requirement, and a shorter hospital stay.

Selection criteria included tumor size and location as well as the severity of the underlying disease. It appears that the selection of patients is quite uniform in the Western experience. The Western most centers are French or Italian, and as reported in the multicenter study of Dagher *et al.* (12), centers use the same selection of patients and surgical techniques. On the opposite, in the Middle Eastern experience, selection criteria were less clear and authors reported that these criteria were similar to the ones of open surgery. In the Middle Eastern experience, for surgical evaluation, the ICG retention rate at 15 minutes represented the most reliable and faithful index of hepatic reserve. More Child-Pugh Class B and/or Class C patients were operated on in Middle Eastern series. No series used the Model for End-Stage Liver Disease (MELD) score for the selection of patients, currently used as a disease severity index of cirrhotic patients awaiting LT. However, the MELD score related with mortality and liver-related morbidities in HCC patients who underwent hepatic resection. A MELD score >8 represented the trigger for intensive treatment to improve patient outcome (35). In the Mayo clinic experience (36), a MELD score >9 was an independent predictor of perioperative mortality and long-term survival after multivariate analysis.

For some Middle Eastern surgeons, tumor location does not seem to be a selection criterion but the type of approach was different from pure laparoscopy. The Middle Eastern experience reported more hand-assisted or hybrid techniques. Huang *et al.* (37) reported a series of LLR with or without the hand-assisted approach and concluded that surgical results between hand-assisted and non-hand-assisted approaches were similar except for higher blood losses with the hand-assisted technique. The authors found that there was a higher use of hand-assisted LLR when liver cirrhosis was present, and less likelihood of using hand-assisted LLR when there was a superficial location of the tumor or lesion. In a comparative study (24), pure LLR was associated with lesser blood loss, and shorter skin incisions than in hybrid and open hepatectomy. Hybrid hepatectomy was associated with a longer operative time. It is probably for these few advantages and mainly for blood loss that Western surgeons prefer to use a pure laparoscopic approach. The hybrid technique in the Western experience was particularly described in cases of living donor right hepatectomies (38).

The laparoscopic approach could be used in cases of HCC recurrence: a previous surgery and the grade of adhesions have not been subject to contraindications (39,40). Fewer adhesions represent an additional benefit of laparoscopic hepatectomy. This could well facilitate an easy reoperation for either a subsequent laparoscopic surgery or an open abdominal surgery to treat HCC recurrence or metastasis. LLR could be proposed as a bridge treatment before LT: LLR facilitated the LT procedure as compared to OLR in terms of reduced operative time, blood loss, and transfusion requirements (41).

With the benefit of experience, pure laparoscopy could be proposed for all tumor locations (42). Regarding the type of resection, the learning curve inherent to LLR reflects the attitude of the different teams for which the more accessible lesions are approached first prior to undertaking more difficult resections. LLR requires expertise in OLR, minimally invasive surgery, and laparoscopic ultrasonography. Resections in posterior and superior segments of the liver and major liver resections should be reserved for centers with a significant experience in laparoscopic liver surgery (42). In all groups, wedge resection and minor resection were more commonly performed. However, major hepatectomies such as right hepatectomies are increasingly proposed nowadays (43,44).

The resection margin is another factor that could well influence survival. A positive margin may have a profound influence on disease-free survival and long-term survival. The incidence of surgical margins <1 cm was reported in 62.5% of Middle Eastern articles. This result was set in contrast with “the dogma” in which a gross resection margin aiming at 2 cm provided better survival outcome than a narrow resection margin at 1 cm (45) for macroscopically solitary HCCs. However, in all case-matched control studies, survival rates, resection margins, and local recurrence rates following LLR were comparable to OLR. Laparoscopic intraoperative ultrasonography can be used to locate the tumor, making it possible to keep the intended margin. Another concern about laparoscopic resection of malignancies is the potential risk of tumor seeding. However, neither peritoneal carcinomatosis nor port-site recurrence were observed following HCC resection by laparoscopy. The use of a plastic bag to remove the specimen could help prevent this complication. The meta-analyses (6,8) have shown that LLR is comparable to OLR for HCC at 1-, 3- and 5-year overall survival. Consequently, LLR should be considered an acceptable alternative for the treatment of malignant liver tumors.

The results of the literature should be construed with caution due to several limitations. First, all data stem from non-randomized trials, and the overall level of clinical evidence is low. However, results have shown that LLR for HCC is superior to OLR in terms of perioperative results and does not compromise oncological outcomes. Consequently, LLR may be an alternative choice in the treatment of HCC.

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Footnote

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Laparoscopic resection for hepatocellular carcinoma: eastern and western experiences

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Hepatocellular carcinoma (HCC) is the most common primary liver cancer (1). The incidence is rising in the last decades due to many factors, especially hepatitis C, alcoholic liver disease and non-alcoholic steatohepatitis. Moreover, the introduction of screening programs in patients with chronic liver disease has led to an increase in HCC diagnosis (1,2). In the western world, 80% to 90% of HCC cases occur in patients with liver cirrhosis (3) while this proportion is lower in some regions in Asia and sub-Saharan Africa, where hepatitis B remains as an important etiologic factor for chronic liver disease (2,4). In 1990, the annual world frequency of HCC was 437,000 cases/year (1), and in 2012 the number reached 782,200 cases/year being responsible for 746,000 deaths (5). Nowadays, HCC represents the 6th most frequent neoplastic disease in the world and the 3rd in mortality (5).

HCC treatment is complex and, for the definition of the best therapeutic strategy, many aspects have to be considered: the size and number of nodules, the presence of vascular invasion, extra hepatic spread and liver function. Currently, treatment modalities considered as curative are resection and liver transplantation (LT) (4,6).

LT have as advantage the possibility to treat simultaneously not only the tumor but the underlying liver disease, however just a limited group of patients can achieve the procedure due to long waiting lists. Dropout due to tumor progression and complications of the liver disease leading to morbidity and mortality while waiting for LT are drawbacks for the procedure. Thus, when evaluating intention to treat, LT and resection present similar results (7,8).

In the last decades, HCC resection has been more frequently performed due to technical improvements and better assessment of liver function leading to better

results. The mortality rate of patients with chronic liver disease submitted to liver resection, fell from 15% in the early eighties for current 2% to 5%, with morbidity rates between 10% and 40% and transfusion rates lower than 10% in specialized centers (4,9). Moreover, liver resection presents as advantages the immediate applicability independent of the size of the tumor, lower morbidity and mortality when compared to LT and, avoidance of postoperative immunosuppression. Other advantage for resection is the possibility of histological and molecular prognostic evaluation of the specimen allowing to a better selection of patients for LT (7,10).

Liver resection is the treatment of choice for patients with HCC and non-cirrhotic livers. In these patients, even major resections can be performed without any concern about liver functional reserve provided a liver remnant larger than 25-30%. Resecability rates larger than 70% and long-term survival rates between 50% and 60% can be achieved (11). On the other hand, in patients with cirrhosis, resection is limited to those with single nodule (or oligonodular disease) and preserved liver function (4,7).

In this context, minimally invasive surgery gained space in the treatment of HCC. Many authors have shown the safety and feasibility for the procedure (12) and, when compared to conventional surgery, laparoscopic liver resection (LLR) showed advantages for patients with chronic liver disease. In comparative series, the advantages of LLR are less bleeding, lower transfusion rates, shorter hospital stay and lower rates of morbidity, especially postoperative ascites. Moreover, we should point out the absence of adhesions leading to an easier re-resection or salvage LT (13,14).

In eastern and western specialized centers, HCC present different epidemiologic and clinical characteristics leading

to different therapeutic approaches. Indeed, until recently, studies comparing eastern and western experiences with HCC are lacking. In a recent paper entitled "Laparoscopic resection for HCC: comparison between Middle Eastern and Western experience", Piardi *et al.* (15) report the results of LLR from these two different surgical schools. They included case series with more than 15 patients, comparative studies or meta-analysis. All studies were retrospective, with a total of 782 patients in western series and 541 patients in eastern series. When compared the epidemiologic data between both study populations, we can note a large number of cirrhotic patients in eastern series (between 50% and 100% of the cases), with a larger proportion of patients Child-Pugh B and C.

When comparing indications for LLR, despite some variations, the majority of groups employ the following criteria: small (<5 cm) peripheral lesions in Child-Pugh A patients, in the absence of portal hypertension or with small esophageal varices, platelet count >100,000/mL and ASA score ≤ 3 . Most western groups consider a major vascular invasion as a contraindication for resection (11). In the Far East, the presence of portal vein tumoral thrombus does not preclude resection (16).

The most frequent LLR for the treatment of patients with HCC are peripheral wedge resections, segment 6 resections, and bisegmentectomies 2-3. There is some data showing that anatomical resections can lead to better results in patients with HCC however, for single and small nodules a non-anatomical approach seems to be effective. A recent meta-analysis comparing anatomical versus non-anatomical resections in more than 1,800 patients with HCC did not show differences in survival or recurrence rates (17). Major resections for the treatment of HCC are exceptional (less than 20% of resections), but for patients with preserved liver function (Child-Pugh A) and a liver remnant larger than 40% can be done with low rates of postoperative liver failure (12,18). Selective portal vein embolization in order to increase the volume of the liver remnant and indirectly test the hypertrophy capacity of the liver is a useful tool in the therapeutic strategy (19).

In the western world most groups employ the volume of the remnant liver as a safety parameter for resection (12,15). However in the eastern world functional evaluation of the liver, mostly with indocyanin green clearance, is used routinely (4,15). The meticulous evaluation of liver function employed by eastern groups may explain the liberal indication and good outcomes for liver resection even in patients Child B and C.

In the Piardi *et al.* (15) review, the laparoscopic modality employed by the majority of western series was pure laparoscopy (98.2% of the resections). On eastern series, pure laparoscopy was done in 86.3% of the cases, the hand-assisted approach in 6.5% and hybrid procedures in 7.3% of the cases. Hand-assisted and laparoscopic-assisted liver resections emerged aiming to overcome some of the limitations faced by totally laparoscopic approach and, therefore, expand the availability as well as the indications of minimally invasive liver surgery. These modalities allow surgical manipulation in a similar way of conventional surgery. Furthermore, the tactile sensation, which is partially lost on pure laparoscopic approach, is brought back. These approaches facilitate not only palpation and identification of deep lesions but also allow parenchymal compression during liver transection, making this step of the surgery safer.

The hybrid and hand-assisted approaches has been used for resection of lesions located in segments of difficult laparoscopic access (segments 1, 4a, 7, 8), multiple resections and major hepatectomies. In our series of 40 patients with HCC operated by minimally invasive approach, 14 (35%) patients were operated by these techniques, especially in cases with nodules in the posterior-superior segments or for major resections.

Laparoscopic-assisted resections are still rarely performed in western centers however, good results, along with the safety reported with this method were responsible for an increasing interest in hybrid surgery, especially in eastern centers. In a recent review, the authors observed that 88.7% of major hepatectomies were performed through hybrid technique in specialized Japanese centers (20).

Regarding operative results, transfusion rates ranged from 1.8% to 50%. Conversion rates were similar worldwide: West (5-19.4%) and East (1.8-18.6%). In a recent paper from our group with pure laparoscopic surgery, conversion rate was 13.3% (18). Morbidity is similar in eastern and western series (0-25% *vs.* 0-26.6%), as well as per-operative mortality rates (0-6.25%). All comparative studies showed lower hospital stay in the laparoscopic group.

Three-year and 5-year survival rates are also similar (west 66-93% *vs.* east 60-100%; west 55-70% *vs.* east 50-76%, respectively). Recurrence rate was also similar between groups (west 21.4-50% *vs.* east 26.9-45.5%). Comparative studies between conventional surgery and LLR did not show difference regarding overall survival and disease-free survival. In our experience, overall and disease-free 3-year survival were 76% and 58%, respectively (18).

We can conclude that the oncological results for

laparoscopic treatment of HCC presented in eastern and western series, despite retrospective, are similar to those from the conventional approach, with an apparent advantage in per operative results. Although most often used in selected cases, the expansion of LLR can be achieved with the use of hybrid and hand-assisted approaches, especially those with posterior-superior lesions requiring complex resections or major hepatectomies. Finally, LLR and its different modalities should be strongly considered in the curative treatment of HCC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Robotic liver surgery

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Abstract: Robotic surgery is an evolving technology that has been successfully applied to a number of surgical specialties, but its use in liver surgery has so far been limited. In this review article we discuss the challenges of minimally invasive liver surgery, the pros and cons of robotics, the evolution of medical robots, and the potentials in applying this technology to liver surgery. The current data in the literature are also presented.

Keywords: Robotics; hepatectomy; minimally invasive surgery

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Overview of minimally invasive liver surgery

Liver resection, once regarded as an operation with prohibitively high mortality and morbidity, has now become a routine operation in expert hands. As laparoscopic techniques for other major abdominal operations such as splenectomy, colectomy, and fundoplication have matured, the interest in applying minimally invasive techniques to liver resection also developed. Technical developments such as more sophisticated energy devices and articulated laparoscopic staplers have enabled surgeons to tackle liver resection laparoscopically.

Some of the major technical challenges in liver surgery include the difficult access to the vena cava and major hepatic veins, precision required for dissection at the hilum, and propensity for the liver to bleed. These are made more difficult with laparoscopy due to the limitations in depth perception, restricted movement by rigid instruments and fixed fulcrum at the ports, unnatural ergonomics, and difficult suturing particularly in presence of hemorrhage. There is a steep learning curve making its practice outside high-volume centers difficult.

As a result, the uptake of minimally invasive hepatectomy has been slow and cautious. But with increasing experience, surgeons have gradually increased the difficulty and complexity of surgery, from staging and deroofing cysts initially, to resecting readily accessible parts of the liver

such as the lateral sector and wedge resections from the anteroinferior segments, to major hepatectomies (1). However, certain scenarios are still considered prohibitively challenging, such the presence of extensive adhesions, resection of the caudate or posteriorly placed tumors, and bile duct resection and reconstruction. In 2008, a panel of 45 international experts on laparoscopic liver surgery gathered in Louisville, Kentucky to discuss the state of the art. There was a consensus that the best indications for laparoscopic resection are in patients with solitary lesions, 5 cm or less, located in segments 2 to 6 (2). Of note, the participants of this consensus conference recommended against routine laparoscopic resection of segments 7, 8, 1. This is due to difficulties in visualizing and working in these areas of the liver with straight laparoscopic instruments.

Single incision laparoscopic surgery (SILS) has been touted as the next stage in minimally invasive surgery with enhanced cosmesis and possibly recovery compared to conventional laparoscopic surgery. Small series of single-port laparoscopic hepatectomy have been published showing its feasibility (3,4). However, limited views, clashing of the surgeons' hands, "sword-fighting" of instruments and inability to triangulate remain significant limitations. Attempts have been made to reduce collision by creating articulated instruments, however they may need to be used cross-handed, an unnatural and un-ergonomical operating position (5).

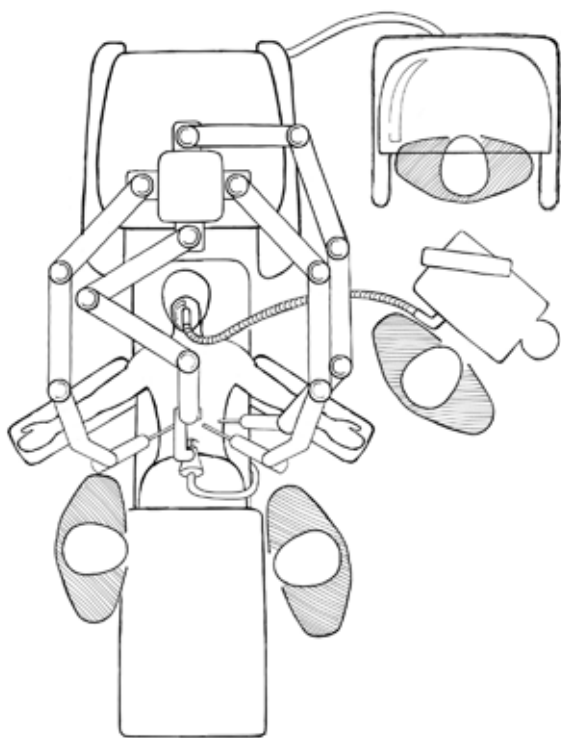


Figure 1 Typical room setup for a robotic hepatectomy.

Pros of robotic surgery

Robotic assistance was developed in part to compensate for some of these limitations. The unfavorable ergonomics of rigid laparoscopic instruments are partially overcome by articulated ones to mimic the dexterity of the human hand. This allows tissue manipulation and suturing in small spaces, at angles not possible with rigid instruments, and facilitates curved transection lines for more complex resections. Tremor is filtered to allow precise suture placement useful for bleeding, and for creating biliary and enteric anastomoses. The surgeon's motions are scaled so that small, precise movements are effected at the patient's end. Operating via a console allows the surgeon to work sitting down in a comfortable position, and the 3-dimensional projection of images partially overcomes the lack of depth perception. The surgeon is in control of the camera, which is mounted on a stable platform, avoiding poor camera work due to a tired or inexperienced assistant. Laparoscopic retractors are also controlled by the surgeon and can be locked into position, further avoiding inappropriate or ineffective retraction.

One of the big theoretical advantages of robotic assistance

in complex surgery is the shorter learning curve compared with conventional laparoscopy. Port placement is more forgiving as instruments are not completely restricted by a rigid fulcrum. Currently complex laparoscopic liver resections are generally performed by surgeons who are both expert hepatobiliary surgeons and expert laparoscopic surgeons. Open techniques are more readily translated to robotics and thus surgeons who are expert in hepatobiliary but not necessarily advanced laparoscopy may become proficient quickly.

An inherent imperfection in surgical training is the need for inexperienced trainees to operate on real patients while overcoming the learning curve of the procedure, thus exposing patients to a degree of risk. Robotic surgery lends itself well to computer based virtual reality training, similar to how pilots train on flight simulators. Such training systems have been developed and validated, such as the dV-Trainer (Mimic Technologies, Inc, Seattle, WA, USA), and the da Vinci Skills Simulator (Intuitive Surgical, Sunnyvale, CA, USA). Studies have found that structured training exercises improved simulator performance, although the translation to actual surgical performance has not been well studied (6,7).

Cons of robotic surgery

There are a number of disadvantages with robotic surgery. The current generation of robots has a large footprint and bulky arms, in addition to the size of the operating console. Spacious operating rooms are required, and dexterity is limited by collision of robotic arms (*Figure 1*). A skilled assistant is needed for suction, change of instruments, application of argon plasma, and stapling. There is no tactile feedback so the retraction pressure on the liver may be more difficult to gauge, and suture breakage may be more common, although experienced surgeons adjust to it by visually judging the tension on sutures (8). Changing patient position requires the robot to be undocked and redocked, adding time to the procedure and interrupting the flow of the operation. The separation of surgeon and patient potentially leading to delays in managing intraoperative complications and emergent conversion can be a source of anxiety for the operating team. Studies have generally shown that robotic surgery take longer time than their laparoscopic counterparts, in part due to time setting up and docking the robot, and time spent changing instruments (9-11). However, with increasing experience and proficiency this is likely to reduce.

The other recent advancements in the field that will improve accessibility of robotic surgery for liver resection

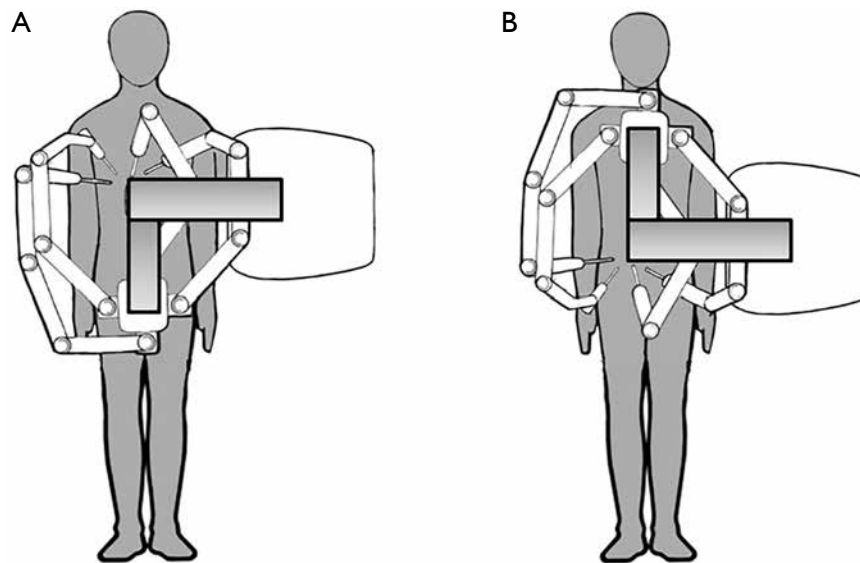


Figure 2 Flexibility for multi-field robotic surgery for the Intuitive Xi Robot. Without moving the patient, or table, or robotic tower, the working arms can be turned 180 degrees to swap from right upper quadrant work (A) to pelvic work (B). This will allow combined hepatectomy and rectal resections.

include the range of new instrumentation that is now available, including robotic suction devices, sealers, and staplers. That has eliminated the routine need for accessory ports and necessity of a skilled bedside assistant. The launch of the Intuitive Xi robot has also allowed ease of multi-field surgery, and provides great ease in repositioning and re-docking (*Figure 2*). This robot is attached to a mobile boom that allows full 180 change in orientation of instruments without moving the patient, or table, or the robot.

Robot malfunction in a variety of general surgical operations has been reported but appears to be relatively uncommon, and rarely lead to significant consequences. Approximately half of documented malfunction cases were attributed to robotic instruments and were resolved by replacing the instruments. Other sources of malfunction included optical systems, robotic arms, and the console. Agcaoglu *et al.* reported 10 cases of robotic malfunction in 223 cases (4.5%), with no adverse outcomes (12). Buchs *et al.* reported 18 cases of malfunction in 526 cases (3.4%), with one conversion to laparoscopy due to light source failure (13). Kim *et al.* reported 43 malfunctions in 1,797 cases of general and urological operations (2.4%), leading to conversion to open in one patient and to laparoscopy in two patients, all due to robotic arm malfunction (14).

One of the major disadvantages of robotic surgery is the high cost. The purchase of a da Vinci robot has been reported to be around US \$1.5 million, with annual

service cost of around \$110,000, plus cost of disposable instruments (15). In a systematic review, Turchetti *et al.* analyzed 11 studies in the English literature which compared the cost of robotic surgery with the laparoscopic approach for various abdominal operations. The cost of the robotic approach was generally higher due to increased operating time (particularly set-up time) and instruments, while the costs of hospital stay were similar (16). However many studies did not include the purchase and maintenance costs which are significant, particularly in lower volume centers. None of the studies in this review evaluated the potential economic benefits of robotics.

Evolution of robots

Even though robotics in medicine have only recently caught the attention of the public, the technology is not new. One of the first applications of robotics to modern medicine was the Puma 560 in 1985, an industrial robotic arm used by Kwoh *et al.* to perform stereotactic brain biopsies. In the 1990s, a number of robots were developed, including the PROBOT at the Imperial College of London for transurethral resection of the prostate, the RoboDoc in the USA for femoral coring for hip replacement, and the ARTEMIS in Germany, a precursor to the modern master-slave manipulator system. Subsequently the robots used in modern surgery were developed by two initially competing

companies (17,18).

One company was Computer Motion Inc based in California. They were contracted by NASA to develop the AESOP, a voice-activated camera control system that was compatible with standard 5 and 10 mm endoscopes. Subsequently the ZEUS robotic system was developed and became commercially available in 1998. The system consisted of a control console and table-mounted robotic arms incorporating the AESOP camera. In the 1980s, the Stanford Research Institute conducted research funded by the U.S. Army to develop telesurgery in the battlefield. Interest arose to extend its application to civilian surgery, and in 1995, Intuitive Surgical Inc was founded in California to further develop this technology. In 1999, Intuitive Surgical released the da Vinci robot in Europe, and in 2000 FDA approved its use in the USA. The da Vinci robot consists of three parts: a control console, a 3- or 4-armed surgical cart that is docked against the operating table, and a vision system. Central to the technology are a high-definition 3-dimensional viewer, a footswitch to allow the surgeon to swap between camera, retractors, and instrument control, and the Endowrist instruments, articulated instruments that mimic the seven degrees of motion of the human hand (18,19). In 2003, Intuitive Surgical and Computer Motion were merged. The ZEUS model was phased out and continued development was focused on the da Vinci system, now the only commercially available robotic operating system in the world. The second generation da Vinci S was released in 2006, and in 2009, the third generation Si model was released with dual-console capability and improved vision. In 2014, the fourth generation da Vinci Xi robot was approved by the FDA, with a redesigned surgical arm cart, smaller, longer arms, and new camera system to allow more flexibility in cart position and port placement (20).

Robotic liver surgery

The indications for robotic hepatectomy are similar to those for laparoscopic hepatectomy. Both benign and malignant tumors can be resected robotically. Patients must have the physiological reserve to tolerate general anesthesia and a prolonged pneumoperitoneum. General contraindications to laparoscopy such as uncorrected coagulopathy should be observed.

Laparoscopic hepatectomy for lesions in the superoposterior segments such as segment VII and VIII are particularly challenging due to their positions and the curved transection

lines. As a result, laparoscopically lesions in these segments may be more commonly resected via a right hepatectomy, sacrificing a substantial volume of normal liver (21). Robotic hepatectomy helps overcome this problem and some authors have reported success (22). Thus the greatest theoretical advantage of robotic hepatectomy may lie in sectoral, segmental, or subsegmental resections in difficult-to-reach positions, where patients may be spared the large incisions and extensive mobilization required in an open approach. On the other hand, major hepatectomies for malignant conditions where large incisions are required for specimen extraction may be better served by a traditional open approach. Difficult hepatic resections such as those for hilar cholangiocarcinoma requiring caudate lobectomy and bile duct anastomoses are generally not performed laparoscopically but the use of a robot may allow these to be approached in a minimally invasive manner.

Image guided surgery is a developing field where pre-operative imaging is used to aid intraoperative maneuvers. There is considerable experience in applying this technology to neurosurgery and orthopedic surgery, but there is increasing interest in hepatobiliary surgery (23). Computer models built on CT or MRI are registered onto the real-life organs by matching landmarks, which then allows intra-operative navigation to be guided. The need for a computer console in robotic surgery makes it ideal for integration of image-guidance as an adjunct to intraoperative ultrasound, creating an augmented reality where images are superimposed onto the field of view which may help surgeons anticipate vascular structures and obtain adequate margins. This is particularly suited to accurate probe placement for ablation of small, difficult to localize tumors. Image-guidance technology in hepatobiliary surgery is still in its infancy with a number of technical challenges such as deformation correction, and further work is needed before augmented reality can be realized.

Robotic assistance can potentially overcome some of the limitations of SILS, for example by swapping the hand controls to eliminate cross-handed operating. Early experiences with robotic single-port hepatectomy have been reported (24), but the technology will likely have to be modified to adapt to the unique challenges of SILS, particularly the propensity for the robotic arms to clash with each other.

In theory, robotic surgery is an ideal platform for telesurgery. Indeed that was one of the driving forces behind the development of the master-slave robotic system. However, the latency between the surgeon's movement and

the observed effect due to transmission of data to and back from the patient is a significant limitation. Marescaux *et al.* reported the first transatlantic robot-assisted telesurgery in 2001, where a robotic cholecystectomy was performed by surgeons in New York, USA, and the patient in Strasbourg, France (25). The authors reported a total time delay of 155 ms; however this was performed on a dedicated high-speed terrestrial optical fibre network. Current satellite-based networks and public-internet based connections are inadequate for the widespread application of telesurgery over long distances, particularly for complex procedures with small margins of error (26).

Current data on robotic liver resection

Early experiences with using a robot in cholecystectomy were reported by Gagner *et al.* and Himpens *et al.* (27,28). Chan *et al.* reported their experience with 55 robotic HPB procedures, including 27 hepatectomies, 12 pancreatectomies (including 8 Whipple's), and 16 biliary operations. Their experience with robotic liver resections for HCC was subsequently also published (29).

The largest series of robotic hepatectomy to date was a single-surgeon series published by Giulianotti *et al.* from the University of Illinois, with 70 patients (60% malignant, 40% benign). Major hepatectomy was performed in 27 patients, including 20 right hepatectomy, 5 left hepatectomy, and 2 right trisectionectomy. Of note, lesions in segments VII and VIII were only attempted if a right hepatectomy was performed. Three patients had a bile duct resection with biliary reconstruction, which is considered by most surgeons as a contraindication to laparoscopic hepatectomy because of the added complexity of a bile duct anastomosis. The median operative time was 270 min; for major resection it was 313 min, minor resection 198 min, and for biliary reconstruction 579 min. Major morbidity occurred in four patients, and there were no mortalities. Median surgical margin was 18 mm. No survival or oncological outcomes were reported (30).

Lai *et al.* from Hong Kong reported their experience of 42 patients with HCC and non-cirrhotic liver or Child-Pugh class A cirrhosis. The type of surgical operation included wedge resection in 10 patients, segmentectomy in 7, bisegmentectomy in 4, left lateral sectionectomy in 12, right hepatectomy in 7, and left hepatectomy in 3. Mean operating time was 229 min and median blood loss was 413 mL. Three patients developed complications, and there were no perioperative deaths. Mean hospital stay was

6.2 days. R0 resection was achieved in 40 patients (93%). Follow-up was relatively short at a median of 14 months. Six patients recurred within the liver and the 2-year overall survival was 94% (10).

The hepatopancreatobiliary group at Memorial Sloan Kettering Cancer Center has performed over 70 robotic hepatectomies (Kingham P and Fong Y, 2014, unpublished data). Twenty-three percent of patients have had previous abdominal surgery, including 5 re-operative hepatectomies. Median operating time was 164 minutes, estimated blood loss 100 mL, and four patients required conversion to open (6.1%). There were no mortalities and no re-operations for complications. The major conclusion derived from this series is: lesions in segment 1, 7, and 8 can be performed safely. Unlike the prior series where investigators saw the goal of robotic hepatectomy as trying to perform major hepatectomies, these investigators saw the robot as a means to accomplish resection of ill placed minor resections. For major resections, it is unlikely that robotic resection will change much the usual outcomes of hospital stay or complications, since the extent of the hepatic resection and not the incision will be the greatest determinant of outcome. For minor resections of ill placed tumors, the incision usually dominates the clinical outcome. These are likely to be those resections where robotic surgery is likely to be proven superior. These are also those cases where expert opinion has recommended against laparoscopic surgery (2). Positioning of patient and the robot has now been improved to facilitate safe robotic resection of tumors in segments 7 and 8 (*Figure 3*).

Few studies have compared robotic to laparoscopic liver resections. Berber *et al.* found non-different operating time, blood loss, and resection margin (31). Ji *et al.* found that robotic resections may have longer operating times than laparoscopic or open resections but comparable blood loss and complications (9). Lai *et al.* found a similar association for patients undergoing minor hepatectomy (<3 segments) only (10). The largest matched comparison between laparoscopic and robotic hepatectomy was published by Tsung *et al.* and the University of Pittsburgh group (11). In this retrospective study, 57 patients undergoing robotic hepatectomy were matched with 114 patients undergoing laparoscopic hepatectomy on background liver disease, extent of resection, diagnosis, ASA class, age, BMI, and gender. They found that operating times were significantly longer in the robotic group for both major and minor hepatectomies. There were no significant differences in complication rates, length of stay, mortality, and negative margin rates.

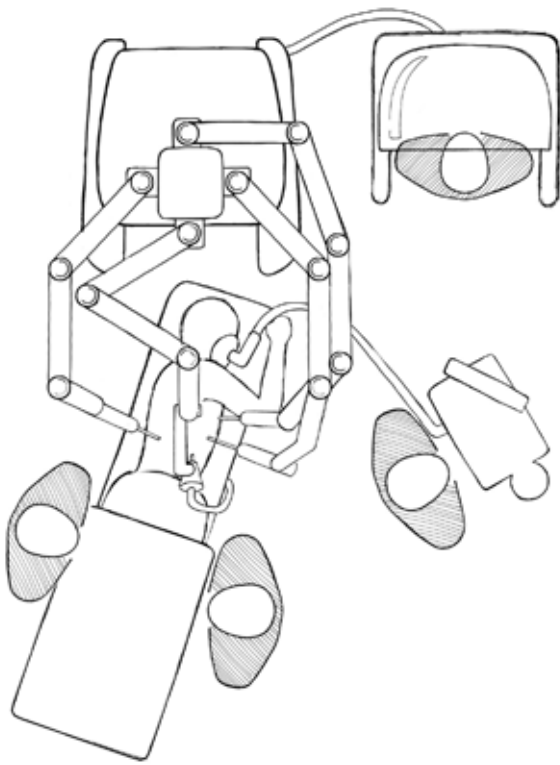


Figure 3 Positioning for robotic hepatectomy for lesions in segment 7 or 8.

There was a trend towards less blood loss in the robotic major hepatectomies compared with laparoscopic major hepatectomies, which the authors attributed to superior inflow and outflow control, as well as magnified optics allowing better identification of vessels during parenchymal transection. Interestingly for the minor resections, the robotic approach was associated with a significantly higher blood loss than laparoscopic approach. The authors also noted that conversion to open rates were comparable, and that patients in the robotic group were more likely to have their surgery performed completely laparoscopically, without hand-assistance or a hybrid laparoscopic-open approach (93% *vs.* 49% for the laparoscopic group) (11).

Conclusions

Current data show that with good patient selection and meticulous technique, robotic hepatectomy is a safe and effective operation that is likely to stay. The goal of robotic assistance is to mimic the techniques of open surgery delivered through a minimally invasive approach. The theoretical advantages of robotic surgery are exciting but the evolution

of the technology has been a slow process. In a review article in 2004, Lanfranco *et al.* outlined the pros and cons of robotic surgery at its relative infancy (18). Ten years later we find ourselves still facing similar limitations. Future directions may include reducing the size of the robot, modifying the arm mechanism to reduce clashing, multi-purpose instruments to reduce the need for frequent instrument exchanges and for an experienced assistant, development of hepatics to allow tactile feedback, and integration of image guidance. There is still skepticism outside the circle of robotic HPB enthusiasts regarding the wide applicability of this technology. For many centers the high cost will be a major deterrent. Despite all its promises, until the benefits are more clearly defined, robotic liver surgery will likely be practiced by a select group of surgeons at high-volume centers.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Liver transplantation for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and is considered an aggressive tumor with mean survival estimated between 6 and 20 months. Hepatitis B and C are the most common etiologies. Pathological, laboratory and radiologic imaging all aid in diagnosis but much controversy exists in the utilization of any given modality. Many treatment options exist for management of HCC, each has its own limitation. Liver transplantation offers the most reasonable expectation for curative treatment while simultaneously removing the burden of the diseased liver. Still, advancements in the field have thus far not yet matched its potential, although new immunosuppressive and chemotherapy regimen may allow transplantation to push the envelope once again.

Keywords: Hepatocellular carcinoma; hepatoma; liver transplantation

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Introduction

Hepatocellular carcinoma (HCC) or hepatoma is the sixth most common cancer worldwide and the third most common cause of death from cancer. In the United States, the incidence is rising and is expected to continue rising over the next two decades. It is the most common primary tumor of the liver accounting for 90% of all primary liver tumors. Mean survival is estimated to be 6 to 20 months without intervention (1). Unfortunately, platinum and adriamycin based chemotherapeutic and radiation therapies do not offer substantial survival benefits. Recently, sorafenib has been approved by the US FDA for the treatment of unresectable HCC (2,3). This new therapeutic option may open more doors that include liver transplantation. Furthermore there is increasing evidence that sirolimus may further improve post transplant cancer disease free survival (4). Over the last thirty years, the treatment of this cancer has changed greatly. Advances in surgical technique and immunosuppression regimens have made liver transplantation a feasible alternative to many patients with HCC.

Etiology

The most common cause of hepatoma is chronic hepatitis virus infection. The prevalence of HCC parallels that of viral hepatitis across the globe. Whereas chronic hepatitis B infection is the most common cause of HCC worldwide and in most African and Asian countries, chronic hepatitis C virus is the leading cause in southern European countries and North America (*Figure 1A,B*).

Chronic hepatitis B infection is well defined as an etiology for hepatoma. Three quarters of the cases of HCC occur in Asian countries where there is a high prevalence of chronic hepatitis B infection. The mechanism remains unclear, but some have postulated that the DNA viral replication plays a role. What is known is that there is an increased relative risk (223×) among carriers to developing this cancer (5,6). Furthermore, there is increasing evidence that active viral replication in hepatitis B patients increases this risk of hepatocellular cancer in those who are chronically infected (7,8). Lastly, there is a positive correlation between specific viral variants, (namely genotype C, precore, basal core and pre-S deletion mutants)

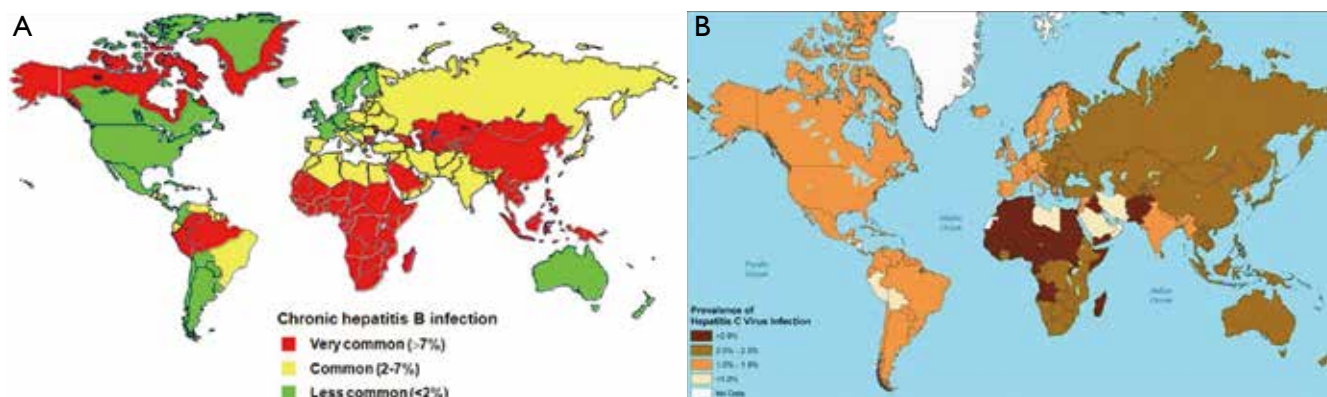


Figure 1 A. Prevalence of Hepatitis B (<http://www.hepbnet.org/about.asp>); B. Prevalence of Hepatitis C (http://relief.unboundmedicine.com/relief/ub/view/cdc-yellow-book/204050/all/Hepatitis_C)

and cancer development (9).

In contrast, chronic hepatitis C infection is a more common etiology in Europe and North America. It is reasoned that this could be related to a hepatitis C viral epidemic thirty years ago in the developed world. Nevertheless, it is known that about four million Americans have chronic hepatitis C and roughly one third will progress to chronic liver disease, many of these patients will go on to develop cancer. This pattern of hepatitis to cirrhosis to carcinoma readily distinguishes hepatitis C patients from their hepatitis B counterparts and carries implications for their treatment and outcomes. Interestingly, also in contrast to hepatitis B patients, the distribution of chronic hepatitis C patients varies between regions and ethnic groups within countries where the disease is endemic, suggesting that there is a social or behavioural component to transmission (10).

In chronic hepatitis patients, regardless of whether the causative virus is B or C, a number of independent risk factors have been identified. Male gender is one - in high risk countries, the ratio is 3:1 (male:female). Advanced age is another, particularly in areas where hepatitis C virus is endemic (11). In hepatitis B endemic areas, incidence rates increase after age 20. Obesity, family history, diabetes and alcoholism increase the cancer risk in chronically infected patients (6). It is known too that liver disease progresses faster in patients with HIV coinfection (12,13). Additionally, hepatitis B - hepatitis C coinfection have a synergistic effect in the development of carcinoma (14).

Aflatoxin is produced from fungi and is a common contaminant in corn, peanuts and soy beans in China including Taiwan. It is a known carcinogen in the development of hepatocellular cancer (15,16). Another

less common etiology of this cancer is hereditary hemochromatosis. Its mechanism is believed to be similar to hepatitis C, in that persistent inflammation leads to fibrosis, cirrhosis and eventual cancer (17,18). Other less common causes of HCC include ethanol ingestion, primary biliary cirrhosis, alpha-1 antitrypsin deficiency, hypercitrullinemia, porphyrias, hereditary tyrosinemia, Wilson's disease and carcinogenic agents such as thorotrast, polyvinyl chloride and carbon chloride (19).

Pathology

The gross pathologic appearance of HCC varies depending on the presence of cirrhosis. Multinodular lesions in noncirrhotic livers typically reflect intrahepatic metastases. Whereas, cirrhotic livers are usually representative of multicentric HCC. Multicentric tumors are common in patients with hepatitis C and tend to grow in the most damaged segments of the liver. The color may be green due to bile production, yellow due to fatty infiltrates, tan-brown, or grey-white.

Hematologic spread most often affects the lungs (48%), followed by the adrenal glands (8.3%), bone (5.6%), gastrointestinal tract (4.7%), bladder (3.5%) and pancreas (3%) (20). Up to one quarter of tumors present with lymph node metastases, typically to the hilar, peripancreatic, perigastric and periaortic nodes.

The histological appearance of this tumor is highly variable. The most common form is the trabecular pattern which encompasses the pseudoglandular, pseudofollicular and mixed trabecular-acinar types. The pseudo-glandular and acinar pattern is characterized by dilated bile

canniculus-like structures, often filled with bile (1). Other patterns that describe the tumor include solid, compact, scirrhous, clear cell, giant cell, pseudocapsular, and sarcomatous. The compact variant is sinusoid-like blood spaces that are slit-like. The scirrhous type is distinguished by marked fibrosis (9).

On cytology, tumor cells of HCC may show fatty change, Mallory bodies, globular hyaline bodies, pale bodies, pleomorphic cells and sarcomatous changes. HCC often contains more than one cytologic variant within the same tumor. The production of bile, the expression of alpha fetoprotein, the canalicular expression pattern of biliary glycoprotein 1 and CD10, lack of reticulin, and the presence of albumin mRNA are all distinguishing features of HCC that separate it from other solid tumors in the liver.

Molecular markers

Alpha fetoprotein (AFP) is highly diagnostic for this tumor. It is present in large quantities during fetal development but decreases rapidly after birth. Normal adult level is typically less than 10 ng. Typically, elevated levels of AFP greater than 400 ng/mL are considered diagnostic. This marker may return to normal after resection and is useful as a marker for tumor recurrence. Mild elevations in AFP may be found in acute viral hepatitis, chronic liver disease, and some metastatic cancers. Fulminant HBV, teratocarcinomas, yolk sac tumors and metastatic tumors from the stomach or pancreas can also produce markedly elevated levels. As a diagnostic tool, AFP is most helpful in concordance with hepatic imaging confirming the presence of tumor.

Two other tumor markers, des-gamma-carboxyprothrombin (DCP) and alpha L-fructosidase (AFP-L3), are also possible markers for HCC. DCP is an abnormal prothrombin protein that is increased in HCC patients. It is highly specific for the disease and may also be a predictor of prognosis. Current Asian consensus guidelines advocate for routine use of AFP and DCP to increase sensitivity in detection of HCC. AFP-L3 is a fucosylated variant of AFP that can help to differentiate an increase in AFP due to HCC versus benign liver disease. Recently Mao *et al.* described using GP-73 as an adjunct to AFP to increase sensitivity and specificity (21,22).

Radiographic imaging

The 2010 practice guideline recommendations of the American Association for the Study of Liver Diseases state

that HCC can be diagnosed on the basis of radiologic findings without biopsy. There are two criteria for diagnosis: arterial enhancement of a nodule and the presence of washout on portal venous or delayed imaging. For this purpose, contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) are the best studies.

Contrast-enhanced ultrasound does have potential utility but its use is limited by the lack of availability of the necessary contrast agents in many countries, including the United States, and the inherent limitations of ultrasound, such as operator-dependent variability and patient habitus. Regardless of imaging technique employed, patients with hepatocellular cancer patients should undergo a metastatic workup. For this purpose, a CT or MRI of the abdomen and pelvis, a CT of the chest and bone scintigraphy should be obtained.

Staging

There are a number of staging systems that assess liver function and tumor burden based on radiological or pathological criteria. Although none have been universally accepted, four have gained widespread acceptance. These will be discussed first, followed by the others. Of these classifications, only two, BCLC and GRETCH, consider performance status. CUPI is the only one to assess symptomatic disease.

The TNM classification was developed by International Union Against Cancer and American Joint Committee on Cancer and has been validated for good discrimination between stages for patients undergoing hepatic resection. It is based on tumor size, the number of tumors and extent of disease, including vascular invasion. This staging system was most recently revised in 2010 to accommodate for prognostic implications of multiple tumors and vascular involvement. The TNM classification has been validated in large cohort trials and is considered the most accurate to define post-transplant outcomes (2). Still, it has been criticized for its complexity and its failure to adequately stratify patients with cirrhosis and large tumors.

In this group of patients, the Okuda classification is considered more useful as a prognostic indicator. This staging system was developed in 1985 and, as it does not stratify patients who are not candidates for resection, is a purely clinical scoring system. The Okuda classification is based on tumor size and the severity of cirrhosis. It is limited by the absence of assessment of tumor burden.

The Cancer of the Liver Italian Program (CLIP) was

introduced in 1998 and validated as a prognostic indicator in 2000. It includes Child-Pugh, tumor morphology and extent, presence of portal vein thrombosis and AFP level. Several studies suggest that CLIP may be better at predicting survival than either TNM or Okuda classifications, particularly in patients undergoing adjuvant therapy (23).

The Barcelona Clinic Liver Cancer (BCLC) system includes performance status, presence of multifocal tumor lesions, vascular invasion, extrahepatic spread, Child-Pugh stage, portal hypertension. This classification is criticized for being algorithmic rather than being patient-centered. However, recent studies have deemed this the best prognostic system (23). The American Hepatopancreaticobiliary Association consensus statement recommends the BCLC scheme for patients with advanced cancer who are not candidates for surgery and the TNM staging for candidates who meet criteria for liver resection (24).

The Liver Cancer Study Group of Japan (LCSGJ) utilizes revised TNM staging for clinical and pathologic staging of primary liver cancer. It includes twelve classifications and has been criticized for its complexity and lack of prognostic correlation.

The Japan Integrated Staging Score (JIS) was developed in 2003 and combines TNM stage and Child-Pugh Stage into a score of 0 to 5. It has yet to be validated in populations outside of Japan. However, it has been compared to the CLIP and BCLC systems and found to be a superior prognostic determinant [Kudo, 2004 #3950]. It remains the most popular staging system that country.

The Chinese University Prognostic Index includes nineteen variables and is proven useful in determining prognosis in Southeast Asian populations with HBV-HCC predominance. The Tokyo score developed with a cohort of Japanese patients with early stage disease who were treated with percutaneous ablation and was validated with a cohort undergoing resection surgery. Lastly the Taipei Integrated scoring system uses total tumor volume to assess tumor burden. None of these has been validated or widely used outside of the populations in which and for which they were developed.

Evolution of transplantation for HCC

The first liver transplant performed in humans was done by Dr. Thomas Starzl in 1963. However, the procedure did not gain widespread acceptance until the 1980s when cyclosporine started being used as an immunosuppressive

agent. The finding that small, incidentally found tumors in explanted livers did not affect survival introduced the idea of liver transplantation as a treatment for HCC. Still, the use of this modality as a treatment for HCC remained limited by high recurrence rates and low 5-year survival.

However, the advent of the 1990s brought evidence that hepatic transplant could be done safely with good outcomes. In 1991, Dr. Iwatsuki *et al.* published data from 105 patients with hepatoma who underwent liver transplantation. 35% of these patients had portal invasion, and 75% had multinodular tumors. The team reported 36% 5-year survival. [Iwatsuki, 1991 #3963] While still poor, these numbers were more satisfactory than previously reported. Two years later, Bismuth and colleagues, reported better outcomes (49% 3-yr survival) in patients with up to three tumors, each less than 3 cm. The group demonstrated better disease free survival rates after liver transplantation compared with hepatic resection (25).

In 1996, in a landmark paper published in the *New England Journal of Medicine*, Dr. Mazzafero published results demonstrating 74% 4 year survival after liver transplantation in patients with solitary lesions less than 5 cm in diameter or up to 3 lesions each less than 3 cm in diameter. This has been designated the Milan criteria (26). Three years later the Bismuth group published new data suggesting similar survival rates in patients with tumors less than 3 cm (27). The “Milan Criteria” quickly became the standard. Currently, HCC is the primary indication for liver transplant for 25% of all cases in Europe and 35% of all cases in the United States.

Expanding criteria for liver transplantation

There is a need to optimize benefits given the limited number of available organs. This has led to the development of stringent criteria for transplantation. Traditionally, most centers employ the Milan criteria. Most notably, the 2010 International Consensus for Transplantation for HCC advocates the use of Milan criteria as the benchmark for selection. But, there is considerable interest in expanding this criteria and certain some centers have shown progress in this area. At the University of California San Francisco, Dr. Yao *et al.* have demonstrated that patients with a single lesions less than 6.5 cm, or up to three lesions each less than 4 cm with a cumulative diameter less than 8 cm have surgical outcomes similar to those transplanted under Milan criteria (28,29).

There is promising new data which suggests that tumor

histology may be more important than tumor burden in determining posttransplant outcomes. In 2004, Dr. Cillo and his colleagues in Italy reported a retrospective analysis which showed that patients with well to moderate grade HCC had acceptable outcomes after transplantation regardless of tumor burden. Thirteen patients in his cohort did not meet Milan criteria (30). More recently, Dr. DuBay at the University of Toronto reported in 2011 that transplantation in patients with advanced moderate to well differentiated adenocarcinoma can be performed safely. The group reported 5-year survival of 70% and a 5-year disease free survival of 66% which was comparable to those who met Milan criteria in their cohort (31).

Loco-regional therapies

In order to maximize the benefit of transplantation, the course of the disease needs to be arrested while awaiting a suitable graft for transplantation, loco-regional treatment is able to accomplish this goal in most circumstances (32-42). Given the current waiting times in the major cities in the US, most programs have adopted the international consensus report that recommends bridging therapies for patients with T2 disease (solitary tumor 2-5 cm, or two to three lesions 2-3 cm) but not for T1 lesions (solitary tumor without vascular invasion). Transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) are the two modalities most widely employed.

It is now known that the majority of the blood supply to hepatic tumors is derived from the hepatic artery. This fact, combined with advances in technology, has enabled targeted chemotherapeutic intervention for hepatocellular cancers, otherwise known as transarterial chemoembolization or TACE. During TACE procedures, a chemotherapeutic agents, such as doxorubicin, cisplatin and mitomycin combinations are injected into the artery supplying the tumor usually with lipiodol or a procoagulant. Lipiodol is an agent that promotes tumor retention of chemotherapy medications (34,37,40,42-45). Similarly, drug-eluting microspheric beads have shown promise as a treatment, possibly with less toxicity (46). Contraindications to this treatment include the absence of hepatopedal blood flow, encephalopathy and biliary obstruction.

Radiofrequency ablation uses high frequency alternating currents from an electrode inserted into the lesion. Ions within the tissue attempt to follow the change in directions of the charge resulting in friction and heat. As the temperature rises above sixty degrees celcius tumor necrosis

occurs This method is best utilized in patients with solitary tumors less than four centimeters (32,47-51).

Alternative treatment options

The Sorafenib in Advanced HCC (SHARP) trial demonstrated a modest, statistically significant three-month survival benefit for this medication compared to placebo. It should be noted that it is a toxic drug associated with increased risk of bleeding, poor wound healing, diarrhea and hepatic decompensation. Furthermore, the SHARP trial was limited to patients with Child's A cirrhosis, making it of limited utility in the general patient population. The median survival in the study group was 10.7 months (33,52-55). Currently, we are awaiting results of phase II trial combining sorafenib and doxorubicin. Still, it is unlikely that medical treatment will offer comparable results to interventional or surgical procedures in the near future.

Graft selection

The critical issue for all patients awaiting liver transplantation is the availability of transplantable grafts. Time is a major determinate of overall survival if one assesses intent to transplant analysis (56-60). The biology of the tumor can impact the time a center is willing to wait for a graft. If there is evidence that the tumor has an aggressive biological behavior, it may be wise to wait (3-6 months) and determine the exact nature of the tumor while tumors that do not demonstrate aggressive behavior should be transplanted as soon as a graft is available. This key clinical difference is very difficult to determine at times (61-64). Living donation is an avenue that is perfect for transplantation in patients with HCC as the time function is eliminated and the transplant can be planned at a time that is optimal in terms of assessing the biological nature of the tumor and minimizes tumor recurrence (65-71). The temptation is to transplant as soon as the donor is worked up, but this may lead to higher recurrence rates. The waiting time allows for self-selection of tumors with favorable tumor biology. It is, at times, difficult for the team to wait once a suitable donor is identified.

Immunosuppression

There is growing evidence that immunosuppressive agents may determine the risk of recurrence after transplantation. Sirolimus is a bacterial macrolide with immunosuppressive

and antineoplastic properties. The mechanism of action appears to work via inhibition of IL-2 mediated lymphocyte proliferation. In laboratory studies, this results in decreased metastatic tumor growth and decreased angiogenesis in the liver. Several studies have demonstrated that a post-transplant regimen of sirolimus within a steroid free protocol and a low tacrolimus target is associated with a decreased risk of tumor recurrence without significant risk of infection or hepatic artery thrombosis (4,72-75).

Conclusions

Transplantation as treatment for HCC has enjoyed increasing attention as improvements in surgical technique, immunosuppression and patient selection have led to increased postoperative survival. Patients that have HCC within the Milan criteria should be treated as any other transplant patient unless there is evidence that the biological nature of the tumor is aggressive. For patients who present with tumors outside of Milan criteria, it is more important to mandate a 3-6 months waiting period to assess the biological nature of the tumor. In all patients during the period of waiting loco-regional therapy should be applied to the tumor. In those patients outside of Milan criteria, the addition of sorafenib should be considered. Similarly, in those patients outside of Milan criteria, a steroid free immunosuppression regimen starting off with a calcineurin inhibitor that is weaned to off with sirolimus started as maintenance immunosuppression around 3 months appears to offer the best chance of long term survival. The role of sorafenib post transplant has not yet been established, but may have a role for those patients at high risk of recurrence.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Review on liver transplant for hepatocellular carcinoma

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Abstract: Orthotopic liver transplant (OLT) is a curative treatment for patients with hepatocellular carcinoma (HCC). It is widely practiced around the world, but there is no specific set of recommendations to guide physicians. Milan criteria (MC) is a starting point in selecting optimal candidates for OLT, but no consensus exists for patients whose tumors exceed beyond MC. This article will review current literature and discuss controversial topics within HCC and OLT.

Keywords: Organ procurement and transplantation network (OPTN); United Network for Organ Sharing (UNOS); hepatocellular carcinoma (HCC); orthotopic liver transplant (OLT); Milan criteria (MC); locoregional therapy (LRT); end stage liver disease (ESLD)

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Introduction

The first solid organ transplant in the modern era was performed in 1883 by Dr. Theodor Kocher, who successfully implanted thyroid tissues in post-thyroidectomy patients (1). The concept of replacing a failed organ through transplant was widely acknowledged soon thereafter. In 1963, Dr. Thomas Starzl performed the first human liver transplant. OLT became the standard of care for end stage liver disease (ESLD) in the 1980s, especially with the invention of various immunosuppressants. Today, the success of OLT is marked by a 1- and 5-yr survival of 85% and 70% (2), in an otherwise terminal condition.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. In some parts of Southeast Asia, it is the most common malignancy, in part due to the endemic spread of Hepatitis B and C viruses. Other common risk factors for developing HCC include cirrhosis, alcohol, and non-alcoholic fatty liver disease. Overall, HCC has become more prevalent globally, causing 250,000 to 1 million deaths annually worldwide (3). Without treatment, HCC has a high mortality rate, with a 5-year survival of 10% (4). OLT offers a potential cure for HCC, especially if the cancer is found in early stages (T1 or T2). Unfortunately, the worldwide shortage of deceased liver donors presents a challenge to justifiably distribute liver

grafts among patients in need of OLT.

Epidemiology and overview

In the years prior to 2002, the overall 5-year survival for HCC was merely 11.7% (5). However, it drastically improved over the last decade, due to earlier diagnosis from better cancer screening, and new treatment options, from locoregional therapy (LRT) to OLT.

Liver allocation has come a long way. In the 1980's, distribution of this scarce resource used to be "ad hoc" basis, solely determined by medical providers. In the 1990's, ICU patients and hospital patients had priority over clinic patients, considering that inpatients are likely to have a higher mortality without immediate intervention. In 1998, minimal listing criteria were instituted using the Child-Turcotte-Pugh (CTP) score (6). This scoring system takes into account encephalopathy, ascites, bilirubin, albumin, and pro-thrombin time. A numeric score was then converted to class A, B, or C, with C being on the more severe end of the spectrum. Despite its seemingly comprehensive determinants, this score became quite subjective, requiring physicians to accurately stage hepatic encephalopathy and ascites.

Finally, in 2002, the Model of End Stage Liver Disease (MELD) score was adopted in prioritizing patients for

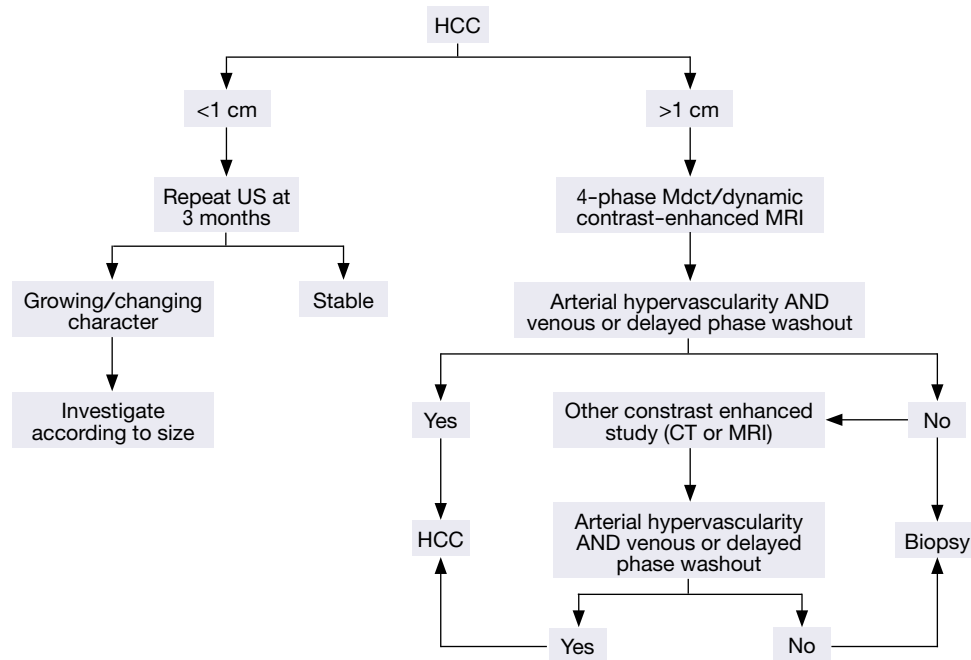


Figure 1 An algorithm for diagnosis of HCC based on AASLD guideline. Printed with permission from AASLD.

liver transplant (7). This score was initially developed to predict mortality in patients with complications of portal hypertension undergoing transjugular intrahepatic portosystemic shunt placement (TIPS) (8). It is calculated based on three objective variables: international normalized ratio (INR), bilirubin, and serum creatinine. This score was subsequently found to be also useful in predicting three months mortality in patients with liver disease, and thus is currently used to prioritize deceased donor liver allocation. Disadvantage of this scoring system is that it does not take into account quality of life issues, such as when hepatic encephalopathy or ascites can be detrimental to patients' lives. Other than the MELD score along, there are several other factors that go into candidacy for a liver transplant, including BMI, social support, cardiac/pulmonary status, portal vein patency, and other malignancy or co-morbidities.

In regards to allocation, the United States is divided into 11 different regions. Deceased donor livers that become available in a certain region can be shared amongst those living within the region (9) (unos.org). The higher the MELD score, the higher on the list one becomes. However, every region has a different MELD average for receiving a liver, thus making certain regions more favorable in receiving a liver than others. Currently, the national average MELD score for liver transplant is 27 (2). However, the

average MELD score in some areas varies from 26-33, depending on blood type. On average, for patients with MELD 21-30, the mean waiting time to OLT is 128 days. For MELD score 31-40, mean time is approximately 29 days. Average wait time can differ drastically by regions, which has resulted in inequity in organ allocation between different areas of the country.

Diagnosis of HCC

In recent years, as a result of better cancer screening, patients with HCC are diagnosed earlier (10). Diagnosis of cancer often requires pathology confirmation; however, HCC is an exception. AASLD published its most recent guideline which states that lesions greater than 1 cm, with triple phase CT or MRI showing arterial enhancement, followed by portal venous phase washout, can confirm the diagnosis of HCC, without a liver biopsy (11). New nodules greater than 1cm in cirrhotic liver showing typical pattern of HCC are nearly 100% specific with high positive predictive power (12-14). If initial imaging does not show typical pattern, then a second imaging modality should be pursued. Atypical imaging pattern on CT or MRI, such as iso- or hypo-vascular enhancing lesion during arterial phase without portal washout should undergo biopsy (Figure 1). Major

complications associated with a biopsy include bleeding and needle tract seeding of tumor, which has been reported in multiple cases (15). A large retrospective study done by Wang *et al.* in China showed a 0.2% risk of implantation of metastases and 0.4% risk of hemorrhage (16).

Molecular markers for detecting HCC

Elevations of alpha-fetoprotein level in the serum is not very sensitive (39-65%) nor specific (76-94%) for the diagnosis of HCC. Most recent AASLD guideline recommends against testing AFP to screen for HCC in cirrhotic patients. On the other hand, AFP has found a role in the monitoring of response and tumor progression after treatments. Diaz *et al.* observed that a reduction in serum AFP level after LRT predicts tumor reduction (17). Also, the pre-operative clinical prognostic factor for mortality and recurrence after treatment was AFP level higher than 300 ng/mL (18). In addition, AFP also has a role in predicting post-transplant outcomes. Several studies showed patients with significantly elevated AFP prior to transplant have poorer outcomes (19). Some experts even feel that AFP >1,000 ng/mL should be the criteria used to delist otherwise eligible patients. However, this is still an area of debate.

Staging of HCC

Once HCC is diagnosed, staging with either CT or MRI of the chest, abdomen and pelvis is required. The Barcelona Clinic Liver Cancer developed a staging system in 1999 that takes into account the performance status, characteristic of the tumor (single nodule or multinodular), vascular invasion, and presence of portal HTN. This BCLC classification system has become a widely accepted algorithm for all HCC patients in earlier disease, linking their current status prognosis with treatment recommendations. The widely accepted TNM staging system of many malignancy, although considered, seems to have inferior prognostic ability of long term survival for HCC, mostly because the severity of liver disease and complications of cirrhosis are not included as part of the staging system (20).

Indications of liver transplant listing: Milan criteria (MC)

When OLT initially became widely practiced, early work on transplanting patients with HCC had high post-OLT

recurrence rate and subsequently high mortality. The poor outcome was in part related to the indiscrete selection of patients. Over the last two decades, investigators began to describe and define tumor characteristics that predict chance of recurrence after treatment and those associated with high mortality. In 1993, Bismuth *et al.* showed that those with at most three tumors, each less than 3 cm had a better outcome with OLT compared to surgical resection (21). In 1996, Mazzaferro *et al.* proposed the MC, which showed that patients with solitary HCC <5 cm or up to three lesions each smaller than 3 cm, without macrovascular invasion or extrahepatic spread, had a 5-year survival of 70% after OLT (22). This survival benefit is comparable to OLT in non-HCC population. Given the excellent outcome, MC has been adapted globally (EASL and AASLD guidelines) in selecting HCC patients for liver transplant (23,24). In addition, to acknowledge the high mortality of HCC (25), patients diagnosed with HCC are given priority listing in terms of extra points to match their mortality. Although MELD score is a useful tool to accurately predict high mortality in ESLD patients, it is less powerful for HCC patients (AASLD guideline). Therefore, to give HCC patients equal opportunity for OLT, they are given 22 points for solitary HCC 2-5 cm or three nodules each <3 cm. In addition, 10% point increase every three months due to estimated 15% mortality increase (26).

The adoption of the MC offered a promising 5-year post-OLT survival at 70%, in keeping with the non-HCC transplant group (22). Although Milan criteria is well validated (*Table 1*), the cutoff size and number are rather arbitrary. Thus, many find MC to be overly stringent, limiting a few potentially acceptable candidates from transplant. In addition, some argue that imaging may underestimate tumor size. Freeman *et al.* evaluated the UNOS database and reported that radiologic exams are not very precise, underestimating tumor load in 27% of the patients while overestimating in 30% of the population (30). Imaging technique, protocols, and expert interpretation are also variable among transplant centers. This further leads to questioning of the cutoff tumor number and size dictated by the MC. For these reasons, a number of experts are looking into expanding or modifying the criteria for OLT listing.

Expanding criteria

Although MC (one nodule <5 cm or up to three nodules, each <3 cm) outlines an acceptable risk to justifiably transplant HCC patients, the precise amount of tumor

Table 1 Outcomes (HCC Recurrence rate, 5-year survival) of HCC patients transplanted under the Milan criteria

Studies	Number of patients	Tumor selection	Selection technique	Recurrence rate	Overall survival (%)
Mazzaferro, <i>et al.</i> (NEJM, 1996) (22)	48	Single <5 cm, or up to 3 nodules, none >3 cm	CT angiogram	8% (at 4 years)	75 (at 4 years)
Bismuth, <i>et al.</i> (Semin Liver Dis, 1999) (27)	45	Single <3 cm, or up to 3 nodules, none >3 cm	CT	11% (at 5 years)	74 (at 5 years)
Llovet, <i>et al.</i> (Hepatology, 1999) (28)	79	Single ≤5 cm	Dynamic CT	4% (at 5.4 years)	74 (at 5 years)
Jonas, <i>et al.</i> (Hepatology, 2001) (29)	120	Single <5 cm or up to 3 nodules, none >3 cm	Explant pathology	N/A	71 (at 5 years)

burden to be considered reasonable is not well established.

An attempt to expand beyond MC was done in 2001 by University California at San Francisco (UCSF). They developed the UCSF criteria: *single nodule <6.5 cm; or multiple nodules with the largest <4.5 cm in diameter and the sum of total diameters <8 cm*. Comparing UCSF to MC, the survival rate after transplant appeared to be similar (19). Although the results were exciting for those who do not initially qualify for MC, critics noted that in this study, only 24% of the population fell outside the MC. This may lead to dilution of poorer outcomes in those with larger tumors burden. Furthermore, the UCSF study is a retrospective analysis based on explants pathology, not pre-transplant radiology (31). The study included explant pathology and microvascular invasion (MVI) in the prognostic model, but these information are not usually available until post-OLT. A later paper by University California at Los Angeles (UCLA) with similar design validated the UCSF criteria, where 40% patients were outside MC but within UCSF (32). However, the UCSF criteria will need additional validation.

Another large meta-analysis was done by Mazzaferro *et al.* (33) in 2009 to study those individuals who do not fit into MC. The study included 1,556 patients transplanted from 36 centers. Their concept of expansion was termed “up to seven criteria”—number of tumors is up to seven, and the sum of tumor diameters up to 7 cm. The 5-year overall survival of this population after OLT is approximately 71.2%. They also initiated the “Metroticket concept”—the further one expands beyond MC, the more one pays in terms of higher recurrence and poorer post-OLT survival.

Currently, expansion beyond MC still requires more validation. Tumor recurrence may be under reported in OPTN database, thus no national data is available to support criteria for expansion (34). Many opponents of

expansion criteria have shown that tumors exceeding the MC may have increased risk of MVI, microsatellites, and poorly differentiated tumor type (29,31,35-39)—all of which are associated with poorer outcomes. Therefore, the decision of expansion still falls on the individual centers to define the maximum cutoff size and number of HCC lesion at which the risk of recurrence may be considered acceptable. Another point of consideration is distributive justice. Due to the shortage in donor livers, this resource should be shared fairly among HCC and non-HCC patients. The post-OLT outcome of the expansion group must be similar or only slightly worse than the MC group to justify fair allocation. Volk *et al.* showed that a liberal approach to transplant selection would lead to a 44% increase in risk of death for all patients on the waitlist (40). He estimated that the 5-year post-OLT survival for HCC group needs to be at least 61%, to not have harmful effect on non-HCC group. To add to the complexity of this issue, there is regional variation in post-OLT success which muddies the nation-wide policy (34).

Downstaging to meet MC for transplant

The MC (single tumor <5 cm, or up to three tumors each <3 cm) is currently used for eligibility to OLT. For tumor burden beyond Milan, there are two ways to achieve a potential transplant. One is by expanding the criteria as explained above, and the other option is to undergo local regional therapy (LRT). LRT allows for shrinkage of tumor burden to meet MC, so one can be listed for OLT. This method is termed downstaging. There are several studies validating downstaging, and they are outlined in *Table 2*.

The technique of choice for downstaging is institution dependent. There is very limited head-to-head comparison

Table 2 studies for down-staging prior to orthotopic liver transplant (OLT) in patients with cirrhosis and hepatocellular carcinoma (HCC)

Studies	Tumor selection	Selection technique	Number of patients		5-year survival	
			Within MC	Beyond MC	Within MC	Beyond MC
Yao, <i>et al.</i> (Hepatology, 2001) (19)	1 nodule ≤ 6.5 cm; up to 3 nodules, none >4.5 cm, total tumor burden ≤ 8 cm (UCSF)	Explant pathology	46	14	72%	N/A
Roayaie, <i>et al.</i> (Ann Surg., 2002) (41)	Not defined	Radiology	None	43	None	44%
Yao, <i>et al.</i> (Am. J. Transplant, 2007) (31)	UCSF criteria	Radiology	130	38	80.7% (Combined)	
Cillo, <i>et al.</i> (Am J. Transplant, 2007) (36)	N/A	Radiology	37	31	75% (at 3 yrs)	90%
Ravaioli, <i>et al.</i> (Am. J. Transplant, 2008) (38)	1 nodule 5-6 cm; 2 nodules ≤ 5 cm; up to 5 nodules ≤ 4 cm with total tumor burden ≤ 12 cm	Radiology	88	32	71% (3 yrs)	71% (3 yrs)
Herrero, <i>et al.</i> (Liver Transpl, 2008) (37)	1 nodule ≤ 6 cm; 2-3 nodules ≤ 5 cm (Navarra criteria)	Radiology	47	24	70%	73%
Silva, <i>et al.</i> (Liver Transpl, 2008) (42)	1 nodule ≤ 5 cm; 2-3 nodules ≤ 5 cm; total tumor burden ≤ 10 cm	pathology	231	26	62%	69%
Mazzaferro, <i>et al.</i> (Lancet Oncol, 2009) (33)	Total tumor burden ≤ 7 cm AND number nodules ≤ 7 (Metroticket)	Pathology	444	283	73%	71%

between different procedures. While some studies follow RECIST (Response Evaluation Criteria in Solid Tumors) as down-staging measure, most use MC as an endpoint. Once the tumor burden is managed within an acceptable range, patients will be monitored closely for at least three months prior to listing (34,43,44). This process allows time to observe the behavior of the tumor. A period of waiting time prior to listing is not without benefit. It allows physician to select out those with aggressive tumors, therefore high risk for transplant. A study from Northwestern University, using living donor model, has hypothesized that fast track transplant for HCC has higher rate of recurrence post-OLT (45).

Currently, no clear guideline exists to exclude anyone from undergoing downstaging (41,46-48). However, distant metastasis or macrovascular invasion usually precludes patients from undergoing the procedure, given the high risk of recurrence. In the United States, only several regions have a clear down-staging protocol in place (43,47). Pomfret *et al.* proposed a limit on downstaging: single tumor <8 cm, or 2-3 tumors each <5 cm, with sum of tumor diameters <8 cm, exclude vascular invasion or number lesions >3 . This proposal was raised in the 2010 report of national conference on liver allocation in patients

with HCC. However, this proposal will need to be further validated (34).

LRT

Many techniques are available for LRT: transarterial chemoembolization (TACE), radiofrequency thermal ablation (RFA), radioembolization, resection, conformal-radiotherapy (CRT) and tyrosine kinase inhibitor sorafenib. The choice of technique is determined by location, size and number of lesions. It is also dependent on the expertise of the institution. The goal of LRT is two folds: one is to downstage the tumor, and the other is to help patient maintain on the transplant list during the waiting period if their tumor grew in size.

TACE utilizes intra-arterial injections of chemotherapeutic drug into the hepatic artery followed by Iodized oil (lipiodol) injection (49). It has been shown to decrease dropout rate (9-14%) (50,51), improve survival (52,53), and allows for longer wait time on the transplant list (211-274 days) (50,51). The term "drop-out" refers to delisting of patients due to tumor progression or complications of HCC that prohibits OLT. Moreover, some showed that TACE prior to transplant may even result in decreased post-transplant recurrence rate (17%

vs. 36% non-treatment) (54-56). However, additional data and validation would be needed to prove that LRT in fact lower HCC recurrence or improve survival after transplant.

RFA employs electrical conduction and heat generated to ablate the HCC lesion. It is done under imaging guidance. This technique requires careful selection of patient to prevent tumor seeding (subcapsular tumors and direct nodule puncture) (57). One study done by Ng *et al.* showed complete tumor ablation in 92.7% of 192 patients. With a median follow-up of 26 months, local recurrence occurred in 28 patients (14.5%) (58).

Resection is rarely used in cirrhosis related HCC, but is the primary mode in non-cirrhotic HCC (59). CRT is an option for patients who failed other LRT or not eligible for other LRT due to the tumor anatomy (60). Sorafenib has been proven effective as well, but has high complication and is associated with high dropout rate (61).

LRT allows patients to stay on the list for a longer period of time and therefore decreasing overall dropout rate (33,62). Several studies showed a dropout rate of only 0-10% at 12 months for low grade tumor (T1 or T2 patients) treated with LRT (50,54,57,63). Another study reports dropout rate being as high as 30% without bridging therapy for those meeting MC. LRT is now widely accepted and practiced, with OPTN data showing that 65% of HCC patients received LRT prior to transplant (34). University of California in San Francisco (UCSF) conducted a review on patients undergoing LRT. They found that those who successfully underwent tumor reduction and subsequently transplant, the 5-year survival is approximately 84% (44). This high survival rate suggests LRT may benefit patients who initially do not meet MC.

Multi-phase CT or MRI should be performed 4-6 weeks after each LRT (34), to measure residual tumor burden. One can also monitor for serum level of AFP. Those with AFP <500 ng/mL have better response than those with AFP >1,000 ng/mL at initiation of down-staging (18,31). AFP in this scenario can be monitored for signs of recurrence in those patients whose AFP returns to normal after treatments.

Drop-outs and wait-list monitoring

Depending on different regions of the country, average wait time to liver transplant varies. However, the limited donor pool often leads to an inevitably long wait time. Longer wait time is associated with more drop-outs from the waitlist. For each month on the list without a liver transplant, the

rate of drop-out is estimated to increase by 4.0% (28).

Major risk factors for tumor progression while on the waiting list include: length of wait time and tumor characteristics. UCSF reports a series of dropout rates for patients within MC: 0% dropout at 3 months, 11.0% at 6 months, 57.4% at 12 months, and 68.7% at 18 months (64). The total dropout rate for a median waiting time of 330 days was 22%. Large tumor size and multi-focality of the lesions also correlate to higher risk of tumor progression, thus higher dropout rates. Other factors associated with high dropout rate include resistance to LRT, and AFP >200 ng/mL. OPTN data shows that AFP <500 correlates with a 7.4% dropout, while AFP >1,000 is associated with 24.9% of dropout rate.

Tumor progression monitoring relies on imaging and serum biomarkers. The standard imaging used in most centers is contrast-enhanced CT or MRI (33). Although the interval to repeat imaging is unclear, AASLD recommends every 3-4 months after initial management. A technique under investigation is dual contrast MRI, which is thought to be more sensitive in detecting small HCC lesions than triple phase CT or MRI. Limited information is available on the use of AFP to follow patients on the waitlist. However, in patients whose serum AFP level was initially elevated, and returned to normal after treatment, a subsequent rise in AFP may suggest HCC recurrence.

If tumor progressed past MC on imaging, patient would be deactivated to undergo downstaging, or delisted for palliative treatment if distant metastasis or vascular invasion is found.

Post-transplant monitoring

Roayaie *et al.* reported that HCC patients post-OLT have 18.3% chance of eventual tumor recurrence (65). This group of patients received OLT from 1988-2002; and the median time to tumor recurrence was 12.3 months. Interestingly, the rate of tumor recurrence dropped from 25.5% down to 8-11% after the MC adoption. Tumor recurrence marked a poor prognosis, with median survival <12 months. The 5-year survival is 22% for the recurrent cohort comparing to 64% for its counterpart. Sites of recurrence include liver alone (16%), both intra and extra hepatic (31%), or extrahepatic alone (53%). Liver, lungs and bones are most frequent metastatic organs. The risk factors of tumor reappearance include tumor size, number of lesions, tumor differentiation, MVI and regional lymph node involvement (66). There is a positive

correlation between the tumor burden prior to transplant and the cancer recurrence rate post-OLT. Similar to waitlist monitoring, post-OLT patients need routine imaging and biomarker surveillance. To detect HCC recurrence early, contrast CT, MR or PET/CT should be done every 6 months to yearly, for the first 3-5 years post OLT (67). Regular ultrasound and AFP are less accurate but also less expensive, may be applied every 3-6 months, up to five years post-OLT. Rise in AFP above 20 ng/mL in patients who had normal AFP should raise the suspicion of recurrence, and one should obtain imaging.

Treatment of HCC recurrence after orthotopic liver transplant (OLT)

Surgical resection is the best option for local HCC recurrence post-OLT. In one study, series of nine patients who underwent resection for HCC recurrence experienced survival rate similar to those who did not have recurrence (68). This surprising results, however, is subject to selection bias and small sample size. If patient is not eligible for resection due to size, location, or multiplicity, radiofrequency ablation or chemoembolization may be next best options. For extrahepatic recurrence post-OLT, surgical management requires those with good functional status, single lesion, and long interval from transplant to recurrence. Bone metastasis survival is especially poor, and most aim to palliate pain with external beam radiation and zoledronate (69).

The SHARP trial published in 2008 showed some benefit with sorafenib to treat unresectable advanced stage HCC (70). Teng *et al.* from Taiwan recently reported sorafenib improves overall survival in HCC post-OLT patients as well (71). The studied patients had pre-transplant tumor beyond MC. Using sorafenib as an adjuvant therapy, there was no tumor recurrence at two years in five studied patients. Using it as palliative therapy after recurrence, there is a trend for survival benefit (50% *vs.* 20% at 18 months) although not statistically significant ($P=0.17$).

Conclusions

The selection of HCC patients for liver transplant is not a trivial task. It requires a balance between maximizing benefit in HCC patients and minimizing harm to non-HCC patients due to the scarce resource. After this review, there is an obvious need to further validate the criteria that is

currently being used. In addition, future research is required to unifying a set of guidelines in LRT and downstaging protocol.

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Selection of patients of hepatocellular carcinoma beyond the Milan criteria for liver transplantation

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Abstract: The Milan criteria have been proven to be reliable and easily applicable in selection of patients with small unresectable hepatocellular carcinomas for liver transplantation. It has been repeatedly shown that patients who met these criteria had a 5-year survival of over 70% after transplantation. Such a result is remarkably good for an otherwise incurable malignancy. The main disadvantage of this set of criteria is that it is rather restrictive. Following it religiously denies transplantation to many patients who have tumor stage slightly more advanced.

There have been many attempts to extend the criteria to include tumors with larger sizes (as in the UCSF criteria) or with a larger number (as in the Kyoto criteria). Alpha-fetoprotein and PIVKA-II, two biological markers in more aggressive tumors, have also been employed in the selection of patients, and biopsies have been used by the University of Toronto to determine tumor aggressiveness before deciding on transplantation. Patients with tumors beyond the Milan criteria yet not of a high grade have been accepted for transplantation and their survival is comparable to that of transplant recipients who were within the Milan criteria. Preoperative dual-tracer (¹¹C-acetate and FDG) positron emission tomography has been used to determine tumor grade, and transarterial chemoembolization has been used to downstage tumors, rendering them meeting the Milan criteria. Patients with downstaged tumors have excellent survival after transplantation. Partial response to chemical treatment is a reflection of less aggressive tumor behavior.

Careful selection of patients beyond the Milan criteria with the aid of serum tumor marker assay, positron emission tomography or tumor biopsy allows transplanting more patients without compromising survival. The use of liver grafts either from the deceased or from living donors could thus be justified.

Keywords: Hepatocellular carcinoma; liver transplantation; Milan

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Introduction

Liver transplantation for hepatocellular carcinoma (HCC) was initially performed for lesions that were large and bilateral and thus unresectable, but recurrence of disease was common and mid-term survival was poor (1). Patients with less advanced disease had better mid-term survival (2). It was the seminal work by Mazzaferro *et al.* of Milan - hence known as the Milan criteria - that established an easy reference for case selection for liver transplantation

for HCC. The criteria state that an HCC patient is selected for transplantation when he or she has either a single lesion not larger than 5 cm or two or three lesions not larger than 3 cm each (3). With the Milan criteria, a 4-year survival rate of 85% was achieved. It compares favorably with those achieved by transplants performed for other indications like liver failure. The Milan criteria have been adopted as a standard to justify allocations of deceased donor liver grafts from a utilitarian point of view.

Table 1 Criteria for liver transplantation for hepatocellular carcinoma at different centers

Criteria	Tumor size (cm)	Tumor number	Remark	Overall survival
University of Hong Kong (12)	≤6.5	1	Not tested	3-year 78%
	≤4.5	≤3		5-year 66%
Chang Gung Hospital (13)	≤6.5	1	Not tested	3-year 96%
	≤4.5	≤3		5-year 90%
Asan Medical Center (7)	≤5	≤6	Not tested	3-year 88% 5-year 82%
University of Tokyo (6)	≤5	≤5	Not tested	3-year 82% 5-year 75%
Kyoto University (14)	≤5	≤10	PIVKA-II ≤400 mAU/mL	5-year 87%
Kyushu University (9)	≤5	No restriction	PIVKA-II <300 mAU/mL	3-year 86% 5-year 83%
Hangzhou (11)	<8 in total	No restriction	If >8 cm, then grade I/II + AFP <400 ng/mL	5-year 72%
DuBay (15)	No restriction	No restriction	Poorly differentiated HCC excluded	5-year 72%

The University of Southern California criteria

Although the Milan criteria provide a reliable and practical guideline for selecting HCC patients to undergo liver transplantation, they are considered rather restrictive. In order to let more HCC patients benefit from liver transplantation, Yao studied consecutive transplant recipients over a 12-year period and formulated a modest expansion of the Milan criteria: solitary HCC ≤6.5 cm, or ≤3 nodules with the largest lesion ≤4.5 cm and a total tumor diameter ≤8 cm. With this new set of criteria, a 5-year survival rate of 75% was achieved.

For this study, one should note that 76%, 16%, and 9% of the preoperative tumor staging was accurate, underestimated and overestimated respectively (4). It is also important to be aware that tumor staging in the study by Mazzaferro was done with preoperative computed tomography (3). Tested in a series by Schwartz of Mount Sinai, the expansion to the UCSF criteria offers the potential benefit of transplanting around 10% more patients with HCC without compromising survival (5).

Criteria from Asian centers

The University of Tokyo adopts the 5-5 rule: patients are selected for transplantation if they have HCC not larger than 5 cm and no more than 5 nodules. With this rule, an excellent recurrence-free survival rate of 94% was achieved (6). At Asan Medical Center, patients with HCC not larger than 5 cm and 6 or fewer nodules without gross vascular invasion are eligible for transplantation. A 5-year

survival rate of 81.6% was achieved (7).

Kyoto University employed the biological marker PIVKA-II and further extended the number of HCC to 10 with the condition that serum PIVKA-II level must be lower than 400 mAU/mL. A 5-year survival rate of 86.7% was achieved (8). At Kyushu University, a 5-year survival rate of 82.7% was achieved in patients with HCC not larger than 5 cm and a serum PIVKA-II level not higher than 300 mAU/mL (9). A study in Japan involving 49 centers and 653 patients reported that patients who were beyond the Milan criteria but had serum alpha-fetoprotein levels not higher than 200 ng/mL and serum PIVKA-II levels not higher than 100 mAU/mL had a disease-free survival rate of 84.3% (10).

The Hangzhou center in China also extended the selection criteria and employed biological marker. Patients who have HCC larger than 8 cm are eligible for transplantation if their serum alpha-fetoprotein level is not higher than 400 ng/mL and their tumor biopsy shows only grade I or II differentiation. A 5-year survival rate of 72.3% was achieved (11) (*Table 1*).

The Toronto and up-to-7 criteria

A radical extension of inclusion criteria was proposed by the University of Toronto on the grounds of the deficiencies of the existing guidelines. It is difficult to identify small lesions accurately in multifocal HCC. Tumor size measurement may not be reproducible. Tumor behavior may not be related to tumor size and number. And overstaging (23%) or understaging (30%) of disease by imaging happens every now and again.

At the University of Toronto, HCC patients whose main lesion biopsy did not show poor differentiation were transplanted even if they had disease beyond the Milan criteria, and the 5-year survival rate of these patients was 70% while that of patients within the Milan criteria was 72% (15) (Table 1).

Tumor biopsy has the potential problem of sampling error. For instance, a nodule-in-nodule tumor can have different tumor grades (16). It has also been demonstrated that even in a single-needle biopsy, adjacent tumor cells can be of different degrees of differentiation (17). Nevertheless, if transplantation is planned for HCC beyond standard criteria, tumor biopsy appears to be a logical approach.

Biological grading of tumors by positron emission tomography has been employed to identify patients with HCC beyond the Milan criteria. However, comparable survival was found between patients beyond and patients within the criteria (18). In fact, it has been shown that HCC which is highlighted by the tracer FDG is more likely of a high grade whereas the tracer ^{11}C -acetate used in dual-tracer positron emission tomography has a closer affinity with low-grade HCC (19). Although high-grade HCC is more likely to have microvascular invasion (20), the mere demonstration of an HCC being FDG-positive does not predict the presence of microvascular invasion (21).

Nevertheless, microvascular invasion alone does not adversely affect patient survival if the HCC is within the up-to-7 criteria, which were proposed by Mazzaferro *et al.* on a basis of 1556 patients from 36 centers (22,23). When the addition of the number of tumors and the size of the largest tumor (in centimeter) results in a number not larger than 7, the up-to-7 criteria are satisfied. In the study by Mazzaferro *et al.*, patients who met the up-to-7 criteria had a 5-year survival rate of 71.2% (22).

Downstaging

Instead of extending the selection criteria, downstaging the HCC to within the Milan criteria is another logical way to transplant more patients. In a study, excellent survival was achieved after the tumors were downstaged with transarterial embolization or percutaneous ethanol injection. Of the eight patients successfully downstaged, only one patient had recurrence of HCC after liver transplantation (13).

In another study, three groups of patients were selected for downstaging using transarterial chemoembolization or

laparoscopic radiofrequency ablation. The three groups were (I) patients with a single tumor ≤ 8 cm, (II) patients with 2 or 3 tumors each ≤ 5 cm and totally ≤ 8 cm, and (III) patients with 4 or 5 tumors each ≤ 3 cm and totally ≤ 8 cm. An observation period of three months after downstaging was mandatory. Patients were offered transplantation if they showed no tumor progression during the observation period. Forty-three of the 61 patients (70.5%) were successfully downstaged. The 35 patients who were transplanted had a 4-year survival rate of 92.1% (24). This “ablate and wait” strategy allows the tumor biology to be manifested more clearly, enabling justification of transplantation and vice versa. HCC progression after ablation is a sign of aggressive tumor behavior which warns against liver transplantation (25).

Salvage liver transplantation

It has also been proposed that patients with HCC beyond the Milan criteria can be treated initially with hepatectomy and be salvaged with liver transplantation if their recurrent HCC is within the Milan criteria and the tumors are less aggressive (26). Asan Medical Center showed that salvage liver transplantation for recurrent HCC within the Milan criteria had outcome comparable with that of primary liver transplantation (27). All too often recurrence of large and multiple HCC after hepatic resection is extrahepatic and contraindicates salvage transplantation. It has been found that around one-fifth of patients have extrahepatic recurrence and detection of recurrence may not be early enough. Moreover, salvage transplantation is applicable to less than one-third of the cases (28). Thus, Asan Medical Center proposed primary transplantation for HCC that comprises 3 or more lesions and meets the selection criteria (number ≤ 6 and size ≤ 5 cm) (7,29).

Tumor stage and characteristics at the time of salvage transplantation are closely related to tumor recurrence, especially recurrence that occurs soon after operation. HCC with a large size, multiple lesions, poor differentiation, vascular invasion and early recurrence warns against salvage transplantation.

Discussion

Hepatitis B is endemic in many parts of Asia, with a carrier rate of over 10% in the population. As hepatitis B virus is an oncologic virus for HCC, the burden of HCC is particularly

heavy in these regions. Although liver transplantation is an effective treatment of HCC, the scarcity of livers donated by the deceased, which is particularly severe in Asia, has limited its application. As a result, living donor liver transplantation has become the alternative to deceased donor liver transplantation. In order to maintain a high ratio of recipient benefit to donor risk, recipient survival has to be high in living donor liver transplantation. Patients with unresectable HCC have extremely poor survival. However, a 50% post-transplant of rate is definitely better than an incurable disease. Given the inevitable donor risk, recipient survival of living donor liver transplantation for non-HCC conditions should be somewhere around 80%. However, donor enthusiasm, supply of deceased donor livers and disease burden of the region may allow some flexibility in accepting a lower recipient survival rate. But flexibility should not be abused routinely, otherwise poor recipient survival would result. It should be borne in mind that poor recipient survival means that a considerable proportion of liver donations are vain efforts.

Close auditing of donor and recipient outcomes time after time enables modification of recipient selection protocols, thereby minimizing the chance of transplanting patients with poor outlook. While published references on upper limits of tumor size and number, tumor marker level and tumor grade (*Table 1*) are useful in guiding clinical decision, we must also exercise judgment based on experience and scientific knowledge. A tumor with a pseudocapsule but without microvascular invasion has a small chance of extrahepatic dissemination even if it is large. Gentle handling of the tumor-housing native liver during recipient hepatectomy prevents spillage of tumor cells into the circulation and is particularly crucial when treating tumors with size beyond standard criteria.

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Liver transplantation for hepatocellular carcinoma: are international guidelines possible?

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Hepatocellular carcinoma (HCC) is an aggressive malignancy that arises in chronic liver disease. It is currently responsible for over 695,000 deaths internationally every year and its incidence continues to rise as liver cirrhosis and its complications persist as major health problems worldwide (1,2). Liver transplantation is considered a potential cure for HCC because it removes both the tumor and diseased liver at risk of malignant transformation. Initially results from liver transplantation for HCC, however, were disappointing due to high post-operative mortality rates, recurrence rates of up to 80%, and poor long-term survival (3,4). It gradually became apparent that successful liver transplantation for HCC was dependent on careful selection of patients with limited disease (5).

The Milan criteria developed by Mazzaferro *et al.*'s pivotal study in 1996 demonstrated that survival among patients with early HCC who underwent liver transplantation could be comparable to survival among patients transplanted for other reasons (6). Early HCC was determined to be a single lesion ≤ 5 cm or three lesions all smaller than 3 cm, no evidence of gross vascular invasion, and no regional nodal or distant metastases (6). Liver transplantation for patients within the Milan criteria have yielded a five year survival rate $>70\%$ and recurrence rates of 13.5-17% (7). Thus, hepatocellular carcinoma now accounts for 19% of liver transplants in the United States annually. Given the shortage of deceased donor organs and increasing demand, however, there is now a smoldering controversy over the appropriate use of liver transplantation for HCC (8). There are currently no standardized or validated methods for tumor burden control while on the transplant waiting list, surveillance of HCC recurrence post-transplantation,

use of living donors in transplantation for HCC, or immunosuppression in the setting of HCC. Furthermore, there is minimal data regarding cost-effective strategies to address these issues, which incur significant expense upon an already taxed healthcare system (9).

Within this context, Clavien *et al.*'s review in the January 2012 issue of *Lancet Oncology* on liver transplantation for hepatocellular carcinoma is of particular interest. Clavien *et al.* explore these issues in depth and provide specific evidence-based recommendations made by an international committee of experts. On December 2-4, 2010, with the support of ten international hepatology and transplantation societies, a consensus conference was held in Zurich, Switzerland. The goal was to establish evidence-based guidelines for liver transplantation in patients with HCC, to guide liver transplantation programs in their allocations and management of patients pre and post-transplantation. The organizing committee determined key topics and appointed 19 working groups of 4-6 experts to review the evidence available on Pubmed, Embase, Scopus and Cochrane. The experts were selected based on their scientific and clinical merits and drafted recommendations based on their literature review. These drafts are publicly available as supplements through *Liver Transplantation* (10). The chair of each working group gave a 15-minute presentation on their topic and allowed for questions and debate from an audience of 300 participants from five continents. An anonymous audience poll was obtained to determine strength of consensus. Finally, a nine-member jury finalized the recommendations, assigning a level of evidence and strength of evidence grade to each. The review published in *Lancet Oncology* was prepared by members of the

organizing committee and circulated among all the working groups to ensure accuracy and consensus.

The international consensus conference reports 37 evidence-based guidelines that encompass the following areas: assessment of candidates with HCC for liver transplantation, criteria for listing cirrhotic candidates with HCC, criteria for listing non-cirrhotic candidates with HCC, role of downstaging, managing patients on the waiting list, role of live donor liver transplantation and post-transplant management. Clavien *et al.* review each guideline, referencing the major studies utilized to help formulate the recommendation. Preliminary data from certain studies, which were not incorporated into the recommendations, are also discussed.

HCC needs to be staged as accurately as possible, to predict risk of recurrence post-transplantation and determine the most appropriate treatment option. There are currently several staging systems available, including the Barcelona Clinic Liver Cancer (BCLC) staging system, Tumor Node Metastasis (TNM) system, Cancer of the Liver Italian Program and Japan Integrated Staging Score. However, there is currently no internationally accepted system (11). Thus, the international consensus conference determined that the evidence was strongest for using the BCLC staging to determine prognosis prior to liver transplantation, while the TNM system, which incorporates explant pathology, is best utilized to determine prognosis post-transplant. The BCLC staging system also has the benefit of linking prognosis to treatment recommendations. For tumors greater than 1 cm in size, dynamic CT or MRI demonstrating arterial enhancement followed by washout on portal venous or delayed imaging was felt to be the best non-invasive means of diagnosing and staging HCC pre-operatively. Extrahepatic staging should also include CT scan of the chest and either CT scan or MRI of the pelvis. Because of these advances in imaging technology, liver biopsy is no longer required in the HCC work-up. A positive tumor biopsy rules in the diagnosis but a negative biopsy raises unanswered questions; the procedure itself risks tumor seeding along the needle track (12).

Due to the limited supply of deceased donor livers internationally, fair allocation has raised moral/ethical, medical and even economical questions. The goal is ultimately to justly distribute this limited resource in a way that benefits the most individuals, provides collective benefit, and minimizes consequences for other potential recipients still on the waiting list (13). Thus, the Milan criteria was still felt to be the best standard for selecting

HCC patients for liver transplantation, with allowance for expanded criteria acceptance for transplant determined on a program by program basis (6). Alpha-fetoprotein may be used in combination with imaging to guide decision making; however the reviewers felt strongly that there is insufficient evidence to recommend biomarkers other than alpha-fetoprotein be used in clinical decision-making (14). As microvascular invasion cannot be detected prior to liver transplantation, the reviewers strongly recommended against relying on it to determine candidacy for transplant (14). The Milan criteria are not applicable to non-cirrhotics with HCC (15).

Downstaging using regional therapy such as radiofrequency ablation, trans-arterial chemoembolization, or liver resection aims to decrease tumor burden so that patients outside of the Milan criteria have a chance of qualifying for MELD exception points. Upon literature review, the international consensus conference felt that successfully downstaging tumor size or number of viable tumors generally achieves five-year transplantation survival comparable to that of HCC patients who did not require downstaging to meet liver transplantation criteria (16). There is, however, currently not enough evidence to recommend any specific downstaging therapy over the others (16).

Waiting lists for organ donation are inherently dynamic, as patients clinically improve or worsen. Thus, the international consensus conference recommended periodic monitoring of waiting lists via imaging and alpha-fetoprotein measurements. Understandably, there is good evidence to suggest that patients who have progressed beyond liver transplantation criteria should be placed on hold and considered for downstaging, with ultimate removal from the waiting list if no longer candidates (17).

Standardized guidelines for post-transplant surveillance of HCC recurrence after liver transplantation are lacking, perhaps due to the relative rarity of recurrence (18). The international consensus committee was only able to weakly recommend, upon review of the evidence, that patients undergo contrast CT or MRI imaging plus alpha-fetoprotein measurements 6-12 months post-operatively (9). Furthermore, there is inadequate evidence to recommend any specific immunosuppression regimen or adjuvant antitumor therapy to decrease the chances of HCC recurrence. The primary consensus was that recurrence is best treated with regional therapy or sorafenib, and that liver re-transplantation would not be appropriate (19).

Clavien *et al.*'s review of recent international consensus is comprehensive and useful, but care must be taken in interpretation of these recommendations. They raise the

question of whether international guidelines are feasible given significant regional variability. It should be noted that of the 37 guidelines, the level of evidence for fourteen were based on case series/expert opinions and the strength of recommendation for fifteen were weak. The international consensus conference also yielded some obvious recommendations, such as patients who fall outside of Milan criteria should not be transplanted. Other recommendations were vague and subjective (ex: liver donor transplants should only occur at centers of excellence). Furthermore, can these guidelines be effectively disseminated? Knowledge translation in healthcare is important but often challenging (20). It has been two years since these international consensus guidelines were released and how widely they have been accepted remains subjective and debatable.

Nevertheless, this review highlights the central role of expert discussion and consensus – working in combination with evidence-based medicine – to guide better care for complex patients. Clavien *et al.* address for the first time some controversial topics surrounding liver transplantation in a collegial and academic approach. The recommendations are helpful in that they were deliberately phrased flexibly while still providing data-supported, expert guidance. This permits adjustments by programs based on their regional circumstances, team experiences and the unique characteristics of local waiting lists, donor organ availabilities.

Clavien *et al.* raise intriguing questions with respect to liver transplantation that need to be more carefully evaluated. Although the number of weak and non-applicable recommendations was high, this highlights areas that need further research. This review will potentially stimulate future exploration into areas such as microvascular invasion, liver tumor markers beyond alpha-fetoprotein, specific downstaging therapies, and ideal surveillance intervals. The recommendations made by the international consensus conference are an encouraging step in the right direction and will hopefully spark the development of more effective guidelines as well as treatment options to optimize our approach to HCC.

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Footnote

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Percutaneous therapies of hepatocellular carcinoma—an update

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Abstract: Percutaneous image-guided tumor therapies have proved important in the treatment of patients with primary liver cancer. The therapeutic spectrum for the management of this patient group includes ablative techniques such as ethanol ablation and radiofrequency ablation for patients with early-stage disease as well as intra-arterial approaches such as radioembolization and transarterial chemoembolization for patients with intermediate and end-stage disease. The tremendous advantage of such therapies is the reduced systemic toxicity combined with efficient local tumor control. However, specific therapeutic algorithms continue to be highly unstandardized and depend on individual experience of the operator. In this review, we will describe the rationale behind several percutaneous techniques, focusing on intra-arterial therapies of hepatocellular carcinoma (HCC) and review the available clinical evidence. We will also discuss new developments such as the combination of intra-arterial therapies with new systemically applicable drugs.

Keywords: Hepatocellular carcinoma (HCC); intraarterial therapy; sorafenib; deb-tace; radioembolization

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent neoplasm and the third most common cause of cancer-related death in the world. With more than 700,000 diagnosed cases per year, it continues to be the leading cause of death in patients with liver cirrhosis. As Asia continues to be the region with the most cases of HCC, there is an increasing incidence of the disease in Europe and North America (1). Advanced diagnostics and effective early treatment of HCC patients enables a median survival of about 5 years, yet the prognosis remains to be poor for a big number of patients (2). Since the 1980s, percutaneous therapies of primary liver cancer became the most frequently performed locoregional procedures in interventional radiology (IR) (3,4). While significantly contributing to the evolution of interventional oncology and gaining interdisciplinary acceptance as a therapeutic option for the treatment of primary hepatic malignancies, some minimally invasive approaches can also be employed

for down-staging prior to orthotopic liver transplantation and resection (5). The management of IR patients with liver cancer requires multidisciplinary cooperation and usually includes hepatologists, surgical oncologists, transplant surgeons, radiation oncologists as well as interventional and diagnostic radiologists (6). While most percutaneous tumor ablation techniques non-selectively target tumor-containing liver tissue, intraarterial therapies of the liver exploit the observation that as opposed to normal liver tissue, most of the liver neoplasms receive their blood supply from arterial blood vessels. This remarkable characteristic allows an operator to use transcatheter intraarterial approaches to deliver high dose treatment selectively to the tumor, while preserving normal hepatic parenchyma (7). Image guidance remains to be a crucial aspect of any percutaneous approach. Several imaging modalities, such as fluoroscopy and cone-beam CT, ultrasound and MR are being used for treatment planning, tumor targeting, treatment monitoring and the assessment of treatment response (8,9). Percutaneous

ablation of small liver tumours in patients with early-stage disease has been a part of IR practice since the early 1980s. It began with the instillation of ethanol (10), which quickly resulted in 5-year survival rates comparable with surgical resection (11). In time, different modalities such as radiofrequency ablation, cryoablation and microwave ablation were developed and new techniques continue to evolve. The initial trials to establish intra-arterial liver therapies dated back to the 1970s and aimed at cutting off the local arterial blood supply of liver tumours in patients with of intermediate- and end-stage disease (12). Although the general principles of intra-arterial therapies remained unchanged, various modifications have been introduced over the course of the last 30 years. The most frequently used image-guided intraarterial liver tumor therapies performed by interventional radiologists include transarterial embolization (TAE), transarterial chemoembolization (TACE) with or without drug-eluting beads (DEBs) and radioembolization using Yttrium-90. While DEB-TACE has been shown to enhance loco-regional drug delivery and to further reduce systemic drug exposure as compared with conventional TACE (13), radioembolization represents an alternative intraarterial method to deliver a high, tumoricidal radiation dose to arterial-fed tumors while sparing healthy liver tissue.

Ablative therapies of HCC-technique

Initial experience with one of the first image-guided, percutaneous liver tumor ablations was collected by Livraghi *et al.*, when 12 patients with various primary and secondary liver malignancies were treated with injections of 95% ethyl alcohol (percutaneous ethanol injection, PEI) (10). PEI proved to safely achieve complete necrosis of small liver tumours, even when applied in tumours near sensitive organs. However, the need for multiple treatments and a frequent local tumour recurrence showed significant limitations of the modality (14). radiofrequency ablation (RFA), the first energy-based ablation technique, uses electrical current to cause thermal-based cytotoxicity, producing coagulation necrosis near the electrode (15). Analysis of safety and efficacy in patients treated with RFA shows excellent results for single HCC nodules (5 cm and smaller) as well as for multiple small lesions (each 3 cm or smaller) (16). An important benefit of RFA is the “oven effect”, defined as heat retention in nodules surrounded by the tumor capsule and cirrhotic tissue (17) thus causing extensive necrosis. However, a physical limitation of RFA

is the “heat sink” effect, defined as the cooling effect of blood flow through large vessels or ascites near the ablation zone (18). This can result in insufficient local tumor response. Microwave ablation (MWA), another ablative technique, appears to be less susceptible to the physical limitations of the “heat-sink” effect (19). This system uses high-frequency electromagnetic energy to rapidly oscillate water molecules, resulting in coagulation necrosis through frictional heat. When compared to RFA, MWA shows higher temperatures and a shorter treatment time. While both, RFA and MWA show similarities for safety and efficacy (20), more studies of MWA effects on long-term survival are needed. Multiple other modalities such as cryoablation, irreversible electroporation as well as image-guided, catheter based high-dose brachytherapy of liver tumours are gaining more attention. However, technical specifics of each method are beyond the scope of this review.

Ablative therapies of HCC clinical evidence

Multiple studies provide clinical evidence for survival benefits of patients with early stage HCC, treated with ablative techniques. A recently published, retrospective study reported the 20-year clinical outcome of 685 HCC patients, treated with a total of 2,147 ethanol injections. With a median follow-up of 51.6 months, an overall survival rate of 49% and a recurrence rate of 60.8% after 20 years, this analysis confirmed the curative potential of PEI, when used in patients with early-stage HCC and small tumors (2.83 ± 1.47 cm) (21). A prospective trial provided long-term survival rates for early-stage HCC patients treated with RFA. Here, a total of 187 patients were treated and minor complications appeared in only 5% of the patients. In this cohort, the median survival rate was 57 months and an overall survival rate after 5 years was 48%. A local tumor progression was observed in only 10% after 5 years (22), once again proving the efficacy of ablative techniques. A most recent prospective, randomized controlled trial compared the impact of RFA alone versus the combination of TACE with RFA on the overall survival of 189 patients (n=94 received RFA and n=95 received TACE-RFA). The treated collective comprised patients with mostly early-stage and some with intermediate-stage disease, a total of 90 patients in both groups classified as Child-Pugh A. The mean tumor size in each treatment arm was 3.47 and 3.39 cm for the TACE-RFA and the RFA alone group, respectively. In the TACE-RFA group, RFA followed the cTACE treatment within 2 weeks. Patients treated with the

TACE-RFA combination had significant benefits regarding overall survival and recurrence-free survival when compared with the RFA group. Specifically, the 4-year survival rate was reported as 61.8% and 45% for the TACE-RFA and RFA group, respectively (23). The results of this study are encouraging and provide a new perspective for the combination of intra-arterial approaches with ablative techniques in patients with intermediate stage HCC.

Transarterial chemoinfusion and embolization

Systemic chemotherapy remains to be the backbone of multiple anti-cancer treatments since early in the 1940s, yet the primary endpoint of anti-cancer research has experienced a shift from survival towards avoidance of toxicities and recurrence (24). Compared with systemic drug administration, regional chemotherapy of the liver offers the advantage of high selectivity, minimized systemic toxicity and maximized local drug concentration (25). Transarterial chemoinfusion (TACI), historically one of the first loco-regional chemotherapeutic approaches, represents a catheter-based intra-arterial therapy that delivers highly concentrated chemotherapeutic agents to liver tumors. TACI offers a relatively low systemic toxicity profile and a minimal risk of hepatocellular ischemia due to its minimal embolization component. Thus, TACI is very useful for the treatment of patients with borderline hepatic function who are otherwise not eligible for conventional TACE (26,27). TACI remains to be the standard of care in multiple Asian countries (28), yet has become less frequently used by interventional radiologists in the US and Europe.

Transarterial embolization (TAE) is another variation of loco-regional, catheter-based tumor treatments of the liver. In this procedure, a variety of embolizing agents (e.g., polyvinyl alcohol, gelfoam, acrylic copolymer gelatin particles) can be delivered through the tumor-feeding artery in order to completely occlude the tumor vasculature. Here, the anti-tumor effects are solely based on tumor ischemia as no chemotherapeutic agents are administered (29). The occlusion of more peripheral vessels can cause extensive necrosis. Although TACE is considered the gold standard and TAE has largely been abandoned as a form of effective IA therapy for primary liver cancer, there are a few studies that suggest sufficient anti-tumor effects of TAE (30). A recently presented randomized, single blind controlled trial compared the outcome of TAE and DEB-TACE in a total of 101 patients with unresectable Okuda stage I or II HCC. This study defined the tumor response rate according to

Response Evaluation Criteria In Solid Tumors (RECIST) criteria as a primary endpoint, while time to progression (TTP), progression free survival (PFS) and overall survival (OS) were defined as secondary endpoints. As a result, no significant difference between the groups was noted and both groups showed comparable tumor response, PFS and TTP (NCT00539643) (30). The use of very small embolization particles in the TAE group, resulting in a very distal embolization of tumor vessels, should be noticed and could have contributed to the results. However, insufficient treatment response and recurrent disease after TAE is frequently encountered. In fact, recent data suggest that hypoxia, generated by TAE, activates a molecular cascade, leading to compensatory angiogenesis (31). The molecular mechanism behind this reaction will be further discussed.

Conventional transcatheter arterial chemoembolization-technique

The concept of the conventional TACE (cTACE) was originally introduced in 1977 by Yamada *et al.*, who exploited HCC's preferential blood supply from the hepatic artery for the delivery of antitumor therapy (7). The initial rationale for cTACE was to increase the intra-tumoral concentration of the chemotherapeutic agents and to combine its cytotoxic effects with tumor ischemia, while reducing systemic toxicity related to chemotherapy (32). During the cTACE procedure, a mixture of chemotherapeutic agents combined with an oil-based contrast medium (Lipiodol Ultrafluide; Laboratoire Guerbet, France) is selectively delivered to the tumor-feeding artery, followed by temporary or permanent embolization. The mixture of chemotherapeutic agents used for cTACE usually contains cisplatin and adriamycin/doxorubicin (33-35). However, other combinations are possible and often include epirubicin, 5-fluorouracil, or mitomycin C (36). Due to the hypervascularized character of most liver tumors and the absence of Kupffer cells, Lipiodol can persist within tumor nodules for several weeks thus embolizing tumor vasculature up to the capillaries (31,37). A recent pre-clinical study of a rabbit HCC model demonstrated that (when examined in CT) Lipiodol uptake strongly affected liver perfusion. In fact, the uptake of Lipiodol can be used as an imaging biomarker for embolization efficacy (38). The subsequent administration of embolic material [such as gelfoam, polyvinyl alcohol (PA) particles or trisacryl gelatine (TG) microspheres] causes stasis in segmental and sub-segmental arterial branches and prevents washout of the previously deposited drug (39).

Embolization with gelfoam (a biodegradable gelatin sponge, The Upjohn Company, USA) as well as with PA particles has proven safe and effective (40), while the recently introduced, non-biodegradable TG microspheres (Embospheres, Guerbet Bio-medical, France) deserve further studies (41). The overall safety and efficacy of cTACE has been demonstrated in a variety of clinical trials. The adverse systemic effects of cTACE can include nausea, vomiting, bone marrow aplasia, renal failure and potentially cardiac toxicity. The self-limiting post-embolization syndrome (nausea, vomiting, fever, right upper quadrant pain and increased white blood cell count) occurs in approximately 10% percent of the patients and reflects the effects of tumor necrosis, acute cytokine release and systemic exposure to chemotherapeutic agents (42,43). Severe complications, such as post-procedural liver failure, abscess, cholecystitis, biloma and hemorrhage are rare and can be reduced by applying super-selective embolization, which was demonstrated to decrease risks and to improve overall survival when compared with non-selective embolization (44).

Drug-eluting beads chemoembolization-technique

The advent of new drug delivery systems such as drug-eluting microspheres (drug-eluting beads, DEBs) enabled a new transarterial approach, the DEB-TACE. This system combines enhanced local delivery of greater concentrations of drugs to the tumor with a reduced systemic drug exposure and has led to a shift away from conventional TACE towards DEB-TACE in the treatment of patients with HCC especially in the US and Europe (13,45). Several drug-eluting microsphere systems have been tested for intratumoral drug delivery. Currently, there are 2 types of microspheres approved for clinical use: superabsorbent polymer (SAP)-based Quadsphere/Hepasphere microspheres (Biosphere Medical Inc., USA) and the DC Bead microspheres (Biocompatibles, UK). The SAP microspheres are non-biodegradable and have the ability to absorb fluids and thus to expand their volume to a size of up to 800 μm . Initial studies with this system show encouraging results in combination with doxorubicin or cisplatin (46). The DC beads are non-biodegradable, can be loaded with doxorubicin or irinotecan and range in size from 100 to up to 900 μm , whereas smaller bead diameters achieve a more distal embolization and a more extensive necrosis as compared with larger beads (47). Studies of pharmacokinetics show that drug elution occurs

gradually and only in an ionic environment once the microspheres are delivered to the tumor. Several *in vitro* as well as animal experiments demonstrated the continuous release of doxorubicin from DC beads to the tissue (48,49). Furthermore, a histopathological study described the high efficiency of DEB-mediated drug delivery and release to the tumor tissue, thus causing local coagulative necrosis and an inflammatory-fibrotic tissue (50). The enhanced systemic pharmacokinetics of drug-eluting beads in TACE have been observed when peak plasma concentrations of doxorubicin were measured for DEB-TACE and compared with conventional TACE, showing significantly lower peak plasma levels of the chemotherapeutic for DEB-TACE in animal models (49) as well as in patients (51). The systemic side effects of doxorubicin and related drugs used in DC Beads can range from alopecia and skin discoloration to mucositis and bone marrow suppression. In a multicenter, randomized, prospective phase II study, that compared the safety and toxicity of DEB-TACE and cTACE in HCC patients, significant toxicity profile benefits were shown for DC Beads over cTACE. The overall frequency of treatment-related adverse effects was lower in the DEB-TACE group as were the toxicity grades and the severe adverse effects. The post hoc analysis of true toxicity incidence in DEB-TACE and cTACE has shown significant events in 11.8% patients *vs.* 25.9% patients, respectively. Alopecia as the most common event in patients treated with doxorubicin was almost absent in the DEB-TACE group with 1 *vs.* 23 events, respectively. Furthermore, major liver toxicities were also lower in DEB-TACE as compared to cTACE (13). In conclusion, DEB-TACE can be viewed as a safe, tolerable and effective technique and thus represents a reliable method of selective locoregional drug delivery to hepatic tumors.

Transarterial chemoembolization clinical evidence

A retrospective, single-center study, designed to assess treatment response and long-term survival outcomes after cTACE, included a total of 172, mainly cirrhotic (91%) patients that received treatment over the course of 9 years (between 2000-2008). According to EASL criteria, 64% of the treated tumors showed response with 23% showing complete response. With a median overall survival of 40.0 months for patients classified as BCLC A (for BCLC B and C 17.4 and 6.3 months, respectively), this study confirmed the efficacy and the survival benefits

previously seen in similar patient cohorts months (52). Another, recently published retrospective multi-center study confirmed the effects of highly selective Lipiodol-based TACE. Here, a total of 199 patients were treated and followed over the course of 10 years. The median overall survival was 3.8 years with a 5- and 10-year survival of 38.8% and 9.4% respectively. However, local recurrence rates for all 199 patients were described as 46%, 58% and 62% after 2, 3 and 5 years of follow up, respectively (53). A most recently published study assessed response rates and the clinical outcome of cTACE, performed "on demand" in 151 consecutive HCC patients. CR was observed in 48% of the treated patients after the first cTACE procedure. While the CR-rate was slightly increased after the second and third procedure, the recurrence rates at 6 and 12 months of follow up continued to be relatively high with 37% and 61% respectively. The median overall survival in non-resected and non-transplanted patients was 25.0 months (54).

As new DEBs became available, more studies to describe clinical outcomes of DEB-TACE evolved. In a first experience with DEB-TACE in the US, a prospective phase II pilot study evaluated safety, efficacy as well as progression-free and overall survival in 20 mostly cirrhotic (80%) patients with unresectable HCC. 75% of the patients were staged as Child-Pugh A, while 60% of the patients were classified as BCLC stage C. After 34 sessions and an overall modest toxicity, 64% were classified as responders according to EASL criteria and 30% achieved CR. After 6 months, only 1 patient showed disease progression according to RECIST. The median overall survival of 26 months confirmed the potential of DEB-TACE in the treatment of patients with intermediate and end-stage HCC (45). In a first international, multicenter, prospective, randomized phase II trial the authors compared the safety and efficacy of cTACE *vs.* DEB-TACE. Here, a total of 212 patients were 1:1 randomized and 201 patients received the treatment according to standardized protocols. The two groups were stratified according to ECOG performance status, and the Child-Pugh class. As a result, patients who received DEB-TACE showed a better imaging-based response according to EASL criteria. In a follow-up 6 months after the first treatment, 26.6% and 22.2% achieved complete response in DEB-TACE and cTACE, respectively. Progressive disease was observed in 32.3% *vs.* 40.7% in DEB-TACE *vs.* cTACE (13). Another, prospective, multi-center study enrolled 173 patients with unresectable HCC into a DEB-TACE treatment protocol.

Designed to assess long-term clinical outcome of patients treated with DEB-TACE, the results of this study shows a 5-year survival of 29.4% and 12.8% for Child-Pugh class A and B, respectively (55). In conclusion, these results show the feasibility and rationale of DEB-TACE in the treatment of unresectable HCC

Combination of TACE with systemic chemotherapy

The main anti-cancer effects of chemoembolization are a combination of ischemia and direct chemotherapy-induced cytotoxicity to the cancer cells. Although chemoembolization can cause massive tumor destruction, tumor recurrence is frequently encountered (56,57). It has been postulated that the reason for tumor recurrence is the stimulation of neo-angiogenic pathways that have been shown to be significantly up-regulated within 36 hours of TACE presumably as a result of the hypoxia caused by embolization within the tumor. Indeed, surrogate markers of tumor hypoxia including the Hypoxia-inducible Factor 1 alpha (HIF-1alpha) as well as the Vascular Endothelial Growth Factor (VEGF) are directly up-regulated after TACE procedures, suggesting direct stimulation of angiogenesis (58,59). Thus, as a result, disturbing the angiogenic pathway during planned treatment with TACE is extremely appealing. One such approach consists of using sorafenib, a multikinase inhibitor with strong antiangiogenic properties, in combination with TACE. In this way, the negative hypoxic changes induced by TACE within the tumor would possibly be counterbalanced by sorafenib (60). Sorafenib had previously been shown to significantly prolong survival over placebo in a randomized trial that led to the approval of the drug for patients with HCC (61). Here, we will review the latest data on the use of combination TACE and sorafenib for patients with HCC.

A single-center prospective Phase II trial designed to evaluate the safety and efficacy of concurrent sorafenib and DEB-TACE therapy (n=35 patients with unresectable HCC) included patients with ECOG performance status of 0 to 1, Child-Pugh liver function up to B7, and segmental portal vein thrombosis (BCLC C). Patients were treated on a 6-week cycle regimen, in which one cycle consisted of 400 mg sorafenib twice daily, initiated 1 week before DEB-TACE. The 35 patients were treated with a total of 128 cycles of therapy. All patients received DEB-TACE (mean dose of doxorubicin decreased over time; cycle one: 75 mg; two: 60 mg; three: 49 mg). The primary end points of the

study were safety and toxicity, the secondary end point was efficacy. All patients experienced at least one treatment-related toxicity during cycle one. However, most toxicities were minor (only 17% of all toxicities were grade 3 to 4). Using EASL criteria, the objective tumor response rate to treatment was 58% and the disease control rate was 100%. This study was truly the first to confirm the safety profile of the DEB-TACE sorafenib combination (60).

The first global trial on the use of DEB-TACE with sorafenib, which was recently presented, is a Phase II randomised, double-blind, placebo-controlled SPACE study (sorafenib or Placebo in Combination with DEB-TACE for Intermediate-Stage HCC), that enrolled patients across 85 centres in Europe, North America and Asia. A total of 307 eligible patients were randomised to either sorafenib (n=154) or placebo (n=153) in addition to DEB-TACE. The patients received a dose of 400 mg sorafenib twice daily or a matching placebo continuously at a cycle duration of 4 weeks. DEB-TACE was used in all patients within the first 3-7 days after the first dose of sorafenib or placebo and subsequently on day 1 of cycle 3, 7 and 13 respectively. The primary end points of that study were efficacy [time to tumor progression (TTP) according to RECIST] and safety. Overall survival, time to vascular invasion and other surrogate markers of progression were defined as secondary end points. Median TTP was 169 days in the sorafenib group and 166 days in the placebo group. TTP at the 25th and 75th percentile was 112/88 days and 285/224 days in the sorafenib and placebo groups, respectively. The overall preliminary results appear to be disappointing showing no statistically significant benefits regarding overall survival and TTP (62). This trend confirms the negative results of a phase III study in Japanese and Korean patients, where a total of 458 patients were randomized to receive TACE with or without Sorafenib. In this trial, sorafenib failed to significantly prolong TTP in patients with tumor response to treatment (63).

Multiple trials investigating the outcome of conventional TACE in combination with sorafenib are also available. In particular, a Republic of Korea non-randomized prospective single-arm Phase II study investigating the Combination of Transcatheter Arterial Chemoembolization and sorafenib for Patients with Unresectable Hepatocellular Carcinoma (COTSUN) focused specifically on safety and tolerability. The initial results appear to be promising with a median TTP of 7.1 months (7.3 months in BCLC stage B; 5.0 months in BCLC stage C), while the 6-month progression-free survival rate was 52% and the safety profile

appeared to be manageable (64). Other ongoing studies should shed even more light as to the potential benefit of this combination therapy. An example is the multi-center Study in Asia of the combination of conventional TACE with sorafenib in patients with Hepatocellular Carcinoma Trial (START) which should provide further insight into progression-free survival (PFS) and TTP hopefully in the next year (65). As already mentioned, other trials are under way, among them a phase III randomized, double-blind, controlled multicenter trial, using the E1208 study protocol. This trial will compare the outcomes of TACE with or without Sorafenib in HCC patients with or without vascular invasion (NCT01004978). Another ongoing phase III randomized trial from the United Kingdom will provide more data on the combination of sorafenib and TACE while comparing the outcome with TACE alone (TACE-2, EudraCT2008-005073-36). The results of both trials should be available at the end of 2014.

Yttrium-90 (Y90) radioembolization-technique

Historically, whole-liver external beam radiation therapy of primary and metastatic liver cancer has been of limited use. Patients with preserved liver-function can tolerate a cumulative dose of up to 40 Gy, yet the incidence of radiation induced liver disease is as high as 50% (66,67). Given the high toxicity profile of external beam irradiation in patients with HCC (68), new intra-arterial approaches to deliver a high dose of radiation directly to the tumors were developed. The infusion of small embolic particles loaded with the radioisotope ⁹⁰Yttrium (Y90) is a suitable technique to achieve tumoricidal effects while preserving healthy liver tissue and reducing systemic toxicities of external beam radiation (69). Currently, there are two embolization agents available for clinical use: the resin-based SIR-Spheres (Sirtex Medical Ltd., Australia) and the glass-based TheraSpheres (MDS Nordion, Canada) (70). The 20-30 µm sized TheraSpheres show a high activity (2,500 Bq/Sphere) and are approved for radioembolization of HCC. The slightly bigger, 20-60 µm sized SIR-Spheres show a lower activity (50 Bq/Sphere) and can be used for the treatment of colorectal metastases to the liver. Both glass and resin microspheres deliver high cumulative doses to the tumor, which can vary from 100 Gy to more than 3,000 Gy. Because of the extremely small size of the microspheres and their highly aggressive content, radioembolization bears the risk of systemic distribution of radioactive isotopes via pulmonary shunts or non-target delivery of Y90 to the

gastrointestinal tract (71). Thus, it is recommended to subject all patients to careful angiographic evaluation as well as to a test injection of ^{99m}Tc -labeled macro-aggregated albumin prior to the procedure. This happens in order to evaluate vessel anatomy, to exclude a high shunting fraction and to estimate the dose delivered to the tumor (72). The incidence of adverse effects, such as fatigue, vomiting, anorexia, fever and abdominal pain after radioembolization ranges from 20% to 50% (73), yet there is evidence that the degree of symptoms and the post-procedural quality of life is increased if compared with cTACE (74).

Yttrium-90 (Y90) radioembolization clinical evidence

In a multi-center trial designed to evaluate the safety and survival of HCC patients treated with Radioembolization, a total of 80 patients was enrolled into the study. Patients with unresectable non-infiltrative HCC, an ECOG performance status of 0-2 and adequate liver, pulmonary, renal and bone marrow function were evaluated for treatment and treated with TheraSpheres. 44% of the Patients showed bilobar disease (47% right lobe, 9% left lobe) and 90% of the patients were staged as Child Pugh A. 27 patients received multiple treatments with 1 patient receiving a maximum of 4 procedures. 28% of the patients showed adverse events with 8 patients showing life-threatening and 1 patient a fatal event. Regarding the overall survival, Child-Pugh A patients showed a median overall survival of 18.6 months while Child-Pugh B patients achieved only a median of 8.04 months (69). This study was one of the first survival analyses for the use of Radioembolization in HCC and multiple studies followed. In a prospective, single-center study designed to validate safety and efficacy of Radioembolization in HCC patients not eligible for TACE, a total of 108 patients were treated with TheraSpheres. 51% of the patients were classified as Barcelona Clinic Liver Cancer (BCLC) stage C and 77% were staged as Child-Pugh A. According to mRECIST 90 days after treatment, 6% of the patients showed complete response (CR), while 35% and 48% showed partial response (PR) and stable disease (SD), respectively and 10% showed progressive disease (PD). The overall survival rate for the entire patient collective after 2 years of follow-up was 16.4 months, again showing significant differences for Child Pugh A *vs.* B (75). In a prospective, longitudinal cohort study designed to show long-term outcomes after radioembolization, a total of 291 patients were treated with TheraSpheres in 526

sessions over the course of 5 years. 45% of the patient collective was staged as Child-Pugh A (52% as Child-Pugh B) and 52% of the patients were classified as BCLC stage C (BCLC A 17%, BCLC B 28%). Using EASL criteria, the overall response rate was reported as 57% (CR 23%, PR 34%), while stratified response rates were significantly better for Child-Pugh A patients (EASL 66%) when compared to Child-Pugh B patients (EASL 51%). The time to progression for the entire cohort was 7.9 months. The median overall survival was 17.2 months for Child-Pugh A patients and 7.7 months for Child-Pugh B patients (76). This study underlines the potential of radioembolization in the treatment of unresectable HCC Patients, specifically emphasizing the benefits of patients staged as Child-Pugh A.

Commentary

After decades of development and research, reduced systemic toxicity combined with efficient local tumor response continue to be the paramount advantages of image-guided, percutaneous therapies of primary liver cancer. Multiple studies demonstrate the advantages of ablative techniques for patients with early-stage liver tumours, showing prolonged overall survival and even curative potential of these modalities. Due to the lack of standardized treatment protocols and the absence of categorical guidelines, no definitive recommendation for the use of one or another modality in patients with end-stage disease can be stated. Trials are needed to evaluate survival benefits of each modality in matched patient cohorts. Currently, different tumor response criteria (RECIST, mRECIST, EASL, WHO) and multiple surrogate markers of survival can be applied to assess tumor response to treatment. Hence, the obvious drawback is the lack of standardization making a comparison between different modalities very difficult and leaving room for interpretation according to individual preferences and center expertise. In summary, further comparative investigation of the available intra-arterial techniques and standardized methods of reporting clinical results are needed to answer the innumerable open questions.

The near future of intra-arterial therapies is promising with multiple innovative technologies, new agents and combination treatments to appear on the horizon. New concepts include molecular targeted treatment of liver cancer metabolism (77) as well as oncolytic immunotherapy (78). The use of new, imageable carrier systems for intra-arterial drug delivery and embolization will provide intraprocedural

identification of undertreated tumor areas (79), while the introduction of advanced intraprocedural imaging, such as dual-phase cone-beam CT will help predicting tumor response immediately after treatment (9). As mentioned before, multiple trials are investigating the outcome of cTACE, DEB-TACE and most recently Radioembolization in combination with systemic chemotherapy with sorafenib (80) and will hopefully contribute to prolonged survival for liver cancer patients treated by interventional radiologists.

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Footnote

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High-intensity focused ultrasound (HIFU) for the treatment of hepatocellular carcinoma: is it time to abandon standard ablative percutaneous treatments?

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Hepatocellular Carcinoma (HCC) is the leading cause of death in patients with cirrhosis (1). Despite recent advances in early detection programs and the diffusion of surveillance protocols in patients with cirrhosis, only 30% to 40% of patients are diagnosed at an early stage and can benefit from radical therapies (1). Surgical resection, liver transplantation or local ablation, either with radiofrequency (RFA) or percutaneous ethanol injection (PEI) are generally considered curative first-line therapeutic options for early-stage HCC. In this setting, in well selected patients, these treatments are associated with 5-year survival rates of 50-70% (1). Among percutaneous ablative treatments, radiofrequency or percutaneous ethanol injection are considered the standard of care for patients with early stage tumors not suitable for surgery (1,2). Although both techniques achieve complete responses in more than 90% of cases with good long-term outcome in tumors <2 cm (1,3), in most instances RFA has replaced multisession PEI due to a significantly better control of the neoplastic disease. The main advantages of image-guided tumour ablation techniques are the widespread availability, the low peri-procedural morbidity and mortality and the short hospital stays (4). However, recurrences occur in the majority of the treated patients (5). Recurrent tumors are frequently treated with a multimodality therapeutical approach and locoregional percutaneous procedures are commonly used in this setting. Data concerning the outcome of patients with recurrences are scanty and difficult to analyze. In a recent retrospective study Kim Y-s *et al.* assessed 10-year outcome of 1,305 CHILDA or B patients, treated with percutaneous RFA as first-line therapy for solitary HCC ≤ 5 cm or plurifocal

HCC (≤ 3 nodules ≤ 3 cm) (5). Most of the patients (62%) experienced recurrences that were treated mainly with RFA or TACE with no mortality and major complications in only 2%. The median survival was 75 months and overall actuarial 3-, 5- and 10-yr survival were 77.9%, 59.7% and 32.3%, respectively.

High-intensity focused ultrasound (HIFU) is a relatively novel technique which ensures non-invasive ablation of tumors. Under magnetic resonance imaging (MRI) or diagnostic ultrasound (US) guidance, the ultrasound beam, generated by a high-power transducer, can be directed to the targeted tissue at a selected depth, resulting in a rapid local temperature increase, that, above the threshold of protein denaturation (65-85 °C), induces coagulative necrosis without damaging the surrounding tissue. Over the last decade, several studies have tested the feasibility and safety of HIFU for the treatment of benign and malignant tumors of the prostate, pancreas, liver, breast, kidney, uterus, bone and brain (6,7).

Concerning liver tumours, the main clinical application of HIFU is currently the ablation of hepatocellular carcinoma and liver metastasis from colon and stomach cancers (7,8). The main advantage of HIFU over other conventional thermal ablation techniques such as RFA is that it does not require puncturing the tumor, thereby avoiding the risk of bleeding or seeding of tumor cells along the needle tract. However, several factors limit the clinical applicability of this procedure. First, HIFU equipment is available in only a few centers; Second, the cost is high especially when MRI is used as guidance; Third, HIFU is a time-consuming procedure; Fourth, it requires either

general or epidural anaesthesia.

Chan and his co-workers explored the feasibility of HIFU and survival in patients with intrahepatic recurrences after a first-line therapy with either hepatectomy or RFA (9). In a non-randomized study, they treated 27 patients with HIFU while 76 patients underwent RFA, either percutaneously (n=46) or open (n=30). Inclusion criteria were: patients with CHILD A cirrhosis with monofocal tumor less than 5 cm or plurifocal with less than 3 nodules ≤ 3 cm. However, selected CHILD B patients were also enrolled and were overrepresented in patients treated with RFA as compared with those who underwent HIFU (32.9% vs. 11.1%, $P=0.03$). Ninety-three % and 72% of patients were males, respectively in the HIFU group or in patients treated with RFA. There was no difference in tumor characteristics between the two groups. In the majority (81%), the recurrence was solitary, with extrahepatic diffusion in 8 (7.7%). Median tumor size was 1.7 cm in the HIFU group and 1.8 cm in the RFA group. HIFU ablation was performed under general anesthesia. Artificial pleural effusion or ascites were created if deemed necessary for improvement in the efficiency of ultrasound transmission. All the patients underwent MRI 1 month after the treatment to assess the efficacy of the therapy. Complete tumor ablation was obtained in more than 80% of both treatment groups (85.2% in the HIFU group and 87.8% in the RFA group). The 3-year survival rates were similar (69.8% in the HIFU group and 64.2% in the RFA group). No difference in survival was observed even after adjustment for the CHILD stage (3-year survival was 70.2% in the HIFU group compared to 64.6% in the RFA group). The morbidity rates were comparable. Skin burns and pleural effusion were the only complications associated with HIFU treatment. No mortality was reported after HIFU but 2 cases of death were related to RFA procedure.

Although the application of HIFU technology in the management of patients with hepatocellular carcinoma is still in its early stages, several studies concerning HIFU treatment of liver tumors have been already reported. In all clinical trials, treated lesions were located in the right hepatic lobe, left lobe, or in both left and right lobes of the liver, and were not candidates for surgical resection, nor suitable for other treatments such as radiofrequency ablation, or percutaneous ethanol injection, because of the size and location of the tumour. As reported for ablative percutaneous treatments, complete ablation of the target region at MRI can be taken to infer histological success (10). The initial experience of HIFU treatment of hepatocellular carcinoma was obtained from researchers in China, using

the JC HIFU system, which was also used in the majority of the trials reported. In a study by Wu F *et al.* (11), 55 patients with large HCC (mean tumour diameter of 8.14 cm) and liver cirrhosis received HIFU treatment. No major complications were observed. Despite the size of the tumours, complete ablation rate was high (69.2%). The overall survival rates were 61.5% at 12 months and 35.3% at 18 months. In another study by the same group (12), the efficacy of HIFU combined with chemoembolization was compared with that of chemoembolization alone in 50 patients with advanced HCC. Survival rate was significantly better in patients who underwent combined treatment than in those who received chemoembolization alone. No severe complication was associated with HIFU treatment. In a trial by Li YY *et al.*, 249 patients with surgically unresectable advanced HCC and liver cirrhosis Child A or B were divided into two groups: 151 received HIFU plus supportive treatment, while 30 patients, who decided to try traditional Chinese medicine or did not want any therapeutic modalities were enrolled in the control arm. No major complications were recorded. In the HIFU group, complete and partial response were achieved in 28.5% and 60.3% of cases, respectively. The overall response rate was significantly greater in the HIFU group than in the control group (88.8% vs. 16.7%). Moreover, in the HIFU arm, the 1- and 2-year survival rate were 50% and 30.9% respectively, which was significantly higher than in controls (13). In recent years, other studies about the use of HIFU for the treatment of HCC in particular settings were performed by Chinese researchers. Zhang L *et al.* treated with HIFU 39 patients with cirrhosis Child A or B and unresectable HCC adjacent to major hepatic veins and therefore ineligible for RFA or PEI due to the location. The results were encouraging as the complete necrosis rate after a single HIFU was more than 50%, indicating that HIFU can achieve complete tumor necrosis even when the lesion is located adjacent to the major hepatic blood vessels. No major complications were observed and the overall survival rates at 1, 3, and 5 years were 75.8%, 49.8% and 31.8 %, respectively (14). Similar findings were reported by Orsi *et al.* who after HIFU achieved complete response in 100% of 6 patients with HCC nodules situated in difficult locations (that is, tumors adjacent to a main hepatic blood vessel, the heart, the bowel, the stomach, the gall bladder and bile ducts), without any complication (15).

When considering the validity of any therapeutic option, the crucial issue is careful evaluation of the procedure-related complications. In this respect, the high mortality

rate reported by Chan after RFA (2.6%) is unexpected. In a systematic review including 9531 patients treated with RFA, Bertot LC *et al.* reported pool mortality and major complications rates of 0.16% and 4.1%, respectively (4). An Italian multicenter study, focused on assessing the safety of RFA, reported 6 deaths (0.3%) with additional 2.3% major complications after treatment of 3,554 focal liver lesions (16). Concerning safety, in the largest series published so far, HIFU was used in the treatment of 1038 patients with solid carcinoma (17). Fever (severe and long lasting in some cases), skin burns and mild local pain were the most common complications. However, six of 474 patients with primary or metastatic liver cancer developed hepatic abscesses within 2-3 weeks of HIFU treatment. Hospital mortality rate can reach 2% with an 8.1% complication rate after HIFU for ablation of hepatocellular carcinoma tumors (median size 2.2 cm, range 0.9-8 cm) (18). Following a median number of HIFU sessions of 1.3 per patient, Li JJ *et al.* observed both systemic and local complications (fever, supraventricular tachycardia, acute cholecystitis, hematuria, cholangiectasis, pleural and pericardial effusions, impairment of peripheral nerves and of vertebral column) (19). However, HIFU has generally proven to induce short to medium-term cancer control, with a low rate of complications comparable to those of established therapies. Chan *et al.* performed HIFU in 103 patients without significant complications. HIFU safely achieved tumor ablation even in patients with HCC nodules positioned in difficult location (14,15).

Although the treatment efficacy and survival benefit of HIFU for patients with liver cancer were well documented in previous studies, clinico-pathological factors that could influence the complete ablation rate and patient survival rates were not studied in details. Further studies are therefore needed. Although HIFU is not widely available, it has proven to be an effective and safe treatment procedure for unresectable HCC, with a favourable survival outcome, though at present very few studies have compared this technique to other tumor ablation techniques. Cheung *et al.* performed a comparative study also in patients with early hepatic cancer (20). They retrospectively assessed the outcome of patients with HCCs smaller than 3 cm after treatment either with HIFU or with RFA. Although Child-Pugh B patients were more frequent in the HIFU group than in the RFA group (34% *vs.* 8.5%) there was no difference in the 3-year survival rate (81.2% *vs.* 79.8%, respectively). No death occurred and only minor complications were associated with HIFU treatment (20).

The main limits of the study of Chan and his co-workers (9) are its retrospective nature and the small study population. Patients were not allocated to each treatment arm on the basis of a randomization, but the choice of treatment for recurrent HCC was related to the sonographic feature of the tumor, its location in relation to adjacent organs and to patient consent. HIFU was offered especially in patients with periductal tumor, who can develop bile duct injury with RFA. However, at the moment, there are no other comparative studies and a randomized trial comparing HIFU and RFA would be difficult to organise. Due to the high costs and the limited availability of HIFU equipment, HIFU should be reserved for the treatment of patients with unresectable tumours, especially when localized in sites difficult to treat with standard ablative percutaneous techniques. Further studies to compare its effectiveness with other ablation modalities are warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Comparison of high-intensity focused ultrasound therapy and radiofrequency ablation for recurrent hepatocellular carcinoma

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Hepatocellular carcinoma (HCC), which accounts for more than 90% of primary liver cancer, is a major health problem worldwide, and is the third most common cause of cancer-related death. It is the fifth most prevalent cancer in men and the seventh in women (1-3). The prognosis for untreated HCC is generally poor, and curative treatments consist of surgical resection, radiofrequency ablation (RFA), and liver transplantation (1-3).

Technical advances in surgery for HCC have improved the survival of HCC patients considerably during recent years. However, only 20% of HCC patients are amenable to surgical resection on presentation (4-6). Locoregional ablative therapies, such as RFA, percutaneous microwave ablation, cryoablation, transcatheter arterial chemoembolization (TACE), and percutaneous ethanol injection offer good alternatives to resection for HCC patients (7).

RFA therapy, an alternative modality to percutaneous ethanol injection, has been widely used as a curative treatment for HCC. Currently, RFA is considered the most promising locoregional treatment for HCC. This modality induces coagulative necrosis and tissue desiccation by delivering high-frequency alternating current via electrodes placed within tissues (7-9). RFA therapy for HCC is primarily accomplished by a percutaneous approach, although open laparoscopic or thoracoscopic approaches can also be used (7-9). RFA provides a valuable treatment option for unresectable HCC. As advances in RFA therapy for HCC continue to be made, it is gradually being performed in patients with resectable HCC, as well as in our country (Japan) (8,9). In addition, RFA is a repeatable procedure because it is less invasive than surgical resection, and it can be safely performed in elderly patients with

potentially comorbid diseases (7,9,10). However, there are several limitations associated with RFA for HCC despite its many potential favorable effects. These limitations include a limited ablation volume, technical limitations, expected complications dependent on tumor location, the heat sink effect, and tumor seeding (11,12).

High-intensity focused ultrasound (HIFU) ablation is an extracorporeal noninvasive ablation mode using focused ultrasound energy, which is capable of causing coagulative necrosis of the targeted HCC via intact skin without the need for surgical incision or insertion of instruments (13,14). This ablation uses a unique frequency of ultrasound waves of 0.8-3.5 MHz, which can be focused at a distance from the therapeutic transducer (13,14). HIFU can provide a potential therapeutic method for the precise ablation of entire liver tumors without damaging vital structure. HIFU also offers the first completely non-invasive approach for HCC and is therefore a promising locoregional treatment modality. Recently, HIFU has been receiving increasing interest for the management of liver tumors (13-15). However, at present, data on the long-term outcome of this treatment are limited. There have been several reports regarding the comparison between TACE plus HIFU and TACE (*Table 1*) (13,16,17), and whether HIFU obtains a survival benefit similar to that of RFA for patients with HCC remains unclear.

In this issue of *Annals of Surgery*, Chan *et al.* demonstrated in their retrospective comparative study, including patients with recurrent HCC, that with a median follow-up period of 27.9 months, the 1-, 2-, and 3-year disease-free survival rates were 37.0%, 25.9%, and 18.5%, respectively, for the HIFU group, and 48.6%, 32.1%, and 26.5%, respectively, for the RFA group (P=0.61).

Table 1 Reports of clinical studies of comparison between TACE plus HIFU and TACE alone (reported in English)

Author/ Country	Year	Treatment	No. of patients	Tumor size	PVTT (yes)	ORR	OS rate (%)	
							1 year	3 years
Feng <i>et al.</i> (13)/China	2005	TACE plus HIFU	24	10.0 cm (mean)	33%	21 (87.5%) [#]	42.9 [#]	NA
		TACE	26	11.3 cm (mean)	50%	11 (42.3%)	0	NA
Li <i>et al.</i> (16)/China	2010	TACE plus HIFU	44	NA	NA	72.8% [#]	72.7 [#]	50.0 [#]
		TACE	45	NA	NA	44.5%	47.2	2.8
Lin <i>et al.</i> (17)/China	2012	TACE plus PVE plus HIFU	32	5.1-12.3 cm (range)	40.6%	25.0%	56.3 [#]	9.3 [#]
		TACE plus PVE	36	4.0-15.3 cm (range)	38.9%	8.3%	30.6	0

TACE, transcatheter arterial chemoembolization; HIFU, high-intensity focused ultrasound ablation; PVTT, portal vein tumor thrombus; ORR, objective response rate; PVE, portal vein embolization; OS, overall survival; #, statistically significant; NA, not available

Additionally, the 1-, 2-, and 3-year overall survival rates were 96.3%, 81.5%, and 69.8%, respectively, for the HIFU group, and 92.1%, 76.1%, and 64.2%, respectively, for the RFA group (P=0.19). There was no hospital mortality in the HIFU group, whereas two deaths occurred in the RFA group. They concluded that using HIFU for recurrent HCC is safe and promising. Although their study was retrospective in nature and had a small sample size, it appears to be a novel and well-characterized study. In their article, they also described the following three advantages of HIFU therapy compared with RFA: (I) extracorporeal conformal therapy of HIFU, indicating no surgical exposure of this therapy; (II) tumor seeding along the needle tract, which often occurs in RFA therapy for HCC, is unlikely to occur and (III) avoidance of targeted tumor puncturing.

In terms of treatment efficacy of HIFU, Chan *et al.* reported that the complete ablation rate was greater than 80% in the HIFU group, which is slightly lower than that of RFA in previous reports (8,9,18). This may be due to the small number of patients in whom they performed HIFU therapy. With sufficient experience in clinical practice for HIFU therapy, the results of treatment efficacy of HIFU for HCC will improve. Notably, the rate of procedure-related morbidity in the HIFU group tended to be lower than that in the RFA group in their study [2 (7.4%) out of 27 patients in the HIFU group *vs.* 25 (22.4%) out of 76 patients in the RFA group, P=0.06] and the hospital mortality rate was 0% in the HIFU group. Their results indicated that HIFU therapy for recurrent HCC was a safe procedure. In Japan, the proportion of elderly patients with HCC and their average age is increasing. In general, elderly patients have a high incidence of comorbid diseases and are considered high-risk patients for treatment-related complications (10). Safety in HCC therapy is an essential issue, as well as

treatment efficacy.

In view of previous studies regarding HIFU for HCC, there are some difficulties that need to be overcome before HIFU can be used in everyday clinical practice (19). The main limitation to clinical application of HIFU is the fact that ablation of large tumors is still time consuming [median total operating time: 151 min (range, 24-360 min)], as reported by Chan *et al.* in this issue of *Annals of Surgery* (15,19,20). In contrast, the duration of a single ablation of RFA is approximately 12 min for the 3-cm electrode of the cool-tip needle (Radionics, Burlington, MA, USA) (8). This may be problematic, especially in patients with a poor physical condition. With technical improvement, the treatment time of HIFU could be gradually reduced in the future. Another challenge in HIFU for HCC therapy is the difficulty in targeting and monitoring because the liver is subject to respiratory movements. The motion of the liver can cause misdirected ultrasound energy, which could potentially result in damage of normal tissue and incomplete tumor ablation. In addition, in cases of HCCs located just behind the ribs, ultrasound energy cannot be easily transmitted through the overlying bone structures (20). Reflection of ultrasound beams by the ribs may cause damage to the bone and adjacent liver tissue (14,20). Therefore, novel technologies in HIFU therapy for HCC should be investigated to overcome these problems.

In conclusion, although there are several difficulties in HIFU therapy for HCC in clinical practice, Chan *et al.* showed in their comparative study of HIFU and RFA that HIFU therapy for recurrent HCC is a safe and promising procedure. With further technical advances, this treatment can be a first line non-invasive ablative therapy for unresectable HCC. Further clinical evidence of this therapy is expected.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Stereotactic body radiation therapy for primary hepatic malignancies and liver metastases

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Abstract: The management of hepatic malignancies presents several unique challenges to providers. Surgical resection is the standard of care, but less than 30% of tumors are amenable to resection at the time of diagnosis. In primary malignancies, such as hepatocellular carcinoma (HCC), orthotopic liver transplantation (OLT) is the only other curative option when a lesion is deemed unresectable. For this reason, various alternative local and regional therapies such as chemoembolization, radioembolization with Yttrium-90 microspheres, and radiofrequency ablation (RFA) have been used to prevent disease progression, palliate symptoms, and to delay liver failure. Historically, radiation has played a limited role in the treatment of hepatic malignancies. Recently, however, stereotactic body radiation therapy (SBRT) has emerged as a non-surgical, non-invasive alternative local therapy for both primary and metastatic hepatic malignancies. Over the past decade, several studies have evaluated the use of SBRT in the treatment of liver malignancies, and have shown that, with appropriate patient selection, SBRT can provide a safe and effective alternative to surgery. This review discusses the application of SBRT in both primary hepatic malignancies and metastases to the liver, highlighting the current literature and future directions.

Keywords: Stereotactic body radiation therapy (SBRT); hepatocellular carcinoma (HCC); liver metastases; bridge to transplant; systematic review

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SBRT in hepatic malignancies

Hepatic malignancies, both primary and metastatic, are increasing in incidence and are associated with significant mortality. Primary hepatic malignancies such as hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC) rank first as the fastest growing cause of cancer death in the United States. The incidence of these diseases has tripled since 1975 (1,2), and the 5-year overall survival rate of primary liver cancer remains dismal at approximately 15% (3). Hepatic metastases from non-liver primaries, such as colorectal (CRC) and breast cancers, are also rapidly rising with approximately 70,000 new cases of CRC liver metastases diagnosed each year. Over the past 40 years, 5-year survival for metastatic CRC has improved from 51% to 65% primarily from improvements

in chemotherapy and increased surgical resection of liver metastases (3).

The currently accepted standard of care in hepatic malignancies is surgical resection when feasible. With resection, 5-year survival is approximately 10-50% for HCC and 30-60% for CRC liver metastases (4,5). Unfortunately, less than 30% of hepatic malignancies are resectable at presentation. When resection is not an option in HCC, orthotopic liver transplant (OLT) is the primary curative option. With transplant, 5-year survival increases to 45-80% (6). When patients are not candidates for curative treatment, non-surgical therapies are offered with palliative intent or in the case of HCC, as a possible bridge to OLT. Non-surgical techniques such as transarterial chemoembolization (TACE), radioembolization with

Table 1 Inclusion and exclusion criteria for prospective trials of stereotactic body radiation therapy (SBRT) for hepatocellular carcinoma (HCC)

Trial	Selected eligibility criteria
RTOG 1112	HCC unsuitable for resection or transplant, Zubrod PS 0-2, Age ≥ 18 , ANC $\geq 1,500$ cells/mm ³ , Platelets $\geq 70,000$ cells/mm ³ , hemoglobin ≥ 8.0 g/dL, Total bilirubin < 2 mg/dL, PT/INR < 1.7 , Albumin ≥ 28 g/L, AST/ALT $< 6 \times$ ULN, BCLC stage intermediate (B) or advanced (C), Child-Pugh score A. Any one HCC ≤ 15 cm, total maximum sum of HCC < 20 cm, No more than 5 discrete intrahepatic parenchymal foci of HCC. Lack of direct extension into stomach, duodenum, small bowel, or large bowel
Phase I trial, Indiana University, Cardenes <i>et al.</i> , 2010 (13)	HCC unsuitable for resection or transplant, Child-Turcotte-Pugh A or B liver function, no progressive or untreated disease outside of the liver, 2/3 of right kidney volume receives < 20 Gy in 3 fractions, 700 mL of normal liver receives < 15 Gy, no history of radiation to the abdomen, Liver function: normal PT/PTT, total bilirubin < 3 mg/dL, albumin > 2.5 g/dL. Kidney function: creatinine < 1.8 mg/dL or creatinine clearance ≥ 50 mL/min. Bone marrow: hemoglobin > 9 g/dL, platelets $\geq 50,000$ /mm ³ , ANC $\geq 1,500$ /mm ³
Phase I trial, University of Toronto, Tse <i>et al.</i> , 2008 (14)	HCC or intrahepatic cholangiocarcinoma, Child-Turcotte-Pugh A, age ≥ 18 , life expectancy of > 3 months, > 800 mL of uninvolved liver, KPS > 60 . Patients excluded if high extrahepatic disease burden, AST or ALT $\geq 6 \times$ ULN, bilirubin $\geq 3 \times$ ULN, creatinine > 200 μ mol/L, INR ≥ 1.3 , hemoglobin < 90 g/L, platelets $< 80,000$ / μ L, clinically apparent ascites, previous right-sided abdominal radiation

Yttrium-90 microspheres, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and even high-dose 3-D conformal radiotherapy have been used in this setting. Unfortunately, these non-surgical locoregional therapies are often limited by tumor size, location, number of lesions or degree of hepatic reserve and only TACE and sorafenib have shown a survival benefit in Child-Turcotte-Pugh (CTP) class A patients with HCC in randomized trials (7,8).

Historically, the role of radiation in hepatic malignancies was limited to palliation given the low tolerance of normal hepatic tissue and risk of toxicity. Recently, however, advances in stereotactic radiosurgery (SRS) have led to the application of this technology extracranially. Improvements in immobilization, tumor volume delineation, image guided technology as well as radiation treatment delivery have permitted the use of high doses of radiation to very precise target volumes. Stereotactic body radiation therapy (SBRT) offers several benefits in treating liver malignancies. In addition to being non-invasive, it offers a highly precise mechanism of delivering ablative doses of radiation to tumors while sparing normal or non-tumor hepatic tissue. In sparing normal tissue, toxicity associated with SBRT has been limited (9-12).

In this review, we aim to discuss the current use of SBRT in the management of both primary hepatic malignancies as well as liver metastases.

Patient selection

As with SBRT for other disease sites, SBRT for primary

liver tumors and hepatic metastases requires precise and reproducible immobilization. Thus, patients who are unable to tolerate supine positioning or who are unable to lie in an immobilization device for several minutes are poor candidates for SBRT. Also, since SBRT is a highly conformal treatment modality, it is most useful in patients whose liver tumors are readily delineated on MRI or dual phase CT. Regarding HCC, patients with unresectable disease and who are in CTP class A or class B with low CTP scores (< 8) have been regarded as the best candidates for SBRT. More detailed criteria for patient selection for SBRT in HCC are informed by previously published phase I prospective trials and RTOG 1112 which is currently open for enrollment, randomizing HCC patients to Sorafenib *vs.* SBRT followed by Sorafenib (13,14). These criteria are summarized in *Table 1*. At our center, a distance to critical organs such as adjacent small bowel or stomach of at least 5 mm is essential, but this involves careful planning, image guidance, and dose analysis to not exceed maximum tolerated dose to these structures. In terms of HCC tumor size, Cardenes and colleagues used a tumor diameter of 6 cm as the upper size limit in their phase I trial although the current RTOG 1112 trial allows cumulative tumor size of up to 20 cm (13).

Selection of patients with metastatic liver lesions for SBRT

Regarding liver metastases, patients considered eligible

for SBRT should have a biopsy-proven unresectable metastatic liver malignancy in the presence of adequate hepatic function, and a life expectancy of at least three months (15-18). Typical exclusionary criteria include untreated or uncontrolled primary disease or extensive/widespread metastatic disease. As outlined in further detail below, close attention to the number and size of liver lesions treated with SBRT in the context of the volume and function of the unaffected liver is paramount because of the risk of radiation induced liver disease (RILD). In prospective series of SBRT for liver metastases, a set of criteria almost identical to those used for HCC have been widely implemented to guide patient selection and treatment planning (15-18). The number of tumors to be treated is generally restricted to three or fewer. Similar to studies for HCC, these series have also used a tumor diameter of 6 cm above which SBRT is not recommended. Guidelines for distance to adjacent organs vary widely based on institutional setup. At our institution, a distance between the PTV and adjacent organs of 5 mm or greater is considered acceptable when image guidance is used. Lastly, it is essential to apply a dose constraint to the volume or percent of irradiated normal liver. A common dose/volume constraint for normal liver [total liver minus cumulative gross tumor volume (GTV)] is 700-1,000 cc of normal liver should receive a total dose less than 15 Gy in 3 fractions (15,17,18).

Derivation of liver dose constraint

Dose constraints for liver SBRT are informed by both the surgical literature, which provides insight into the proportion of normal liver which can be safely resected (19), and a conservative conversion from published experiences of conventional fractionation (17). From the surgical literature, it is known that 75-80% of non-cirrhotic liver can be resected safely (19). With the average liver volume being approximately 2,000 cc, one quarter of that is 500 cc. Requiring at least 700 cc of normal/non-cirrhotic liver be spared leaves a volume buffer on average of about 40%. From the conventional fractionation literature, the entire liver has been shown to tolerate at least 33 Gy in 22 fractions (17). The biologically equivalent dose (BED) of this schedule is 49.5 Gy assuming an α/β ratio of three and no repopulation (20). Keeping these assumptions constant, 15 Gy in 3 fractions has a normal tissue BED of 40 Gy, which is less than the expected tissue tolerance observed in conventional fractionation schemes. The maximum total

dose to any point in the stomach or small intestine and spinal cord should not exceed 30 and 18 Gy, respectively and the percentage of total kidney to receive a total of 15 Gy assuming 3 fractions should be less than 35% (18).

The risk of developing RILD was further informed by dosimetric studies done by Dawson and colleagues, which revealed a particularly strong correlation of the volume of liver irradiated and mean liver dose to the development of RILD (21,22). From this finding, they developed a method to calculate complication probability factors for non-uniformly irradiated normal liver using dose volume histograms and complication probabilities for uniform partial liver irradiation. In this effective volume (Veff) method, each partial volume element of the histogram is analyzed independently through a power law dose volume relationship (23). With this approach, a non-uniform dose volume histogram is converted to a uniform one with a Veff and a dose equal to the maximum dose to the organ. The complication probability is then obtained from known complication probabilities for uniform partial organ irradiation (21,22).

Technical considerations

SBRT of liver cancer is technically challenging. There is significant inter- and intra-fractional organ motion induced by respiration, and the radiation tolerance of normal liver is low (24,25). The former necessitates the use of larger margin, while the latter discourages it. To make matters worse, liver masses are not typically easy to delineate against the normal liver with in-room cone beam computed tomography (CBCT), leading to uncertainties in image registration and setup (25-29). Since dose-response relationships exist in both primary and metastatic liver cancer, with higher dose resulting in improved outcome, the narrowest possible safety margin is prerequisite in maximizing the therapeutic ratio (30). Consequently, the most accurate and precise target localization technique(s), which minimizes margin size, is essential in liver SBRT. Given the higher doses and tight margins, an effective immobilization and image guidance method is essential to achieve accurate and reproducible treatment delivery. Commonly employed immobilization methods for liver SBRT are synthetic body molds and customized external vacuum cushion bags (18,31). In addition, tumors in the liver may move as much as a few centimeters during the respiratory cycle given the high degree of deformation of the liver. This breathing-related tumor motion can be

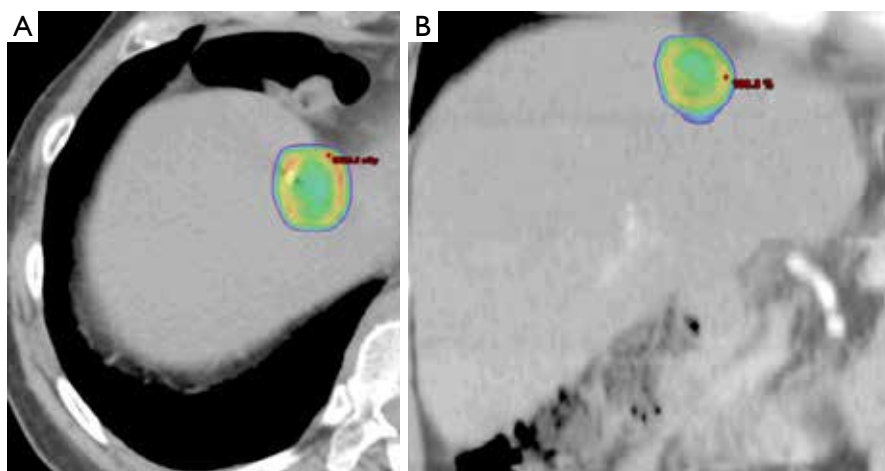


Figure 1 Axial treatment planning computed tomographic (CT) scan (A) with coronal reconstructions (B) of stereotactic body radiation therapy (SBRT) to 60 Gy in 3 fractions prescribed to the PTV for hepatocellular carcinoma in a 60-year-old gentleman with chronic hepatitis C and CTP A liver function. The dose color wash depicts the volume receiving 95% of the prescription dose. The tumor volume was 6.14 cm³. SBRT was delivered in this case as bridging therapy prior to transplant.

controlled to a degree and must be measured and accounted for in all stages of treatment preparation (CT simulation and treatment planning) and treatment delivery (7,32,33). Accurate measurement and control of respiratory target motion also allows for reduction of GTV margin expansion to create the PTV. Fiducial markers, small radio-opaque seeds, can be placed with CT guidance prior to simulation and treatment. These can be used for setup verification and to monitor liver motion. In patients previously treated with TACE using the embolic agent Lipiodol, some studies have shown that the embolized area can potentially serve as a direct surrogate for tumor localization on CBCT when combined with active breathing control to minimize setup error and potentially reduce CTV-PTV margins (34,35).

Breathing-related tumor motion can be dampened with active breathing control (i.e., controlled breath hold technique) or abdominal compression. Alternatively, breathing-related tumor motion can be accounted for with respiratory gating or tumor tracking. Published clinical trials of SBRT for HCC and for liver metastases have GTV margin expansions with active breathing control of 5 mm radially and 10 mm cranio-caudally. With abdominal compression, volume expansions were 7 mm radially and 15 mm cranio-caudally (13,14,18). When respiratory gating or 4D-CT is used, an internal tumor volume (ITV) is created to define the target volume in which the GTV includes the tumor position in all phases of the respiratory

cycle. A small margin is added to the ITV to create a PTV accounting for daily setup variation. Representative SBRT treatment plans for a patient with HCC and for a patient with a metastasis to the liver are depicted in *Figures 1* and *2*, respectively.

As stated, the use of stereotactic body frames, active breathing control, and abdominal compression plates have been popular in limiting most diaphragm motion to less than 10 mm (36-41). Even with reduced motion, however, the problem with image registration uncertainty still remains. An effective solution to this lack of soft tissue contrast is the use of percutaneously inserted fiducial markers as a surrogate (42-46). This approach is quite effective because the metal markers are radio-opaque and are thus readily visible in X-ray projections. Therefore, using markers to characterize the daily liver motion and subsequently adjusting the treatment setup is an effective strategy to increase treatment accuracy. At our institution, this has been the regular practice. We use three implanted fiducials placed within 3 cm of the tumor edge but not in the tumor itself to avoid metal induced artifacts in CT and possible spreading of the cancerous cells during its insertion. At the treatment table, we employ kilovoltage (kV) X-ray imaging, CBCT, and kV fluoroscopic imaging in sequence to assess the respiratory-induced liver motion as well as to make adjustments based on their movement characteristics. We recently analyzed the motion characteristics of twenty

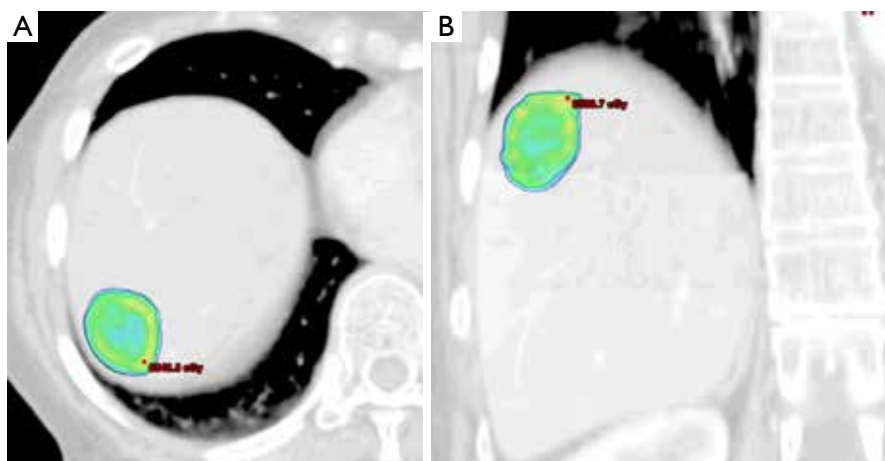


Figure 2 Axial treatment planning 4-dimensional computed tomographic (4D-CT) scan (A) with coronal reconstructions (B) of stereotactic body radiation therapy (SBRT) to 60 Gy in 3 fractions prescribed to the PTV for an isolated metastasis of non-small cell lung cancer to the liver. This patient was deemed by the hepatobiliary surgeon to be a poor candidate for resection due to the location of the lesion. The dose color wash depicts the volume receiving 95% of the prescription dose. The tumor volume was 6.08 cm³.

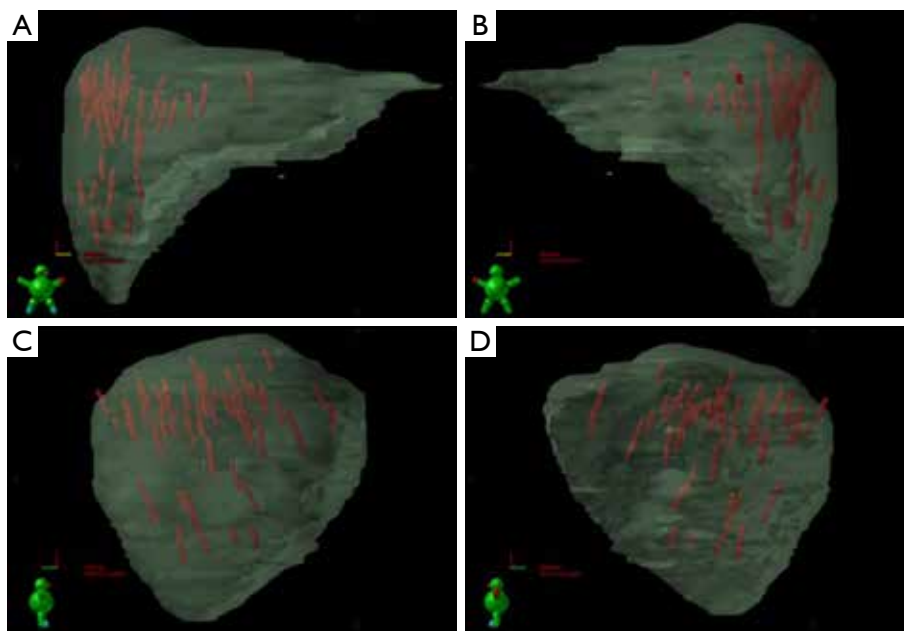


Figure 3 Orthogonal projections of 49 fiducial marker trajectories overlaid on a representative liver contour, reconstructed from CBCT scans. These are viewed from the (A) anterior, (B) posterior, (C) left, and (D) right beam's eye view, showing the degree and direction of liver motion. As shown, the most dominant motion is in the craniocaudal direction. Adapted from Park *et al.* (26).

liver SBRT patients (26). The motion trajectories of the implanted fiducials are reconstructed and nicely visualized in *Figure 3*.

Real-time tumor tracking is another method of

accounting for respiratory motion employed by the Cyberknife[®] system and Novalis ExacTrac[®] patient positioning system known as Brain-LAB (ExactTrac; BrainLab Inc, Westchester, IL). The Cyberknife[®] system

(Accuray Inc, Sunnyvale, CA) requires the placement of 3 to 6 internal fiducial makers 3 to 5 mm in size. A 3-5 mm GTV expansion for liver tumors is typical in series using Cyberknife® (47). In the Cyberknife® system, a kV camera mounted on the robotic arm alongside the linear accelerator performs real-time fiducial tracking and respiratory motion modeling. For institutions using the Brain-LAB patient positioning system, external body fiducial markers are monitored from ceiling-mounted infrared cameras and respiratory gating is obtained using a relaxed, end-expiratory breath-hold technique.

Review of SBRT for hepatic malignancies

One of the earliest studies to explore the use of SBRT in hepatic malignancies for inoperable or non-surgical patients was published by Blomgren *et al.* in 1995. The study included 42 tumors in 31 patients with solitary hepatic, lung or retroperitoneal tumors that ranged in size from 2 to 622 cm³, with a mean volume of 78 cm³. Using total mean doses from 8-66 Gy with a mean dose of 41 Gy, they reported a progression free survival of 80% over a period of 1.5-38 months. Additionally, 50% of the tumors showed a reduction in size or disappeared (48).

Following this initial study, a phase I/II dose-escalation trial was conducted by Herfarth *et al.* using single-dose SBRT for inoperable hepatic malignancies. Thirty-five patients with 55 tumors, including both primary and metastatic lesions, were treated to doses between 14 and 26 Gy in a single fraction. Size ranged from 1 to 132 cm³, with a median size of 10 cm³. After 6-weeks of follow-up, 54 (98%) of the tumors were locally controlled. Local control rate was reported as 81% at a median follow-up of 18 months after accounting for dose-escalation and learning phase (9).

In a retrospective study by Wulf *et al.* involving both primary liver tumors and hepatic metastases, higher dose regimens were found to significantly improve local control. Five patients with primary hepatic malignancies and 39 patients with 51 liver metastases were included. Using "low-dose" regimens of 3×10 and 4×7 Gy, they reported actuarial local control rates of 86% and 58% at 12 and 24 months, respectively. "High-dose" regimens of 3×12-3×12.5 and 1×26 Gy resulted in local control rates of 100% and 82% at 12 and 24 months, respectively. At a median follow-up of 15 months, all primary liver malignancies were controlled, whereas nine local failures were seen in the hepatic metastases group (12).

A prospective, phase I-II trial by Méndez Romero *et al.*

involving 45 unresectable hepatic lesions, both primary and metastatic, showed local control rates of 94% and 82% at 1 and 2 years, respectively with a median follow-up of 12.9 months. Dose was adjusted for larger lesions or the presence of cirrhosis. Most lesions received 3 fractions of 12.5 Gy, however, lesions ≥4 cm or HCC with cirrhosis were treated to lower doses or with more extended schedules, such as 5 5-Gy fractions or 3 10-Gy fractions. This trial found toxicity to be greater in patients with more severe liver disease, such as patients with CTP-B liver disease (49).

These early studies showed that SBRT is an effective, safe, and feasible option in the local control of unresectable hepatic malignancies. However, there is little consensus on dosing and fractionation schedules among the studies. Several recent prospective studies have aimed to address these issues while selectively limiting their observations to either primary liver malignancies (*Table 2*) or hepatic metastases (*Table 3*). Because the quality and functioning of the non-tumor liver parenchyma becomes important in determining maximum tolerable dose and because it varies between primary and metastatic hepatic malignancies, it is helpful to discuss target volumes, dosing and fractionation individually.

Primary hepatic malignancies

In a small study by Choi *et al.* involving 20 patients with small (2-6.5 cm), inoperable HCCs in the setting of CTP-A or -B class liver disease, overall response rate was reported as 80% at a median follow-up of 23 months using 50 Gy in 5 or 10 fractions. One and 2-year survival rates were 70% and 43%, respectively with a median survival of 20 months. Similarly, 1- and 2-year disease free survival rates were 65% and 32.5%, respectively with a median disease free survival of 19 months (50).

Similarly, Tse *et al.* conducted a phase I trial involving 41 patients with unresectable primary hepatic malignancies, 31 CTP-A HCCs and 10 IHCs. Dose was adjusted to reflect the volume of liver irradiated, taking into account the estimated risk of liver toxicity. Lesions were larger, ranging in size from 9 to 1,913 mL with a median size of 173 mL. Patients were treated to doses between 24 and 54 Gy with a median dose of 36 Gy in 6 fractions over two weeks. Median survival was 11.7 months for HCC patients and 15 months for patients with IHC (14).

In a prospective, single institution study by Takeda *et al.*, 16 patients with small (<100 cm³), solitary HCCs were

Table 2 Summary of SBRT studies involving primary hepatic malignancies

Author, year	Study design	Patients HCC/ICH	Number and size of lesions	Dose/Fractionation	Median follow-up, months [range]	1-/2-year LC	1-/2-/3-year OS
Blomgren, 1995		11	78 cc (2-622 cc)	8-66 Gy in 1-4 fx	12 [1.5-38]	100%/NR	65%
Herfarth, 2001	Phase I/II	4/0	4	14-26 Gy in 1 fx	6	NR	NR
Wulf, 2006		5		Low: 30 Gy in 3 or 28 Gy in 4 fx High: 36-37.5 Gy in 3 fx or 26 Gy in 1 fx	15 [2-48]	100%/NR	72%/32%
Choi, 2006		20	3.8 cm (2-6.5 cm)	50 Gy in 5 or 10 fx	23 [3-55]	NR	70%/43%
Mendez-Romero, 2006	Phase I/II	8	11 3.2 cm (0.5-7.2 cm) 22 cc (1.1-322 cc)	w/o cirrhosis or <4 cm: 37.5 Gy in 3 w/o cirrhosis or ≥4 cm: 25 Gy in 5 or 30 Gy in 3 fx	12.9	75%/NR	75%/40%
Dawson, 2006	Phase I/II	33/12	293 cc (2.9-3,088 cc)	24-57 Gy in 6 fx		NR	NR
Tse, 2008	Phase I/II	31/10	173 cc (9-1,913 cc)	24-54 Gy in 6 fx	17.6	65%/NR	48%
Takeda, 2008	Prospective	16/0	<100 cc	35-50 Gy in 5-7 fx	20.3 [8.1-31.5]	NR	NR
Cardenes, 2010	Phase I/II	17	25 <6 cm	36-48 Gy in 3 fx CTP-B: 40 Gy in 5 fx	24 [10-42]	100%/NR	75%/60%
Louis, 2010		25/0		45 Gy in 3 fx	12.7 [1-24]	95%/95%	79%/52%
Kwon, 2010		42/0	15.4 cc (3-81.8 cc)	30-39 Gy in 3 fx	28.7 [8.4-49.1]	NR	92.9%/NR/58.6%
Seo, 2010	Prospective	38	40.5 cc (11-464 cc)	33-57 Gy in 3-4 fx		74%/NR	NR/61.4%
Andolino, 2011		60	3.2 cm (*)	44 Gy in 3 fx CTP-B: 40 Gy in 5 fx	27	NR/90%	NR/67%
Facciuto, 2012	Retrospective	27/0	39 2 cm (*)	28-36 Gy in 2-4 fx		NR	NR
Bujold, 2013	Phase I/II	102	117 cc (1.3-1,913 cc)	24-54 Gy in 6 fx	31.4	87%/NR	NR

HCC, hepatocellular carcinoma; IHC, intrahepatic cholangiocarcinoma; Fx, fractions; CTP, Childs-Torcotte-Pugh; LC, local control; OS, overall survival; NR, not reported; *, maximum tumor diameter.

treated to 35-50 Gy in 5-7 fractions over 5-9 days. With a median follow-up of 611 days, 15 of the 16 patients showed either a complete response (CR) or stable disease. Six of the patients developed intrahepatic recurrences outside of the treated volume (51).

At Indiana University, Cardenes *et al.* conducted a phase I dose escalation trial using SBRT for primary HCC in unresectable, CTP-A or -B patients with 1-3 lesions. Seventeen patients with 25 lesions were included. Dose was escalated from 36 to 48 Gy in 3 fractions for patients

Table 3 Summary of SBRT studies involving liver metastases

Author, year	Study design	Patients	Number and size of lesions	Dose/fractionation	Median follow-up [months]	1-/2-year LC	1-year OS/2-year OS
Blomgren, 1998		17	21 46 cc (2-263 cc)	20-45 Gy in 1-5 fx	9.6 [1.5-24]	95%, crude	NR
Herfarth, 2001	Phase I/II	33	56 10 cc (1-132 cc)	14-26 Gy in 1 fx	5.7 [1-26]	81% (18 m)	72%/NR
Wulf, 2006		39	51	Low: 30 Gy in 3 fx or 28 Gy in 4 fx High: 36-37.5 Gy in 3 fx or 26 Gy in 1 fx	15 [2-85]	92%/66% Low: 86%/58% High: 100%/82%	72%/32%
Mendez-Romero, 2006	Phase I/II	17	34 3.2 cm (0.5-7.2 cm) 22 cc (1.1-322 cc)	37.5 Gy in 3 fx	12.9	100%/NR	85%/62%
Kavanagh, 2006	Phase I/II	36	<6 cm	60 Gy in 3 fx	19 [6-29]	93% (18 m)	NR
Dawson, 2006	Phase I/II	34	293 cc (2.9-3,088 cc)	24-57 Gy in 6 fx		NR	NR
Hoyer, 2006	Phase II	44	35 mm (10-88 mm)	45 Gy in 3 fx	51.6 [2.4-75.6]	NR/79%	67%/38%
Katz, 2007	Retrospective	69	174 9.9 cc (0.11-950 cc)	30-55 Gy in 7-20 fx	14.5 [1-38]	76% (10 m)/57% (20 m)	NR
Lee, 2009	Phase I	68	75.2 cc (1.2-3,090 cc)	27.7-60 Gy in 6 fx		71%/NR	NR
Rusthoven, 2009	Phase I/II	47	63 15 cc (0.75-98 cc)	36-60 Gy in 3 fx	16 [6-54]	95%/92%	NR/30%
Goodman, 2010	Phase I	19 of 26	<5 cm 32.6 cc (0.8-146.6 cc)	18-30 Gy in 1 fx	17.3 [2-55]	77%/NR	61.8%/49.4%
Rule, 2011	Phase I	27	36 2.5 cm (0.4-7.8 cm) 9.5 cc (0.75-135 cc)	30 Gy in 3 fx, 50 Gy in 5 fx, or 60 Gy in 5 fx	All: 20 [4-53] Surviving: 37 [6-53]	(2 yr) 56%, 89%, 100%	(2 yr) 56%, 67%, 50%

Fx, fractions; LC, local control; OS, overall survival; NR, not reported.

with CTP-A class disease. During the study, patients with CTP-B disease developed significant toxicity at 3×14 Gy. The protocol for CTP-B disease was then amended, extending the fractionation schedule to 40 Gy in 5 fractions. At a median follow-up of 24 months, local control and stabilization of disease were reported as 100%. Overall survival at 1- and 2-year was 75% and 60%, respectively (13).

More recently, a series by Louis *et al.* included 25 patients with HCC and CTP-A or -B liver disease who were either

unresectable or ineligible for other treatment modalities. Using SBRT delivered with Cyberknife® system, lesions were treated to 45 Gy in 3 fractions over 10-12 days. At a median follow-up of 12.7 months, six patients had died. Actuarial local control at 1- and 2-years was reported as 95% and 1- and 2-year overall survival was 79% and 52%, respectively (52).

In 2010, Kwon *et al.* reported on long-term effects of SBRT for HCC lesions that were ineligible for locoregional therapies or unresectable. Forty-two patients with small

(≤ 100 cc, median volume 15.4 cc) HCCs were treated to 30-39 Gy in 3 fractions. At a median follow-up of 28.7 months, 86% of patients experienced either a complete or partial response, with most achieving a CR. Smaller tumors (< 32 cc) had significantly better in-field progression free survival and overall survival. In-field progression free survival at 1 and 3 years was 72% and 67.5%, respectively. Overall 1- and 3-year survival rates were 92.9% and 58.6%, respectively (53).

Similarly, a Korean, prospective trial by Seo *et al.* evaluated SBRT as a salvage therapy for inoperable HCC (< 10 cm) following hepatic TACE. The study included 38 patients treated with SBRT to 33-57 Gy in 3-4 fractions. Doses were adjusted for tumor volume with most tumors ranging in size from 11 to 464 cc. At 2-years, overall survival was reported as 61% and progression-free survival was 66%. Univariate analysis showed ITV < 100 cc and SBRT doses < 42 Gy in 3 fractions to be significant prognostic factors of overall survival; whereas, multivariate analysis identified SBRT dose as the only prognostic factor (54).

In another study at Indiana University by Andolino *et al.*, SBRT was evaluated in the bridge to transplant setting as well as a definitive therapy in transplant ineligible patients. Sixty patients with HCC confined to the liver and CTP-A or CTP-B liver disease were treated to 44 Gy in 3 fractions or 40 Gy in 5 fractions, respectively. Most tumors were small (≤ 6 cm), with a median tumor diameter of 3.2 cm. At a median follow-up of 27 months, 2-year local control was reported as 90%, progression free survival was 48% and overall survival was 67%. Following SBRT, 23 patients underwent liver transplant (55).

A retrospective analysis by Facciuto *et al.*, involved 27 patients with unresectable HCC totaling 39 lesions and CTP-A or -B cirrhosis who were treated with SBRT prior to OLT. Dose and fractionation ranged from 28 Gy in 4 fractions to 36 Gy in 2 fractions, with most patients receiving 28 Gy in 4 fractions. Seventeen patients with a total of 22 lesions underwent OLT. In addition to radiographic review of response to SBRT, response to treatment of lesions in patients who underwent OLT was also assessed pathologically. On radiographic review of 27 of the 39 treated lesions, 30% showed a CR, 7% showed a PR and 56% were stable. Only 7% showed progression of disease. On pathologic review of 22 of the treated lesions in the 17 transplanted patients, 37% showed either a complete or partial response; whereas, 63% showed no response (defined as less than 30% tumor necrosis) at a mean time of four months after SBRT (56).

Most recently, in sequential phase I (Trial 1) and II (Trial 2) trials at Princess Margaret Hospital by Bujold *et al.*, SBRT was evaluated in the treatment of 102 patients with HCC and CTP-A liver disease. Trial 1 had no tumor number or size limits. In Trial 2, no more than five discrete liver tumors were allowed with a maximal dimension of 15 cm. Patients were treated to doses between 24 and 54 Gy in 6 fractions, with a median dose of 36 Gy. Local control at 1 year was reported at 87% with 11 patients achieving a CR, 44 patients with a partial response and 45 patients with stable disease. At a median follow-up of 31.4 months, 67 patients had died. Overall median survival was 17 months and on multivariate analysis, absence of tumor vascular thrombosis (TVT) and remaining on Trial 2 were associated with improved overall survival (57,58).

Liver metastases

In an interim analysis of a multi-institutional, phase I/II prospective trial, Kavanagh *et al.* reported excellent in-field local control using SBRT for liver metastases. Thirty-nine patients with tumors < 6 cm in maximum diameter and a total of ≤ 3 lesions were included. Dose to 700 cm³ of the normal liver was limited to ≤ 15 Gy. Lesions were treated to 60 Gy in three 20 Gy-fractions over the course of 3-14 days. At a median follow-up of 18-months, local control for 28 of the lesions was 93% (10).

In a phase I/II study by Dawson *et al.* at Princess Margaret Hospital, dose-adjusted SBRT was used to treat 79 patients with either primary or metastatic hepatic malignancies. Forty-five patients with primary liver malignancies were treated including 33 patients with HCC and 12 patients with IHC. Thirty-four patients had liver metastases. Tumors ranged in size from 2.9 to 3,088 cc, with a median size of 293 cc. Prescription dose was adjusted based on a normal tissue complication probability (NTCP) model to limit estimated risk of RILD. Doses ranged between 24 and 57 Gy, with a median dose of 36.6 Gy. All patients were treated in 6 fractions. The primary objectives of the study were to determine the rate of RILD and severe toxicities and to stratify the risks based on both diagnosis and effective liver volume irradiated. The final results of this trial are not yet published. However, as of 2006, dose-limiting toxicity had not been observed. The conclusion at that time was based on initial analysis individualized, image-guided, iso-NTCP liver SBRT appears feasible (23).

Hoyer *et al.* looked at the use of SBRT in the treatment of metastases specifically from CRC primaries in a phase II,

prospective study. Forty-four of the 64 patients had hepatic metastases. Lesions ranged in size from 10 to 88 mm, with a median size of 35 mm. All lesions, including extra-hepatic lesions, were treated to 45 Gy in 3 fractions. At a median follow-up of 4.3 years, 2-year tumor based actuarial local control was reported as 79%, but because several patients had more than one metastasis, patient based local control was lower at 64%. Two-year progression free survival was 19% with a median time to progression of 6.5 months. Overall survival was reported as 67%, 38%, 22%, 13%, and 13% at 1, 2, 3, 4 and 5 years following SBRT (59).

In a retrospective study by Katz *et al.*, 69 patients with a total of 174 hepatic metastases were treated with SBRT. Twenty-eight patients received concurrent chemotherapy. Lesions ranged in size from 0.6 to 12.2 cm, with a median maximum tumor diameter of 2.7 cm. Doses ranged from 30 to 55 Gy, with a median dose of 48 Gy and a preferred fractionation of 50 Gy in 5 fractions. Dose was adjusted for preexisting, but non-malignant liver disease. At a median follow-up 14 months, 10- and 20-month local control was reported as 76% and 57%, respectively. Most patients (75%) developed additional lesions in the liver, with a median time to progression of 6.6 months. Progression-free survival was reported as 46% and 24% at 6 and 12 months, respectively. The median overall survival was 14.5 months (60).

Lee *et al.* conducted a phase I study of 68 patients with CTP-A liver disease and unresectable liver metastases of variable sizes using individualized SBRT doses that were adjusted for estimated risk of RILD. Tumors ranged in size from 1.19 to 3,090 cc, with a median volume of 75.2 cc. Lesions were treated to doses between 27.7 and 60 Gy, with a median dose of 41.8 Gy in 6 fractions. One-year local control was reported as 71%. Median overall survival was 17.6 months, however, the median survival of patients with CRC liver metastases was slightly shorter at 14.6 months (16).

In a multi-institutional, phase I/II trial by Rusthoven *et al.*, excellent local control was reported using 60 Gy in 3 fractions for lesions ≤ 3 cm. Forty-seven patients with 63 metastatic liver lesions were included. Tumor size ranged from 0.4 to 5.8 cm, with a median maximum tumor diameter of 2.7 cm. In the first phase of the study, dose was escalated from 36 to 60 Gy in 3 fractions. The second phase of the study used 60 Gy in 3 fractions. At a median follow-up of 16 months, 1- and 2-year local control was reported as 95% and 92%, respectively. For lesions ≤ 3 cm, 2-year local control was 100%. Median overall survival was reported as 20.5 months. For favorable primaries, such as breast, CRC,

renal, carcinoid, gastrointestinal stromal tumor, and sarcoma, however, median survival was longer at 32 months (18).

Recently, in a phase I, dose-escalation study by Goodman *et al.*, single-fraction SBRT was evaluated in the treatment of unresectable, primary and metastatic hepatic malignancies. Twenty-six patients with CTP-A liver disease, ≤ 5 lesions and a maximum tumor diameter of ≤ 5 cm were included. Nineteen patients had hepatic metastases, including six metastases from CRC. Size ranged from 0.8-146.6 cc, with a median size of 32.6 cc. Lesions were treated to doses between 18 and 30 Gy in 4 Gy-intervals. At a median follow-up of 17 months, 1-year local control was approximately 77%. Two-year actuarial overall survival was 50.4% and median survival was 28.6 months (61).

In another phase I, dose-escalation trial by Rule *et al.*, 27 patients with 37 small liver metastases, adequate hepatic function, and less than 5 lesions, were treated using SBRT. Tumors ranged in size from 0.4-7.8 cm, with a median diameter of 2.5 cm. Three cohorts of nine patients were treated to 30 Gy in 3 fractions, 50 Gy in 5 fractions or 60 Gy in 5 fractions. Dose to 700 cm³ of the normal liver was limited to <21 Gy. Two-year local control rates for the 30-, 50- and 60-Gy cohorts were reported as 56%, 89% and 100%, respectively. Median overall survival for all groups was 37 months and 2-year overall survival for the 30-, 50- and 60-Gy cohorts was 56%, 67% and 50%, respectively (62).

Toxicities

The most common complication of liver radiation is RILD, or radiation hepatitis. Originally described by Reed *et al.*, RILD is a syndrome of fatigue, right upper quadrant pain, ascites, anicteric hepatomegaly and elevated transaminases (63). The syndrome typically occurs within 1-2 months of treatment and is associated with total liver irradiation at doses greater than 30-35 Gy in standard 2 Gy fractions. Early studies of normal tissue tolerances by Emami *et al.* found that whole liver radiation to 30 Gy in 2 Gy fractions was associated with a 5% risk of liver failure within 5 years; whereas, whole radiation to 40 Gy was associated with a 50% risk of RILD (64). Despite this risk of inducing more rapid liver failure with radiation, most of the early SBRT studies found this risk to be minimal with proper patient selection and strict dose-volume constraints (9,10,14,49,59,65).

In a recent meta-analysis by Sawrie *et al.*, toxicity data was compiled from several of the earlier prospective trials

involving SBRT for HCC and liver metastases (11). Toxicity was correlated with the dose-volume constraints, calculated BED and single-fraction equivalent doses (SFED) for the liver and surrounding organs at risk including the kidney, spinal cord, stomach, bowel, esophagus and heart. Most of the earlier studies limited the dose to 30-33% of the liver to between 7 and 21 Gy. With this constraint, the crude rate of RILD was found to be approximately 2.4%. Other liver related toxicities included portal hypertension, ascites, and elevated liver enzymes (49). Mendez Romero reported a single incidence of grade 5 liver toxicity in a patient with HCC, cirrhosis and hepatitis B virus infection. In these studies, the stomach was constrained to doses between 7 and 30 Gy. Grade 1 and 2 loss of appetite and nausea were relatively common, with toxicity being more severe for lesions located closer to the stomach. Diarrhea was a common bowel-related toxicity. One study reported duodenal ulceration and colonic perforation, however, these episodes occurred at bowel doses greater than 30 Gy (48). Reported skin toxicity included erythema, pain, dermatitis and one study reported skin breakdown six months post treatment (10). In addition to organ-related toxicities, constitutional toxicities such as fatigue, fever, chills and analgesia were common, but mild (9,65). Renal, cardiac, esophageal and spinal cord related toxicity was nominal in all studies.

Future directions

Currently, the role of SBRT in hepatic malignancies is primarily limited to settings in which resection is not feasible. No study has yet addressed SBRT in the setting of potentially resectable liver metastases. There is an ongoing multicenter randomized phase III trial (RAS study) of liver SBRT *vs.* RFA for patients with CRC liver metastases by the International Liver Tumor Group (www.livertumor.dk).

The role of SBRT in combination with small molecules with activity against HCC is currently under investigation in a large multi-center cooperative group randomized clinical trial (RTOG 1112). Sorafenib is a small molecule, tyrosine kinase inhibitor (TKI) which has been shown in two randomized trials [Sorafenib HCC Assessment Randomized Protocol (SHARP) (8) and the Asian Pacific Trial (66)], to improve survival in patients with advanced BCLC stage HCC. Sorafenib blocks angiogenesis through its potent activity against the c-raf, VEGFfr2/3 and PDGF-alpha kinases. The SHARP trial, which was comprised of 602 HCC patients, found an improvement in

median survival from 7.9 to 10.7 months and median time to progression from 2.8 to 5.5 months in the sorafenib arm compared to placebo, with no difference in adverse events between the two treatment arms. In the Asian-Pacific trial, overall median survival improved from 4.2 to 6.5 months. In both of these trials, the majority of patients ultimately progressed in the liver and died of liver failure. The high-prevalence of progression in the liver provided the rationale for RTOG 1112 which adds local therapy (SBRT) to sorafenib. Despite this rationale, there are few retrospective or prospective studies on the combination of sorafenib or similar agents with RT. One retrospective review by Chi and colleagues in Taiwan of 23 patients with advanced HCC treated with RT to a median dose of 52.5 Gy in 15 fractions and sunitinib which is a TKI with a mechanism of action similar to sorafenib reported an objective response rate of 74%, a median survival of 16 months, and a 1-year survival rate of 70% (67).

Two additional phase I studies (one for patients with liver metastases and the other for those with HCC) combining 6 fractions SBRT plus dose-escalation of sorafenib have provided insight into how these treatments can be safely combined both in future clinical trials and in off-protocol clinical practice (68,69). In the HCC trial, 12 patients were evaluable for post-treatment toxicity after receiving continued sorafenib post-SBRT. There was no dose limiting toxicity (DLT) in the three evaluable HCC patients treated with SBRT with a low effective liver volume (Veff 30%) combined with 400 mg sorafenib. In patients with a liver Veff of 30-60%, 2 of 3 evaluable patients treated with sorafenib 400 mg daily developed DLT (grade 3 small bowel obstruction and grade 3 GI bleed); thus, sorafenib was de-escalated to 200 mg daily. In the liver metastases trial, there was no DLT among the 15 evaluable patients (3 at dose level 200 mg twice a day, 6 at dose level 600 mg and 6 at 800 mg for 4 weeks). In light of these data, sorafenib will be delivered following RT rather than concurrent with RT in RTOG 1112 to reduce the risk of toxicity (68,69).

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Footnote

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C-arm dual-phase cone-beam CT: a revolutionary real-time imaging modality to assess drug-eluting beads TACE success in liver cancer patients

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Abstract: The advent of cone-beam computed tomography (CBCT) in the angiography suite has been revolutionary in interventional radiology. CBCT offers 3 dimensions (3D) diagnostic imaging in the interventional suite and can enhance minimally-invasive therapy beyond the limitations of 2D angiography alone. The role of CBCT has been recognized in transcatheter arterial chemoembolization (TACE) treatment of liver cancer especially with the recent introduction of dual-phase CBCT (DP-CBCT) for unresectable hepatocellular carcinoma (HCC) treatment. Loffroy and colleagues proposed the use of intraprocedural C-arm DP-CBCT immediately after TACE with doxorubicin-eluting beads to predict HCC tumor response at 1-month magnetic resonance (MR) imaging follow-up. They reported a significant relationship between tumor enhancement seen at DP-CBCT after TACE and objective MR imaging response at 1-month follow-up, suggesting that DP-CBCT can be used to predict tumor response after TACE. If confirmed in larger studies, this imaging modality may play a key role in the improvement of treatment planning, especially with regard to the need for repeat treatment. More important, a potential clinical implication of using intraprocedural DP-CBCT in these patients might be elimination of 1-month follow-up MR imaging.

Keywords: Transcatheter arterial chemoembolization (TACE); hepatocellular carcinoma (HCC); dual-phase cone-beam computed tomography (CBCT); 3 dimensions (3D) roadmap; drug-eluting beads

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Liver cancer kills nearly 20,000 Americans each year, and is much more prevalent outside the United States, where it is among the top three causes of cancer death in the world (1). Experts cite the rising numbers of hepatitis C infections, which cause chronic liver inflammation and are a leading risk factor for hepatocellular carcinoma (HCC). Several studies and well-designed randomized trials have shown a positive effect of transcatheter arterial chemoembolization (TACE) on patient outcome and survival (2-6).

Early assessment of TACE effectiveness and monitoring

of tumor response are crucial for identifying failed procedures, guiding therapy, and determining the optimal interval for repeat treatments. Magnetic resonance imaging (MRI) and, far more rarely, computed tomography (CT) are used to assess response one to three months after follow-up using the Response Evaluation Criteria in Solid Tumors (RECIST) (7). However, assessment of anatomic response in the early post-treatment period can be misleading because the absence of a reduction in tumor size does not mean an absence of response and often does not correlate

with the degree of tumor necrosis (8). Consequently, a reduction in tumor enhancement at imaging has been used more accurately as a biomarker of tumor response. Imaging a month after the procedure with MR makes the results too late for intraprocedural modification, which is especially difficult when patients need repeat treatment. Post-TACE imaging with doxorubicin-eluting beads can be done with CT or MRI a day after the procedure, but a procedure that could predict tumor response at the time of treatment would be even better in as much as tumor response has been shown to be an independent predictor of survival (2).

Using two successive pairs of C-arm cone-beam CT (CBCT) scans, Loffroy and colleagues have recently produced real-time images of liver tumors dying from direct injection of anticancer drugs (doxorubicin-eluting beads) into the tumors and their surrounding blood vessels (9). Within a minute, the images showed whether the targeted chemotherapy did or did not choke off the tumors' blood supply and saved patients a month of worry about whether the TACE treatment, was working or not, and whether repeat or more powerful treatments were needed. Indeed, a dual-phase angiography procedure based on CBCT principles was used during TACE and predicted treatment response in HCC tumors long before MRI is traditionally applied at one-month follow-up.

In their study of patients with HCC, Loffroy and colleagues reported a significant relationship between tumor enhancement at angiography-based CBCT right after TACE and MR imaging response a month later, suggesting that the CBCT technique can be used to predict response without waiting for follow-up (9). They analyzed 50 HCC lesions in 29 patients who had undergone TACE after injecting beads loaded with 100 mg of doxorubicin hydrochloride (25 mg/mL) and mixed with an equal amount of nonionic contrast. All patients underwent the C-arm angiography-based CBCT technique (Allura Xper FD20, Philips Healthcare) before and immediately after TACE. This system was equipped with XperCT software that enabled CBCT-like acquisition and volumetric image reconstruction on a separate computer. The dual-phase CBCT (DP-CBCT) prototype feature, not yet commercially available, enables the XperCT option to be modified to obtain two sequential, back-to-back CBCT scans encompassing both early arterial and delayed or venous phases in a single contrast injection. CT tumor enhancement was evaluated retroactively by readers blinded to the MR results. The group used logistic regression models to compare tumor enhancement between modalities.

One-month follow-up imaging with MR showed complete or partial tumor response in 74% of lesions on the arterial phase and 76% in the venous phase. Paired t-test analysis showed significant reduction in tumor enhancement in both modalities ($P < 0.001$). The volume enhancement reductions correlated linearly with MR findings, with high estimated correlations for first ($k=0.89$) and second ($k=0.82$) phases. In addition, multilogistic regression showed a significant relationship between CBCT tumor enhancement after TACE and complete or partial tumor response at MR for arterial and venous phases.

Recently, C-arm CT has emerged as a new and widely used imaging technology in the angiography suite, enabling the acquisition of a 3 dimensions (3D) dataset generated from one rotational run with use of cone-beam CT principles. C-arm CT is enabling the acquisition of 3D datasets in a single rotation of the C-arm using CBCT, which can be used to examine tumor-feeding vessels and parenchymal stain during TACE procedures. Indeed, the role of CBCT has been recognized in TACE treatment of liver cancer especially with the recent introduction of DP-CBCT for unresectable HCC treatment. DP-CBCT can be used not only to localize liver tumors with the diagnostic accuracy of multidetector CT and MRI, but also to guide intraarterially guidewire and microcatheter to the desired location for selective therapy (10,11). A new development used by the authors allows two-phase images to be acquired with a single contrast injection with two sequential back-to-back acquisitions that show both arterial and venous phases rather than requiring two separate acquisitions and contrast injections (10-12). The newer DP-CBCT scans, in which X-rays are detected by a device the size of a large laptop that can be placed directly below or above the operating room table, have the added advantage of being performed in the same room, or interventional radiology suite, as patients getting TACE. In their new study, Loffroy and colleagues found that the initial shrinkage seen with DP-CBCT scans taken before and after TACE with drug-eluting-beads matched up almost perfectly with MRI scans taken a month later (9). Tumor death was 95 percent, the same as that seen by MRI. A total of 47 tumors were closely monitored in the study to assess how well DP-CBCT tracked tumor death after TACE. In DP-CBCT scanning, a chemical contrast dye is injected into the artery that supplies blood flow to the liver and tumor right before the chemotherapy drug is injected, to enhance the X-ray image. The first set of scans highlights key blood vessels feeding the tumor, as dye flows in and

out of the tumor. The second set of scans is performed immediately after TACE, to gauge tumor and key blood vessel death. Computer software is used to sharpen and analyze differences between the images. The entire DP-CBCT scanning time is between 20 and 30 seconds, and the total amount of radiation exposure from the dual scanning averages 3.08 mSv, which is less than half the amount of radiation involved in a modern abdominal 64-CT scan. Cone-beam CT scanners also emit an X-ray, but unlike other CT scanners, the cone-beam type of X-ray is projected onto one large, rectangular detector, roughly a foot and a half long and produces a telltale conical shape. The size of the CBCT detector allows for single scans that can capture images the size of most people's entire liver.

In their study, Loffroy and colleagues showed that intraprocedural DP-CBCT allowed monitoring and quantification of changes in tumor enhancement during TACE and assisted in accurate prediction of response to therapy (9). Early assessment of treatment response is important, especially in determining the need for repeat treatment, as previously said. Recent studies have demonstrated changes in vascular and cellular biomarkers including contrast enhancement and diffusion within hours after therapy, and these changes generally precede anatomic changes measured by RECIST guidelines (13,14). However, the optimum time for assessing TACE response remains unknown, with the results of two previous contrast-enhanced ultrasound studies favoring anywhere from two days to a week (15,16). Previous studies couldn't address whether changes in tumor enhancement at TACE could be used to predict response via European Association for Study of the Liver (EASL) guidelines, which this study accomplished with the use of integrated angiography and CBCT (8). Contrast enhancement is a reflection of cellular viability, where areas of tumor enhancement are considered viable and unenhanced regions reflect tissue necrosis. In comparison to other systems (angiography and MR units), this approach of using CBCT has the added advantage of being readily available in many practices internationally. And although the use of DP-CBCT didn't increase prediction of tumor response by more than a single acquisition in the arterial phase, the technique demonstrated tumor-feeding vessels in the early arterial phase and enhancing parenchyma in the delayed venous phase. The angiography-based DP-CBCT technique also gets by on one contrast injection rather than two using conventional techniques, saving contrast and reordering workflow to cut procedure time. The software allows

simultaneous comparison of MR to CT or pretreatment to post-treatment images. Furthermore, patients should not have to endure the uncertainty of waiting weeks or more to find out if their TACE treatment was successful in fighting their liver cancer. Dual-phase CBCT avoids such delays, which also could allow the cancer to grow and spread and, ultimately, compromise chances of remission. Avoiding delays is particularly important for people with moderate to advanced stages of the disease, when liver tumors are too large or too numerous to surgically remove, and for whom TACE is the main treatment option.

This new scanning method was allowed to give the interventional radiologists almost instant feedback about the value of injecting antitumor drugs directly into liver tumors and their surrounding blood vessels in an effort to quickly kill them, and to prevent the cancer from spreading. If further testing proves equally successful, the paired use of CBCT scans, which are already approved for single-scan use by the U.S. Food and Drug Administration, could supplant the current practice of MRI scanning a month after TACE to check its effects. This could be a real revolution in interventional radiology for liver cancer patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Proton therapy for hepatocellular carcinoma

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Abstract: Proton radiotherapy has seen an increasing role in the treatment of hepatocellular carcinoma (HCC). Historically, external beam radiotherapy has played a very limited role in HCC due to a high incidence of toxicity to surrounding normal structures. The ability to deliver a high dose of radiation to the tumor is a key factor in improving outcomes in HCC. Advances in photon radiotherapy have improved dose conformity and allowed dose escalation to the tumor. However, despite these advances there is still a large volume of normal liver that receives a considerable radiation dose during treatment. Proton beams do not have an exit dose along the beam path once they enter the body. The inherent physical attributes of proton radiotherapy offer a way to maximize tumor control via dose escalation while avoiding excessive radiation to the remaining liver, thus increasing biological effectiveness. In this review we discuss the physical attributes and rationale for proton radiotherapy in HCC. We also review recent literature regarding clinical outcomes of using proton radiotherapy for the treatment of HCC.

Keywords: Proton radiotherapy; hepatocellular carcinoma (HCC)

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Introduction

Hepatocellular carcinoma (HCC) is one of the most significant causes of cancer mortality worldwide (1,2). It generally has a poor prognosis as it is an aggressive tumor often found concomitantly in the setting of cirrhosis. The presence of cirrhosis, hepatitis B, and hepatitis C are key risk factors (3), but HCC is a complex disease involving many patient factors. There are several risk stratification systems which aim to address the challenge of determining prognosis and outcomes of HCC (4). Ultimately, HCC is a rapidly infiltrating malignancy with patients presenting with large, multifocal tumors with vessel invasion. Thus, there is a strong impetus to develop better methods of local treatment for HCC.

Treatment of HCC is most effective in the early stages of disease, but diagnosing early-stage HCC is often difficult since symptoms are vague. Surveillance programs are recommended for individuals with any of the aforementioned key risk factors (5-7) and diagnosis may

be established with biopsy or radiographic studies alone. Once the diagnosis of HCC has been established, surgical resection should be the first consideration as it has shown to provide the best long-term survival (8). Unfortunately, most HCC patients do not qualify for surgery due to a number of medical comorbidities. Nor do they meet the strict eligibility for liver transplantation. There is high morbidity and many HCC patients are too ill to tolerate these surgeries (9-11). Several other local treatments are available for unresectable HCC or for tumor down-staging while awaiting liver transplantation. Other ablative therapies include transarterial chemoembolization (TACE), alcohol injection, cryotherapy, radiofrequency ablation, and focused ultrasound therapy. Nonetheless, the patient suitability of each of these local therapy remains rather limited (12).

It is apparent that an effective local-regional therapy is needed which can be applied to a broad range of patients. The 5-year survival rate for patients diagnosed with HCC remains poor at approximately 3-5% (13). The role of

external beam radiotherapy has historically been considered ineffective for treating HCC because the doses of radiation necessary to cure HCC far exceeded liver tissue tolerance to radiation. There is accumulating evidence that dose escalation can improve both tumor response and survival in HCC patients (14,15). One particularly challenging aspect of HCC is the fact that radiotherapy is guided not only by the characteristics of the tumor but also by the function of the cirrhotic liver. Modern three-dimensional radiotherapy techniques have allowed clinicians to increase dose conformity while escalating dose to the tumor while sparing more normal liver, thus, largely avoiding radiation-induced liver disease (RILD). Several reports have shown that high-dose irradiation to a portion of the liver could be delivered safely with reasonable treatment efficacy (16,17). Charged particle therapy, in particular proton therapy, shows great promise in treating HCC since it allows for tumor dose escalation while sparing critical normal structures.

Characteristics of proton therapy

Proton therapy, among other charged-particle therapies, offers distinct dosimetric advantages in comparison to photon radiotherapy. The depth dose characteristics of these two beams are qualitatively different. Due to physical laws, photons are absorbed exponentially in a specific tissue whereas protons exhibit a finite range depending on the initial proton energy.

A proton beam loses its energy via coulombic interactions with electrons as it traverses tissue. The energy loss of a proton beam per unit path length is small until the end of the beam range. Near the end of the proton range the residual energy over the beam is lost over a very short distance and the beam itself comes to rest. This results in a distinctive sharp rise in the dose absorbed by the tissue, known as the “Bragg peak”. The low-dose region located between the Bragg peak and the beam entrance is called the “plateau”, with its dose being approximately 30% to 40% of the maximum dose.

The Bragg peak is narrow in nature. This poses a problem when it comes to irradiating larger targets. To overcome this, clinical proton beams are modulated to extend the length of the Bragg peak. Several beams of similar energy are closely spaced and superimposed to create a region of uniform dose over length of the target. These extended regions are called “spread-out Bragg peaks” (18).

The rationale for proton therapy in HCC

The above mentioned physical characteristics of proton

beams confer significant dosimetric advantages as compared to photon radiotherapy. The extent of scatter which accounts for lateral penumbra of the beam is less in proton beams when compared with photon beams. The dose delivered to tissues by a proton beam rises to a maximum value at a particular depth and then falls off exponentially to lower doses once the Bragg peak depth has been reached. This dosimetric advantage can be seen for each individual beam in a proton radiotherapy treatment plan. This allows for improvements in dose conformity and sparing of normal organs around the liver including the remaining uninvolved liver, heart, spinal cord, kidneys, bowel, and stomach. Proton radiotherapy is also able to completely spare one kidney more often than photon radiotherapy. More modern treatment techniques such as intensity-modulated proton therapy (IMPT) allow for more conformal high dose delivery while sparing nearby tissues at risk. Dose comparison studies have shown significantly reduced dose toxicity to regular tissues when compared to photon plans equivalent target coverage (19). IMPT has also demonstrated considerable sparing of normal liver tissue in comparison to photon-based intensity-modulated radiation therapy (IMRT) (20)

Dose conformity aside, proton radiotherapy delivers lower integral dose to tissue when compared to photon radiotherapy. Many HCC patients have severe liver disease with low functional reserve. Therefore, it is critical to limit the integral dose to the liver as much as possible. Modern photon therapy techniques such as intensity-modulated radiation therapy (IMRT) may achieve prescription conformity similar to that of a proton treatment plan, but the amount of dose scattered to the remainder of the liver is still higher owing to the physical nature of photon beams. There is evidence that normal liver function is significantly positively correlated to the percentage of normal that is not irradiated (21). Reduction of integral dose to remaining liver may help preserve liver function, decrease the risk of secondary malignancies, and also allow for future retreatment of the liver.

HCC radiation treatment planning with proton therapy

The unique physical properties of proton beams pose challenges not encountered in photon radiotherapy. Unlike photon beams, a distal beam edge must be defined for a proton beam. Since the majority of a proton beam's dose is delivered at the end of its range at the Bragg peak it is

crucial to define accurately where the beam stops. The use of compensators in the treatment gantry allows the physician to control the location of the beam's distal edge. A "smearing algorithm" is then applied to ensure dose coverage along the entire extent of the target region. However, due to variations in daily patient setup a certain amount of normal tissue beyond the distal extent of the target will receive some dose of radiation. At some institutions, 4-dimensional CT treatment planning is utilized which takes into account the patient's free breathing. One method is a breath-hold technique whereby the patient is asked to inhale deeply and hold his breath until the scan is complete. Other institutions apply a respiratory gating technique which maps a sinusoidal pattern of the patient's respiratory motion. The beam is then synced and turned during the same phase of each breathing cycle. Image acquisition during the portal venous and arterial enhancement phases may show differences in tumor and normal tissue attenuation. Thus, it is essential for each institution to develop a scanning protocol that allows for optimal target delineation (22).

The aforementioned variation in daily patient set-up and target motion is a challenge encountered in photon radiotherapy as well. However, range uncertainty is a unique problem encountered by proton radiotherapy. In the setting of external beam radiotherapy there is variable beam attenuation seen in the beam path. This occurs when the radiation beam traverses tissues of different density along its path. Proton beams deposit nearly all its energy within the tissue with very little exit dose. These range uncertainties stem from artifacts in computed tomography (CT) scans and errors in converting CT Hounsfield units into proton stopping power. These errors occur due to changes in organ motion during normal respiration or variations in daily set-up. For example, a high-density rib adjacent to air-filled lung moving into and out of the beam path during normal respiration creates uncertainty in the beam path. A similar phenomenon may be seen if the beam traverses loops of bowel which shift position each day. Ultimately, this range uncertainty may result in areas of target and normal tissues unexpectedly being overdosed or underdosed.

The relative biological effective (RBE) of proton beams, as compared with photons, is assigned a value of 1.1 by consensus at most institutions. This means that a physical dose of 1 Gy delivered using a proton beam is considered biologically equivalent to 1.1 Gy delivered using a photon beam. The assignment of relative biological effectiveness (RBE) is dependent on a number of biological endpoints which are often unpredictable (23,24). Because of this

unpredictability and the aforementioned issue of range uncertainty, beam arrangements are often selected so that they do not stop directly in front of critical organs or structures.

From a dosimetric standpoint, liver tumors have a benefit of being located within a relatively homogenous liver organ. There is less variable density within the liver itself. On that same note, however, dose conformity may be restricted if the beam angle selection is confined to only those that travel entirely through liver tissue. Doing so may also increase the integral dose delivered to the normal liver since the beam is traversing more normal liver tissue and the proximal extent of the beam is often less conformal than the distal extent. However, dose conformity with sparing of adjacent normal liver may lend itself to post treatment dosimetric verification utilizing CT changes in order to assess geometric accuracy of treatment delivery (25).

Dose constraint models for proton-based planning

The liver is a relatively radiosensitive organ which has a limited ability to tolerate the significant dose needed to control HCC. Radiation induced liver disease (RILD) is a clinically defined entity that occurs in the liver after being exposed to high doses of radiotherapy. It is associated with a 2- to 4-fold increase in hepatic enzymes, ascities, fatigue, and anicteric hepatomegaly. The normal tissue complication probability model for RILD developed at the University of Michigan has found widespread application in clinical practice. However, this model is based on RILD that arose in patients treated with hyperfractionated photon radiotherapy (26). Many proton radiotherapy protocols for HCC utilize hypofractionated treatment regimens which are not well-represented by this model.

Another biological model based on the equivalent uniform dose (EUD) was developed by the proton radiotherapy group at Massachusetts General Hospital (27). In this model the 2-dimensional information from the dose-volume histogram (DVH) of inhomogeneously irradiated liver is expressed as a single dose value. The EUD expresses mean dose while taking into account volume irradiated. Early application of this model found tumor dose escalation to be limited by adjacent non-liver normal tissues, such as biliary stenosis, rather than liver toxicity.

Aside from reducing the risk of RILD, patients with cirrhosis often undergo advancement of their Child-Pugh score after a course of radiotherapy to the liver. This

portends to worse outcomes and decreased quality of life. The volume of normal liver sparing has been associated with a decreased risk of advancing Child-Pugh class in cirrhotic patients (28). Other structures in the beam path such as ribs post a risk of late post-radiotherapy complication. Rib fracture has been reported as a late complication following external beam radiotherapy. One series looked at 310 ribs which were irradiated during a course of hypofractionated proton radiotherapy (29). Twenty-seven (8.7%) of these irradiated patients developed rib fracture. The volume of rib receiving at least 60 Gy (V60) was found to be the most statistically significant parameter predicting late rib fractures. Other parameters which were found useful for estimating rib fracture risk were V30, V120, and maximum dose (Dmax) to a point.

There are also reports of a two-step surgical treatment which involves the surgical placement of a spacer into the gastrointestinal tract (30). The intent of the spacer is to create a firm, reproducible separation between the radiation target and adjacent normal tissues. Of course, placement of this spacer as a second surgery will expose the patient to the additional risks also seen in other surgeries. The variety of tissue-sparing precautions selected for any individual patient must take into account medical comorbidities and underlying conditions. Nonetheless, it is evident that great care must be taken while finding ways to assess and limit normal organ toxicity during hypofractionated proton radiotherapy.

Clinical outcomes of HCC treated with proton radiotherapy

Many of the studies looking at the use of proton radiotherapy in liver tumors were performed in Asia (31). One of the first large retrospective series was presented by Chiba *et al.* (32). In this series 162 patients were treated with proton radiotherapy, all treatments delivered with hypofractionated regimens (3.5-5 CGE) with total doses ranging from 50 CGE (10 fractions) to 84 CGE (24 fractions) with a median dose of 72 CGE in 16 fractions over 29 days. Portal vein thrombus was seen in 25 patients (15%). At a median follow-up interval of 31.7 months, the 5-year local control rate was 86.9% and overall survival rate was 23.5%. However, over 50% of deaths were due to complications from cirrhosis rather than tumor progression. The acute side effects in this study were limited primarily to liver enzyme elevation. Only 3% of the patients experienced grade 2 or higher late toxicity. Several recent retrospective

studies show similar overall survival and local control rates in a similar population (33,34).

More recently, Komatsu *et al.* reported on the retrospective review of 343 consecutive patients with HCC treated at the Hyogo Ion Beam Medical Center with proton or carbon ion therapies (35). For the 285 patients for which both proton and carbon ion beams were available, treatment planning with both modalities were performed and the better treatment plan was selected based on dosimetric criteria. A total of 242 patients were treated with proton therapy using 8 different dose and fractionation protocols from 2001-2009. Pooled results show for proton therapy show 5 year local control rates of 90.2% with 5 year overall survival of 38%. Results of carbon ion therapy appear non-inferior, but limitations with treatment delivery resulted in the majority of patients (66%) being treated with proton therapy.

Patients with portal venous thrombosis may especially benefit from the dosimetric advantages offered by proton radiotherapy. Larger volumes of liver often need to be irradiated in the setting of portal venous thrombosis. Many of these patients have poor functional reserve remaining in the liver and photon therapy may result in unacceptable toxicity. A series of 35 patients with HCC portal venous thrombosis received treatment of 50 to 72 CGE which resulted in local control rates of over 45% at 2 years. Only 3 of these patients developed severe acute toxicity (36). The excellent conformality of proton beams may open up the possibilities for retreatment in the case of HCC progression or for synchronous tumors arising elsewhere in the liver. The Tsukuba proton radiotherapy group has reported on the efficacy, feasibility, and safety of HCC retreatment in a series of 27 patients with 68 total lesions (37). The median dose delivered was 66 CGE in 16 fractions with a median time interval of 24 months between the first and second course of treatment. They reported a 5-year local control rate of 87.8% and 5-year overall survival rate of 56%.

As mentioned before, cirrhotic patients have very little functional reserve in the liver and are at high risk for hepatic insufficiency. A study examining proton therapy in HCC showed correlation with grade of cirrhosis and toxicity. One third of the patients in this study had Child-Pugh class B cirrhosis with a 40% rate of grade 3 toxicity and 27% of patients eventually developing hepatic insufficiency (38). Damage to the alimentary tract is another cause of great concern as the doses necessary to control HCC are high and often greater than bowel tolerance. One series of 47 patients with HCC located within 2 cm of the alimentary

tract underwent treatment of 72.6 CGE in 22 fractions or 77 CGE in 35 fractions (39). After a median follow-up period of 23 months the overall survival was 50% and progression free survival 88.1%. Grade 2 and 3 alimentary tract hemorrhage was observed in 6.4% and 2.1% of patients, respectively. Beams were edited off of bowel in this study to avoid excess radiation delivered to the alimentary tract.

Prospective data for the use of proton radiotherapy in HCC is rather limited. One randomized study from Japan looking at 30 patients with local HCC reported a 3 year overall survival rate of 62% and local control rate of 95%. All tumors in this study did not invade into the gastrointestinal tract. Well-compensated hepatitis C was present in 90% of the patients with bilirubin <3.0 mg/dL. The dose delivered was 76 CGE in 20 fractions to the tumors which were entirely encompassed within the target volume (38). Another more recent randomized study of 51 patients in Japan reported a 5 year overall survival of 38.7% and local control of 87.8%. A dosing scheme of 66 CGE in 10 fractions was delivered to the tumor. This study included larger tumors as well as patients with symptomatic hepatitis C infections. Approximately two-thirds of the patients in this study had received prior local therapy as well (40).

One of the larger prospective studies was a phase II trial examining outcomes of proton radiotherapy in HCC patients with cirrhosis demonstrated a 66% 2-year overall survival rate after delivering 76 CGE in 3.8 CGE daily fractions (36). Loma Linda University reported results of the largest prospective phase II trial describing the use of proton radiotherapy in patients with HCC. Patients without cirrhosis, with extrahepatic metastases, tense ascites, or greater than 3 liver lesions were excluded. Patients were eligible regardless of tumor size, transplant candidacy, or alpha-fetoprotein (AFP) level. All patients had documented stability of ascites. Fluctuating levels of ascites could impact treatment planning by altering the path of beam attenuation. Shifting fluid content during the course of treatment due procedures such as a paracentesis would affect the targeting of treatment volumes. As such, all patients were required to have documented stability of ascitic fluid levels prior to treatment. Preliminary results were initially reported with 34 cases of unresectable HCC were treated with 63 CGE in 15 fractions (41). The 2-year overall survival rate was 55% and the local control rate was 75%. Mild acute radiation-induced toxicity was noted in 60% of patients but no radiation induced liver disease (RILD) was observed. Patients continued to be enrolled on this trial

and updated results were recently reported (42). In this report, 42 additional patients were accrued for a total of 76 evaluable patients. Median progression-free survival for the entire group was 36 months, with a 60% 3-year progression free survival in patients within the Milan criteria. Eighteen patients subsequently underwent liver transplantation, with 6 explants showing complete pathological complete response and 7 explants showing only microscopic residual. The overall survival rate was significantly better in patients receiving liver transplant in comparison to those who did not, 70% vs. 10%, respectively.

Post treatment toxicity was minimal with no patients exhibiting RILD or significant changes in MELD scores. Grade 2 GI toxicity was noted in 5 patients with GI bleeding and/or endoscopic evidence of ulceration. All cases were managed medically without surgical intervention. All 5 cases were observed in the first 30 patients as greater care was taken to reduce field margins when tumors occurred adjacent to the bowel after the toxicities were observed. Overall, this is the largest prospective study reported with extensive follow-up that shows that proton therapy is safe and effective for the treatment of HCC. A randomized control trial is underway, comparing proton therapy to transarterial chemoembolization.

Overall, proton radiotherapy has demonstrated some of the most promising outcomes in terms of HCC treatment. The potential for toxicity in treating HCC is highly variable based on the location of the tumor within the liver and baseline liver function. The dosimetric advantages seen with proton radiotherapy appear to allow more feasible tumor dose escalation.

Conclusions

Historically, radiation therapy did not play a prominent role in HCC treatment. Earlier radiation techniques often delivered substantial doses to the liver causing a high incidence of RILD. The liver has a rather limited ability to tolerate substantial doses of radiation. Computerized and three-dimensional treatment planning has allowed better dose conformity thus allowing dose escalation to the tumor. The distinctive physical properties of proton beams confer unique advantages over photon radiotherapy. Many HCC patients have a number of morbidities which make them non-candidates for surgical resection or transplantation. The excellent toxicity profiles and durable in-field local control rates make proton radiotherapy an attractive option for localized HCC.

In principle, it is likely that the greater sparing of uninvolved liver using proton radiotherapy may be safer in patients with cirrhosis or poor liver reserve. The importance of normal liver-sparing is also evident in patients with portal venous thrombosis, since they often require greater volumes of liver to be irradiated. Centrally located lesions or lesions located near critical structures such as vessels may be especially suitable for proton radiotherapy. Proton radiotherapy is becoming increasingly available globally. Nearly 30 clinical proton radiotherapy facilities have been established worldwide. The integration of proton radiotherapy into treatment algorithms requires a great deal of multidisciplinary collaboration and highly individualized optimization for each patient. Nevertheless, there is accumulating evidence demonstrating the safety and efficacy of proton radiotherapy for liver-directed HCC therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Systemic therapy for hepatocellular carcinoma

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Abstract: The prognosis is poor for patients with advanced hepatocellular carcinoma (HCC). Sorafenib is the only accepted standard of care for advanced disease. The benefits of this agent are modest and the precise mechanism of antitumor activity in HCC is unknown. Since the approval of sorafenib, there has been intense investigation into strategies that block angiogenic pathways. Unfortunately, the results of three randomized phase III trials that compared newer anti-angiogenic treatments to sorafenib failed to demonstrate their superiority or non-inferiority. Thus, there remains a critical need for both continued molecular characterization and aggressive drug development in hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma (HCC); hepatocarcinogenesis; sorafenib; anti-angiogenic therapy; drug development

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Introduction

Historically, several therapeutic strategies for the treatment of advanced hepatocellular carcinoma (HCC) have been studied; however, no approach has resulted in an improvement in patient outcomes (1). In the last decade, intensive investigation into the molecular pathogenesis of liver cancer has led to new mechanistic insight, particularly regarding the angiogenic dependence of HCC (2). This has resulted in the successful clinical development of the sorafenib, a multi-kinase inhibitor (3). The success of sorafenib has galvanized the global medical research community, and currently, there are approximately 60 small molecule targeted therapeutics in various stages of clinical development, and over 200 ongoing or completed advanced HCC specific clinical trials worldwide (www.clinicaltrials.gov). Despite these advancements, several critical questions and challenges remain for HCC treatment and drug development. In this manuscript, we will conduct a brief review of the molecular pathogenesis of HCC followed by a discussion of development of anti-angiogenic therapy in this disease. Remaining clinical and translational research questions as well as the challenges of clinical trial design in

context of HCC will also be highlighted herein.

Molecular and cellular biology of hepatocellular carcinoma

Hepatocarcinogenesis is a complex, multistep process whereby recurrent hepatic injury results in the accumulation of aberrant genomic, chromosomal, and epigenetic events (4). Such events define the malignant phenotype; activate numerous developmental pathways and signal transduction cascades; disrupt cell-cycle checkpoints and normal apoptotic pathways; and lead to uncontrolled cellular proliferation, growth, survival, and angiogenesis (5).

The WNT/ β -catenin pathway, a tightly regulated signaling cascade in normal embryogenesis and hepatocyte differentiation, is heavily dysregulated in HCC (*Figure 1*). Activating somatic mutations within in the gene encoding β -catenin, *CTNNB1* (~30%), or in mutually exclusive inactivating mutations in *AXIN1* (~15%) or *APC* (~2%) have been observed by numerous investigators (6-11). High level chromosomal imbalances also occur on several loci that contain genes known to modulate WNT signaling (i.e., *FZD3*, *WISP1*, *SLAH-1* and *AXIN2*) (12).

Furthermore, overexpression of *FZD7*, a component of Frizzled (i.e., the WNT receptor), is observed in up 90% of HCC human tumors (13). The functional consequences of global changes in this pathway as well as the individual contributions of each alteration to tumorigenicity require more detailed characterization. However, it is clear that a large subset (up to 50%) of HCC is characterized by functional WNT pathway activation, and that such aberrant signaling, in part, drives HCC proliferation and growth (14,15). Other developmental pathways are implicated in hepatocarcinogenesis and these include the hedgehog (16), notch (17), and the c-MET proto-oncogene/hepatocyte growth factor receptor (HGF) pathways (18,19).

Mitogen-activated signaling cascades are also critical in HCC biology; however, unlike other malignancies, driver mutations in these pathways do not occur at a high frequency (9-11). The phosphatidylinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) (14,20), and classic mitogen-activated protein kinase (MAPK) (21-23) pathways are activated in HCC (*Figure 1*). Blockade of these individual signaling cascades suppresses tumor growth *in vitro* and *in vivo* (24). Importantly, overproduction of mitogens [i.e., vascular endothelial growth factor (VEGF), and platelet derived growth factor (PDGF)] by the tumor and the surrounding cirrhotic microenvironment serves to sustain the neoplastic clone, drive downstream signaling cascades, and stimulate neo-angiogenesis (2). Over-expression and/or activation of the receptor tyrosine kinases linked to these oncogenic pathways, including the epidermal growth factor receptor (EGFR) (18), VEGFR-1/-2/-3 (25-27), PDGFR (19), insulin-like growth factor receptor (IGFR) (28), and fibroblast growth factor receptor (FGFR) (29) are frequent in HCC. Finally, impairment of negative regulators of growth factor-dependent signaling, such as decreased PTEN activity in the case of PI3K-AKT-mTOR pathway, serves to further deregulate normal signals for growth and cell survival (30).

Evasion of normal apoptotic mechanisms and cell-cycle checkpoints by HCC also promote cancer formation and progression. Transforming growth factor (TGF)- β , via the SMAD proteins and other downstream effectors, exhibits potent anti-proliferative properties in normal hepatocytes (*Figure 1*) (31). Alterations in this pathway, particularly loss of SMAD4, can result in escape of the growth inhibitory properties of TGF- β (32). In this setting, TGF- β paradoxically promotes growth, invasion, and angiogenesis, and induces epithelial-mesenchymal

transition (31). *TP53*, a tumor suppressor gene and cell-cycle checkpoint, is inactivated by somatic mutation in up to 50% of HCC (9,10). Further, impairment of *RBI/p16* function, which limits cell replication in the setting of DNA damage, is suppressed by promotor hypermethylation and other mechanisms in a majority of tested tumors (33). Finally, alterations in epigenetic modifiers (*ARID1/2*, *MLL*, *MLL3* and others) (10,11) and mutations within non-coding regulator promoters (*TERT*) (10,34) are common and the implications of these changes are only now being explored.

Moving forward continued molecular characterization of HCC will likely clarify the consequences of the above alterations and give insight into new therapeutic targets and novel combination strategies. Although targeting WNT appears to be priority in HCC, “drugging” this pathway has been difficult and we are only now seeing these compounds entering phase I clinical trials. Agents predicted to impair HCC growth, specifically by blocking VEGF signaling and other related mitogen-activated signal transduction cascades, have been extensively studied. The ensuing discussion will focus on the successes, failures, and ongoing studies in this area.

Inhibition of angiogenesis

Sorafenib

Sorafenib is a small molecule that targets tumoral angiogenesis and neoplastic proliferation leading to tumor-cell apoptosis in preclinical models (35). Its anti-angiogenic effects are thought to be mediated by blockade of VEGFR-2/-3, PDGFR- β , and other receptor tyrosine kinases. The compound also appears to inhibit the RAF kinases, critical components of the MAPK pathway, in both biochemical and cellular experimental systems. Given that the molecular pathogenesis of HCC is dependent upon both exuberant angiogenesis mediated, in part, by VEGF (2), and aberrant MAPK signaling (21-23), strong preclinical rationale exists for sorafenib as a therapy in HCC. Several clinical trials established the utility of sorafenib in this disease, and as such, the European Commission and the United States Food and Drug Administration licensed it for the treatment of advanced HCC in 2007 (3,36-39). In the subsequent year, the State Food and Drug Administration of China and other international agencies approved sorafenib for the same indication.

The clinical efficacy of sorafenib in HCC was firmly established by a multicenter phase II study (3). One-

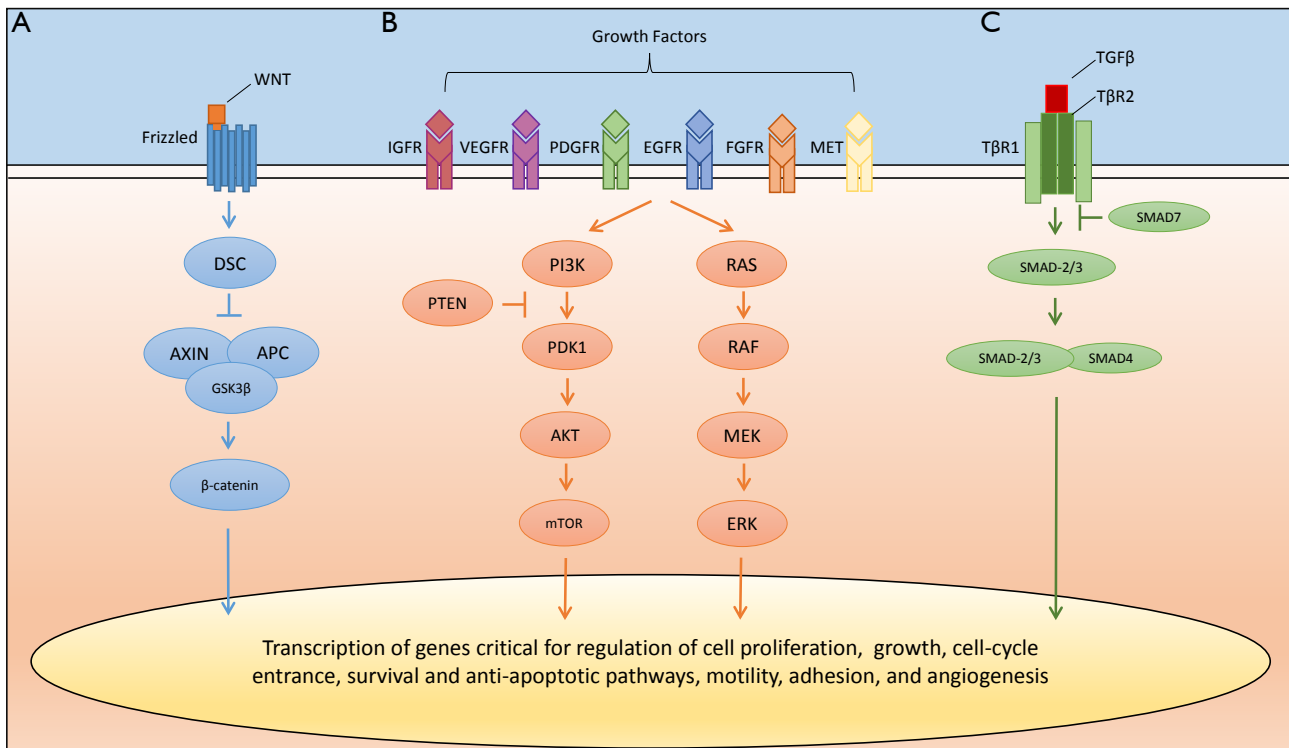


Figure 1 Schematic of signal transduction cascades relevant to hepatocellular carcinoma biology. The WNT/ β -catenin, PI3K-AKT-mTOR, MAPK and TGF- β pathways are heavily disrupted in HCC. (A) In canonical WNT/ β -catenin signaling, engagement of the WNT receptor, Frizzled, leads to the activation of disheveled (DSC). Once activated DSC inhibits the β -catenin destruction complex, which is composed of Axin, adenomatosis polyposis coli (APC), glycogen synthase kinase 3 β (GSK3 β), and other regulatory molecules. In this setting β -catenin avoids ubiquitination and subsequent proteasome digestion thereby allowing it to translocate to the nucleus to activate numerous regulatory genes; (B) MAPK and PI3K-AKT-mTOR pathway activation is complex and signal modulation between each pathway is well documented. In physiologic circumstances, external growth factors engage the appropriate receptor tyrosine kinase (RTK) embedded in the phospholipid bilayer at the cell surface. Ligand binding leads to dimerization of the RTK followed by transphosphorylation of the cytoplasmic components of the receptor. The phosphorylated cytoplasmic tail recruits a variety of accessory molecules. In the case of the MAPK pathway, sequential activation of RAS, RAF, MEK, and ERK ensues leading to the modification of a number of substrates (i.e., Cyclin D, Myc, Elk, etc.) that in turn regulate protein synthesis, transcription and entrance into the cell cycle. In the PI3K-AKT-mTOR pathway, activation of the RTK leads to sequential modification of phosphatidyl inositol residues in phospholipid bilayer. In the terminal step of this enzymatic process, PI3K generates phosphatidyl inositol (3-5) triphosphate (PIP3). PIP3 recruits AKT to the cell membrane and in association with PDK1 activates AKT. AKT then modulates the activity of a number of downstream substrates including mTOR, thus promoting angiogenesis, proliferation and cell survival. By reversing the effects of PI3K, PTEN is a negative regulator of this pathway; (C) The end result of canonical TGF- β signaling in normal circumstances is to prevent proliferation. Isoforms of TGF β engage the TGF β receptor type 2 (T β R2) dimer at the cell surface. This in turn leads to recruitment and phosphorylation of the TGF β receptor type-1 (T β R1). Subsequent phosphorylation of SMAD-2/3 proteins alters their conformational structure allowing complexing with SMAD4 and translocation to the nucleus. Here, the SMAD-2/3/4 complex causes the transcription of a number of genes necessary for apoptosis, cell-cycle arrest, and extracellular matrix formation. SMAD7, a product of TGF β signaling is an important negative regulator of this pathway.

hundred and thirty-seven patients with systemic treatment-naïve, inoperable HCC and varying hepatic reserve (72% Child-Pugh A, 28% Child-Pugh B) received the agent. The primary objective of the study was to determine the

objective response rate to sorafenib, and the predefined boundary to establish cytotoxic efficacy was set at a 7% confirmed response rate. Although only 2.2% of the study population achieved a confirmed objective response by

Table 1 SHARP and Asia-Pacific studies patient outcome and response metrics

Response metric	SHARP		Asia-Pacific	
	Placebo (n=303)	Sorafenib (n=299)	Placebo (n=76)	Sorafenib (n=150)
Response rate				
Complete response	-	-	-	-
Partial response	1%	2%	1.3%	3.3%
Stable disease	67%	71%	27.6%	54.0%
Progressive disease	-	-	54.0%	30.7%
Disease control rate	32%	43%	12%	53%
TTRP (months)	2.8	5.5	1.4	2.8
TTSP* (months)	4.1	4.9	3.4	3.5
Median OS (months)	7.9	10.7	4.2	6.5
1-year survival rate	33%	44%	-	-
Hazard ratio for survival	0.69 (CI: 0.55-0.87)		0.68 (CI: 0.50- 0.93)	

Abbreviations: TTRP, time to radiographic progression; TTSP, time to symptomatic progression; OS, overall survival; CI, confidence interval.

WHO criteria, 42% percent of the study population had extended disease control. The median overall survival was 9.2 months, which was encouraging when compared to historical controls. A second study composed exclusively of an Asian population obtained similar favorable results (37).

Subsequently, two pivotal, multicenter, double-blind, placebo-controlled, randomized phase III studies of sorafenib versus best supportive care in patients with advanced HCC demonstrated a statistically significant improvement in overall survival in favor of sorafenib (*Table 1*) (38,39). The SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial enrolled 602 patients with advanced HCC who had not received prior systemic therapy (39). The majority of the study population, which was recruited predominately from Europe and Australasia, had HCC with macroscopic vascular invasion, extrahepatic spread or both. Preserved liver function was a strict inclusion criterion of the study, and in fact, only 3.3% of participants had Child Pugh class B hepatic function. HCC etiologic factors were well distributed amongst participants with roughly 28%, 26%, and 18% of cases related to HCV, alcohol, and HBV, respectively. Patients were randomly assigned to receive sorafenib at 400 mg orally twice a day (n=299) or best supportive care (n=303). The co-primary endpoints of the study were overall survival and time to symptomatic progression. Sorafenib rarely resulted in tumor shrinkage; however, the agent was associated with an absolute increase in the disease control rate of 11% when compared with placebo. This cytostatic effect translated

to a statistically significant longer time to radiographic progression and an absolute 11% increase in the 1-year survival rate. Median overall survival was 10.7 months in the sorafenib arm versus 7.9 months in the cohort receiving best supportive care (HR=0.69, 95% CI: 0.55-0.87). Predefined subset analysis indicated that the survival benefit of sorafenib was independent of performance status and disease burden.

Designed in parallel with SHARP, the Asia-Pacific study assessed the efficacy and tolerability of sorafenib in comparison with best supportive care in the patients with advanced HCC geographically localized to Republic of Korea, and China including Taiwan (38). The study was therefore well positioned to assess the potential impact of known regional differences in HCC etiologic factors on responsiveness to treatment. By providing a closer representation of the worldwide HCC patient population, the Asia-Pacific study also minimizes theoretical confounding factors (e.g., environmental aflatoxin exposure, socioeconomic variables, etc.) that might be unique to Asia and not adequately represented by the SHARP study population. As expected and in contrast to SHARP, the Asia-Pacific study was enriched with patients with HBV-related HCC (73% of the total study population), and in general, was compromised of a greater proportion of patients with poorer ECOG performance status and greater disease burden. Despite these differences, the trial confirmed that sorafenib, when compared to best supportive care, was tolerable and led to a statistically significant improvement

in disease control, time to radiographic progression, and overall survival.

It is important to note that the magnitude of the overall survival benefit on the Asia-Pacific study was not as substantial as observed on the SHARP study—the median overall survival was only 6.5 and 4.2 months for patients receiving sorafenib and placebo, respectively. The inclusion of patients who were more ill prior to beginning therapy than those patients on the SHARP study might, partly or even fully, explain this slight survival difference. Another postulate is that the observed differential outcomes on the two trials were due to differing treatment patterns between Asia and Western countries. Aggressive local regional therapies might be more common in Asia, thus leading to the selection of patients on the Asia-Pacific study who are presenting later in the course of their disease. The inclusion criteria for the Asia-Pacific study; however, do not necessarily support this assertion. Alternatively and provocatively, specific viral etiologic factor might affect prognosis and influence the responsiveness of liver cancer to sorafenib.

In an unplanned subset analysis of the SHARP study, patients with HBV-related HCC (n=60) who were treated with sorafenib had a modest prolongation in median overall survival over placebo (9.7 *vs.* 6.1 months) but similar disease control rates (34.4% *vs.* 32.1%) and near equivalent time to progression (2.7 *vs.* 4.2 months) (40). In contrast, HCV-related HCC patients (n=167) treated with sorafenib appeared to derive much greater clinical benefit, with substantial improvements over placebo in overall survival (14.0 *vs.* 7.4 months), disease control rates (44.2% *vs.* 29.6%), and time to progression (7.6 *vs.* 2.8 months). Retrospective analysis of initial phase II study of sorafenib observed similar etiologic-dependent trends in survival (41). Patients who were infected with HCV lived longer (n=13, 12.4 months) than did patients infected with HBV (n=33, 7.3 months, P=0.29). Finally, the recently reported phase III study of first-line sunitinib indicates that there may in fact be differential outcomes relative to disease cause and ethnic origin, with median overall survival for HCV-associated HCC ranging from 18.3 months for patients with living outside of Asia to 7.9 months for patients living in Asia (42).

A caveat to drawing a firm conclusion on the matter of variable sensitivity to sorafenib is that sample size is small and *ad hoc* subgroup analyses are notoriously subject to confounding secondary to population imbalance. Certainly if differentially, antitumor activity exists, etiologic-dependent genomic differences in HCC might explain

improved outcomes to sorafenib in patients with HCV-related HCC. *CTNNB1* mutations are more commonly observed in HCV-related but not in HBV-related HCC and are associated with a specific WNT gene expression profile (9,14,15). Sorafenib can modulate this gene signature, interfere with WNT signaling output, and lead to HCC growth suppression in preclinical models (15). Etiologic-dependent differences in outcome might also be explained by HCV core protein-induced upregulation of the sorafenib target CRAF, among other kinases (43). Finally, *in vitro* data suggest that sorafenib can directly inhibit HCV viral replication, though the clinical importance of this observation is debatable (44). Although more exploration is certainly required, it should be emphasized that the utility of sorafenib is not undercut by this observation and it remains an effective and life prolonging therapy for HCC, irrespective of etiologic factor.

Sorafenib combination strategies

In the attempt to improve upon the modest results observed with sorafenib, investigators have proposed combination strategies with cytotoxic chemotherapy and novel biologic agents. Prior to the approval of sorafenib, doxorubicin was evaluated as monotherapy or in combination with sorafenib in a randomized, double blind, phase II study (45). The trial enrolled 96 patients with treatment-naïve advanced HCC and Child-Pugh A liver function. The primary endpoint of the study was time to progression. Importantly, both time to progression, as determined by independent review, and progression-free survival were increased by approximately 4 months, and the median overall survival doubled in favor of combined therapy (13.7 *vs.* 6.5 months, P=0.006). Cardiac toxicity was notable, with a higher proportion of patients on the combination experiencing left ventricular systolic dysfunction (19% *vs.* 2%). Although the majority of such cases were asymptomatic, the median cumulative doxorubicin dose was limited to 165 mg/m².

The dramatic increase in survival over placebo was striking; however, the lack of sorafenib as a comparator arm limits the interpretation of the trial. Doxorubicin may contribute little to outcome. The observed benefit in the doxorubicin-sorafenib group may be due to the effects of sorafenib alone. Alternatively, the combination may be synergistic. Inhibition of the MAPK pathway by sorafenib may restore chemosensitivity by enhancing pro-apoptotic pathways and dampening multi-drug resistance (MDR) pathways. Anthracycline-induced cytotoxicity is mediated

by the pro-apoptotic kinase ASK1 (46). Growth factor-induced MAPK activation, via FGF, has been shown to abrogate ASK1 activity. Blockade of the RAF kinases by sorafenib might therefore augment the antitumor activity of doxorubicin. Furthermore, MAPK activation leads to the induction of MDR-1 pump (47). Sorafenib decreases ATP-binding cassette/MDR protein gene expression thereby restoring HCC sensitivity to doxorubicin *in vitro* (48). A randomized phase III study of sorafenib versus sorafenib and doxorubicin in the first-line setting (www.clinicaltrials.gov NCT01015833) and a phase II study of the regimen in second-line setting after sorafenib failure (www.clinicaltrials.gov NCT01840592) are currently underway.

Gemcitabine and oxaliplatin (GEMOX) therapy has established efficacy in HCC (49), and there is reason to believe that addition of sorafenib to gemcitabine might offer synergistic anti-tumor effects (48). GEMOX-sorafenib versus sorafenib was recently tested in a randomized phase II study (GONEXT) (50). The trial enrolled 95 patients with advanced HCC (CLIP 52% 2/3), excellent performance status (69% WHO PS 0), and Child-Pugh A liver function. The primary endpoint was 4-month progression-free survival of greater than or equal to 50%. The combination of GEMOX plus sorafenib resulted in a 4-month PFS rate of 61% compared to 54% in sorafenib monotherapy group. The combination was feasible and efficacy data were encouraging (ORR 16%, DCR 77%), though grade 3/4 neutropenia, fatigue, thrombocytopenia, diarrhea, and sensory neuropathy were common. More data will be required to define the role of this sorafenib combination strategy in HCC. In addition, several other trials are evaluating sorafenib in combination with other forms of cytotoxic chemotherapy.

In addition to its application with anti-angiogenic agents such as bevacizumab, sorafenib is being combined with antisense technologies; receptors tyrosine kinase inhibitors and monoclonal antibodies blocking EGFR, c-MET, FGFR and IGFR; multiple small molecule inhibitors of the MAPK and PI3K-AKT-mTOR pathways; histone deacetylase inhibitors; and novel immune-based therapies. The majority of these biologic combinations are still in early drug development and it is premature to comment on how they might improve upon sorafenib, though emerging data are promising and there remains enthusiasm for drug development in this area.

Erlotinib, an EGFR tyrosine kinase inhibitor, and sorafenib are the first novel pairing to reach later stages of clinical development. Although there is a theoretical

benefit to blocking both EGFR and VEGFR in HCC, the addition of erlotinib to sorafenib did not produce additive or synergistic effects *in vitro* or *in vivo* (51). A phase I study that evaluated sorafenib and erlotinib in 17 patients with various solid tumors, included a single case of HCC (52). This patient received the recommended phase II dose and had a best overall response of stable disease with ~5% tumor growth on study. In an extension cohort of this trial, an additional evaluable HCC patient progressed after 75 days of combination therapy (53). The SEARCH trial confirmed that the addition of erlotinib to sorafenib provided no benefit in HCC (54). In this randomized, placebo controlled, double blind, phase III study the combination of sorafenib and erlotinib were compared to sorafenib alone in the first-line setting in 720 patients with advanced HCC. There was no statistically significant difference between study arms with regard to the primary endpoint of overall survival (combination 9.5 months, sorafenib 8.5 months, HR=0.93, 95% CI: 0.78-1.11).

Multi-targeted receptor tyrosine kinase inhibitors

Several small molecule, orally available, receptor tyrosine kinase inhibitors with the ability to inhibit VEGFR, and other kinases, have undergone extensive evaluation or are being tested in clinical trials of varying stages for the treatment of advanced HCC. These agents include sunitinib, axitinib, regorafenib, brivanib, linifanib, vandetanib, cediranib, pazopanib, TSU-68, vatalanib, and lenvatinib. Thus far, emerging results have been disappointing with the major phase III studies of anti-angiogenic therapy failing to improve upon sorafenib in the first-line setting, and no clear benefit over best supportive care of additional anti-angiogenic monotherapy in the second-line setting.

Sunitinib inhibits VEGFR-1/-2 with greater potency than sorafenib (55). Additionally, the agent targets PDGFR- α/β , c-KIT, FLT3, RET, and other kinases. Three separate phase II studies of sunitinib evaluated three different dosing schedules of the agent as a treatment for advanced HCC (56-58). A subsequent randomized phase III study of sunitinib, dosed continuously, versus sorafenib in patients with advanced HCC and Child Pugh Class A liver function was initiated and rapidly enrolled 1,073 patients (42). The study, powered to test the dual hypotheses of non-inferiority and superiority with regard to overall survival, was halted by an independent data monitoring committee due to futility and safety concerns. Median overall survival

for the sunitinib cohort was 8.1 months as compared to 10 months in sorafenib arm (HR=1.31, 95% CI: 1.13-1.52, P=0.0019). Axitinib and regorafenib, which inhibit similar molecular targets to both sunitinib and sorafenib but exhibit a slightly different spectrum of toxicities, are now being evaluated as monotherapy after progression on sorafenib (www.clinicaltrials.gov NCT01334112, NCT01273662, NCT01210495, and NCT01774344).

Brivanib, a dual inhibitor of VEGFR and FGFR, demonstrated modest antitumor activity in both treatment-naïve and those patients who had failed prior anti-angiogenic therapy in two separate phase II studies (59,60). Based on these data, a large randomized phase III study compared brivanib to sorafenib in patients with systemic treatment-naïve, advanced HCC (61). This non-inferiority trial did not meet its primary endpoint; median overall survival with brivanib treatment was 9.5 *vs.* 9.9 months with sorafenib (HR=1.06, 95% CI: 0.93-1.22, P=0.3730). Albeit, antitumor activity and disease control rates were similar between each group. A randomized phase III study of brivanib after progression of disease on sorafenib versus best supportive care also failed to meet its primary endpoint of improved overall survival (62).

Linifanib, a selective inhibitor of VEGFR and PDGFR (63), also failed to improve upon the modest survival advantage of sorafenib (64). Early efficacy data were encouraging (65); however, these results did not translate into success in a large multicenter, randomized, phase III study of sorafenib versus linifanib as a first-line therapy for advanced HCC (64). Patient composition was similar to prior pivotal studies. Failing to meet the both pre-specified endpoints of superiority and non-inferiority, the median overall survival for linifanib was 9.1 *vs.* 9.8 months for sorafenib (HR=1.046, 95% CI: 0.896-1.221). A higher proportion of patients attained an objective response on linifanib (13% *vs.* 6.9%); however, serious adverse events were more common in this cohort than compared with sorafenib.

Cediranib, vandetanib, pazopanib, TSU-68, vatalanib, and lenvatinib have not reached later stages of clinical development. Cediranib, a pan-VEGFR inhibitor, has been associated with a high incidence of toxicity with minimal efficacy (66,67). Vandetanib, a small molecule inhibitor that blocks signaling through VEGFR and EGFR, is tolerable but has limited clinical activity (68). Pazopanib (69), TSU-68 (70), vatalanib (71), and lenvatinib (72) block VEGFR and other targets. Currently, these agents have an established safety profile, modest efficacy, and represent an important area of continued investigation.

Monoclonal antibodies

Over 20 separate clinical trials have assessed or are assessing bevacizumab, a monoclonal antibody directed against VEGF, in patients with advanced HCC. Evaluated regimens include monotherapy and combination therapy with chemotherapy, targeted agents, and embolization procedures. In general, completed studies have reported higher response rates than those observed with RTK inhibitors; however, adverse events such as arterial/venous thrombotic events and variceal hemorrhage (some fatal) are more common. A phase II study of bevacizumab monotherapy at two different doses in patients with advanced, liver-limited HCC demonstrated an objective response rate of 13% in 39 evaluable patients, with one patient obtaining a complete response (73). Grade 3 or 4 hypertension, hemorrhage and thrombosis occurred in 15%, 11% and 6% of the study group, respectively. One fatal esophageal hemorrhage due to varices occurred early in the course of the study. Subsequently, prophylactic variceal treatment was required prior to study enrollment. A second phase II study in advanced HCC with extrahepatic disease observed similar efficacy (ORR 14%) with bevacizumab monotherapy (74). It has not advanced to later stage development due to safety concerns regarding bleeding.

The addition of cytotoxic chemotherapy or targeted therapy to bevacizumab may augment antitumor activity. Response proportions (CR + PR) with various cytotoxic combinations range from 9-20%, with disease control rates reportedly as high as 78% (75-77). Bevacizumab and erlotinib may offer enhanced antitumor activity with a response rate of 24% and favorable patient outcomes with a median overall survival of 13.7 months (78,79). These results were not corroborated in a second study that reported minimal activity in a comparable patient population with similar disease assessment parameters and an identical dosing schedule (80). This observation serves to illustrate the heterogeneous nature of HCC and the potential for subtle differences in patient specific factors (i.e., disease burden, Child-Pugh class, etiologic factor) to either cloud interpretation of early stage trials or, as in the case of etiologic factor, potentially influence responsiveness to therapy. As seen above, it is also possible that erlotinib adds little to the effects of anti-angiogenic therapy. To clarify this issue, a multicenter, randomized phase II trial of bevacizumab combined with erlotinib (www.clinicaltrials.gov NCT00881751) versus sorafenib monotherapy is ongoing. Several other additional phase II studies are

evaluating bevacizumab with sorafenib, everolimus, temsirolimus, and other treatment modalities.

Ramucirumab, a monoclonal antibody blocking VEGFR-2, was recently assessed in a phase II study comprised of 43 patients with systemic treatment-naïve advanced HCC. The majority of study participants had extrahepatic disease with excellent hepatic function. The median progression-free survival was 4.3 months with a disease control rate was 50% (7% of patients had a partial response). The agent was tolerable, but like bevacizumab, severe hypertension and hemorrhage with drug-related deaths were reported. Based on these data a randomized phase III study of ramucirumab versus best supportive care in the second line setting is ongoing (www.clinicaltrials.gov NCT01140347). Several other novel anti-angiogenic monoclonal antibodies are entering early stage development in HCC (81). Such agents may offer a more favorable safety profile, with a lower incidence of hemorrhage, which might be ideal in the HCC patient population.

Critical questions in targeting angiogenic pathways

Several important considerations remain in the treatment of this heterogeneous malignancy and for future drug development. Perhaps the most critical question is to define (if possible) the mechanistic basis for the antitumor activity of sorafenib in HCC. As discussed above, three drugs, which were perceived to be more potent and precise inhibitors of angiogenic pathways than sorafenib, failed to demonstrate greater efficacy in the clinical setting. In addition to directly interrogating patient tumor samples, there are renewed efforts to develop preclinical animal models that adequately recapitulate the features of human disease (i.e., etiologic factor, cirrhotic background, etc.). Such approaches will be important for a mechanistic understanding of angiogenesis and translating basic science breakthroughs to the clinic and vice-versa.

Establishing biomarkers of responsiveness is also a priority. Molecular sub-categorization of tumors will identify the biologic profile that might make a patient's tumor more susceptible to a specific targeted therapy. Thus far, these attempts have been unsuccessful for sorafenib. Pretreatment serum-based response surrogates, such as VEGF, VEGFR-1, VEGFR-2, VEGFR-3, Ang-2, FGF, and several cytokines are not predictive of benefit to anti-angiogenic therapy (82). Trends toward enhanced survival from sorafenib were observed in patients with high circulating c-KIT or low hepatocyte growth factor

(HGF, the ligand for c-MET) concentration at baseline. Oncogenic pathway activation as assessed by pretreatment phosphorylated-ERK, the downstream effector of the MAPK pathway, was associated with longer time to progression on sorafenib (3). In contrast, activation of the transcriptional regulator c-Jun is associated with a poor response to sorafenib (83). These observations obviously require further validation and clarification. Other areas of intense biomarker exploration include the study of circulating tumor cells, HCC gene expression profiles, and importantly the application of next-generation sequencing technologies to define cancer genotypes that are more likely to respond to targeted therapy (84,85).

Finally, defining the optimal method of radiographic assessment in HCC will be critical to assess early efficacy in phase I and II clinical trials. Thus far, anti-angiogenic therapy appears to suppress growth and disrupt the vasculature, but does not yield dramatic tumor shrinkage. Clinical benefit occurs without tumor response. Thus, standard Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which assesses the sum of one-dimensional measurement in multiple target lesions, may not adequately reflect the cytostatic effect of anti-angiogenic therapy on tumor viability (86). New response assessment tools have been developed to incorporate the concept of tumor viability, reflected by tissue density due to vascular enhancement. Modified RECIST incorporate decreased intra-tumoral enhancement to define a response. Limited data are available to indicate that this approach, which was never prospectively validated, is a superior surrogate to RECIST in the metastatic setting in response to anti-angiogenic therapy (87). Other proposed schemas include the ratio of tumor necrosis to tumor volume (41), volumetric measurement (86), and the application of functional MRI imaging such as dynamic-contrast enhanced (DCE), blood oxygen level dependent (BOLD), diffusion weighting, and image subtraction to assess for tumor response (41). Large prospective studies evaluating these techniques will be required before implementation of global standard.

Selected therapeutic strategies in late stage drug development

Given the multitude of drugs under evaluation in early stage clinical trials or with early safety and modest efficacy data available, an exhaustive review of each agent or each agent class will be forgone and the remaining discussion will focus

on those agents that are currently under investigation on active phase III clinical trials.

Targeting the HGF/c-MET axis

Overexpression of c-MET and its ligand HGF occur in up to 80% of human HCC tumors (19). Transgenic mice that overexpress MET in hepatocytes developed HCC and inactivation of this transgene leads to tumor regression, mediated by apoptosis and growth suppression (88). Downregulation of MET *in vitro* using RNA interference (89), micro-RNAs (90), or transfection of NK4 (an antagonist of HGF) (91) reduces the migratory and invasive capacity of HCC cells. Finally, blocking MET with several different multi-targeted TKIs induces *in vitro* HCC growth suppression, cell-cycle arrest and decreased viability as well as growth suppression and survival prolongation *in vivo* (92). Given these data, MET has emerged as a promising target in HCC.

Tivantinib, a selective MET receptor tyrosine kinase inhibitor, was evaluated at two doses in a randomized, placebo-controlled phase II in advanced HCC patients who had progressed after first-line therapy (93). This study reported two critical findings. First, a statistically significant difference in outcomes between high-MET expressing tumors in favor of tivantinib. For patients with high MET expressing tumors, tivantinib therapy resulted in a median time to progression of 2.7 months in comparison to 1.4 months for placebo (HR=0.43, 95% CI: 0.19-0.97) and a median overall survival of 7.2 compared with 3.8 months for placebo (HR=0.38, 0.18-0.81). Importantly, no such differences between the agent and placebo were observed in low-MET expression tumor. This strongly suggests that MET expression is a predictive biomarker for MET-directed targeted therapy in HCC. Second, in those patients on the placebo arm, high tumoral MET expression was associated with an improved overall survival when compared with low tumoral MET expression (3.8 vs. 9 months, HR=2.94, 95% CI: 1.16-7.43). This observation indicates that MET expression may also be prognostic in this disease. Given these data, tivantinib is being compared with placebo in double-blind, randomized phase III study in patients with advanced HCC and high-MET expressing tumors in the second-line setting (clinicaltrials.gov NCT01755767).

Cabozantinib, an inhibitor of MET and VEGFR-2, has also shown promising efficacy data in a cohort of 41 patients with advanced HCC (94). In 78% of patients, tumor regression was observed by RECIST with a 5% confirmed

partial response rate. Median progression-free survival for the cohort was estimated at 4.2 months. Unfortunately baseline MET expression has not been reported. A phase III study cabozantinib is in planning. Several other agents are entering HCC-specific clinical trials, and these include oral MET inhibitors such as foretinib, golvatinib and INC280, MET blocking monoclonal antibodies, and novel combination strategies.

Targeting the mammalian target of rapamycin pathway

The mTOR pathway plays a critical role in hepatocarcinogenesis, and in xenograft mouse models, blockade of this pathway results in HCC growth suppression and lengthening of survival (20). These observations, as well as retrospective data indicating enhanced survival among patients receiving sirolimus immunosuppression following liver transplantation for HCC, piqued interest in developing these compounds in this disease. A phase I/II study of everolimus established that 10 mg daily was a safe dose (95). The phase II portion, a two-stage efficacy design, did not meet its pre-specified boundary for expansion to the second stage. Of 25 evaluable patients, 1 (4%) had a partial response and 10 (40%) had stable disease. Median time to progression was 3.9 months and median overall survival was 8.4 months. Presently, everolimus is being investigated in the second line setting after sorafenib failure in the phase III, randomized, placebo-controlled EVOLVE-1 study (www.clinicaltrials.gov NCT01035229). Temsirolimus, AZD8055, as well as multiple combination strategies are ongoing.

Targeting metabolic pathways

The biosynthesis of the nonessential amino acid arginine occurs as part of the urea cycle and is dependent upon the enzymes argininosuccinate synthetase and argininosuccinate lyase. Messenger RNA encoding argininosuccinate synthetase is not present in subsets of hepatocellular carcinomas, therefore arginine must be extracted from the circulation (96). Pegylated arginine deiminase (ADI-PEG 20) is an arginine degrading enzyme isolated from *Mycoplasma* that is formulated with polyethylene glycol (molecular weight 20 kilodalton). In preclinical models, ADI-PEG 20 decreases HCC cell viability at low nanomolar concentrations, reduces serum arginine levels to undetectable levels, and prolongs survival in HCC xenograft mouse models. A phase I/II study demonstrated

an excellent safety profile in a patient population comprised with a high burden of disease and impaired hepatic function (~49% study population Child Pugh B or C) (97). The most common events were injection site reactions and isolated lab abnormalities such as elevated fibrinogen. Of 19 patients evaluable, 2 (10.5%) had complete response, 7 (36.8%) had a partial response and 7 (36.8%) had stable disease. The duration of response ranged from 37 to >680 days. Two subsequent randomized phase II studies that compared escalating doses demonstrated less marked antitumor efficacy (98,99). Glazer and colleagues reported a disease control rate of 63.1% and 2.6% objective response rate and a median overall survival of 11.4 months (98). This exclusively European patient population was composed predominately of HCV-associated (79%) HCC confined to the liver (84%) with otherwise excellent hepatic function (81%). In contrast, Yang and colleagues tested the agent in a heavily pretreated Asian population with HBV-associated (69%) extrahepatic (58%) hepatocellular carcinoma. In this study, no objective responses were noted and the median overall survival was 7.3 months. Currently, a double blind placebo controlled study of ADI-PEG 20 after prior systemic therapy is ongoing (www.clinicaltrials.gov NCT01287585).

Conclusions and future directions

Despite the availability of sorafenib as a standard of care for HCC, there is a substantial need to enhance the armamentarium of therapies in the metastatic setting. Presently, the global standard of care for a patient presenting with metastatic hepatocellular carcinoma is either clinical trial enrollment or sorafenib monotherapy. Although several, high-profile, phase III clinical trials have failed to improve on the current standard, the pipeline for drug development is robust, preliminary phase II data are promising for several agents, and the international research community is committed to continued collaboration to understand this complex disease. In the laboratory, interrogation of HCC genome may isolate novel targets. It is also likely that more trials will attempt to select molecular profiles that are predicted to respond to specific targeted therapy, as in the case of MET inhibition. Looking forward, there will certainly be a greater attention to immune based therapy. Tremelimumab, a CTLA-4 blocking antibody, demonstrated durable disease control in a recent phase II study in addition to exhibiting antiviral activity (100). Several trials evaluating other immune checkpoint

modulators (i.e., anti-PD-1 and anti-PDL1) are ongoing or are being planned. Engineered viral stains, termed oncolytic immunotherapeutics, are capable of selectively targeting tumors by inducing both viral replication-dependent tumor death and tumor-specific immunity (101). This approach has shown promising activity as well. Finally, efforts will continue to target the WNT pathway, which is heavily disrupted in HCC. Hopefully, the international field will continue to witness meaningful progress for the treatment of patients with metastatic hepatocellular carcinoma.

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Footnote

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Beyond chemotherapy: systemic treatment options for hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a major worldwide problem. Multiple chemotherapeutic agents have been used both as single agents and in combination to treat advanced HCC, but until recently none have been shown to improve overall survival. Sorafenib is a multitargeted tyrosine kinase inhibitor (TKI) that was the first systemic therapy to demonstrate improved overall survival among patients with advanced HCC in a phase III trial. Although sorafenib shifted the focus of HCC therapeutics to targeted agents, it produced differential outcomes among HCC patients according to etiology [i.e., hepatitis C virus (HCV) versus hepatitis B virus (HBV)] reflecting the difficulty of treating a heterogenous malignancy like HCC. A large number of additional targeted agents have subsequently been evaluated in HCC, such as sunitinib, regorafenib, and brivanib, and have proven inferior to sorafenib. However, several new agents that target c-MET and VEGF have shown promise in the phase II setting and are now being evaluated in randomized trials. This review will review the failures and recent successes reported in the HCC literature with a focus on targeted agents.

Keywords: Hepatocellular carcinoma (HCC); systemic therapy; tyrosine kinase inhibitor (TKI); chemotherapy; unresectable; targeted therapy

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Introduction

Hepatocellular carcinoma (HCC) is a major worldwide health problem. It is the fifth leading diagnosis of cancer, and the second most frequent cause of cancer death in the world, accounting for estimated 782,000 new liver cancer cases and 746,000 cancer deaths (1). While hepatitis B and C are the main worldwide culprits of HCC, alcohol related cirrhosis and NASH cirrhosis are thought to be the major contributors in the United States (2). HCC treatment depends on the size and location of the tumors. If discovered early, curative approaches include resection and liver transplantation. Local ablative procedures such as transarterial chemoembolization and radiofrequency ablation can convert ineligible patients into transplant candidates. Unfortunately, most patients present with advanced disease. In the setting where patients are not candidates for curative therapy or have failed local control

approaches, systemic therapy is the next option. In this review, we will briefly review historical systemic options and then focus on sorafenib and the new targeted agents.

Chemotherapy

Single agent chemotherapy

HCC is a chemoresistant tumor. Multidrug resistance protein expression, such as P-glycoprotein and p53, and drug efflux mechanisms render chemotherapeutic agents only minimally effective (3,4). In 1975, Olweny *et al.* published one of the first studies using single agent doxorubicin in 14 patients with histologically proven HCC (5). The results were promising, with 3 of 11 evaluable patients showing a complete response and an overall 79% response rate. However, subsequent trials failed to show meaningful benefit and also documented significant toxicities from

Table 1 Single agent chemotherapy

Study	Agent	No. of patients	Response rate (%)	OS
Olweny <i>et al.</i> (5)	Doxorubicin	14	79.0	8 months
Lai <i>et al.</i> (6)	Doxorubicin	106	8.3	10.6 weeks
Tan <i>et al.</i> (8)	Epirubicin	13	23.0	11 weeks
Pohl <i>et al.</i> (9)	Epirubicin	52	9.1	16.2 months (in responders)
Yang <i>et al.</i> (14)	Gemcitabine	28	17.8	18.7 weeks
O'Reilly <i>et al.</i> (15)	Irinotecan	14	7.0	8.2 months
Patt <i>et al.</i> (16)	Capecitabine	37	11.0	10.1 months
Lai <i>et al.</i> (10)	Mitoxantrone	20	0	13 weeks

treatment. Even among studies supporting chemotherapy activity, the benefit was of short duration (6,7). Epirubicin and mitoxantrone are other anthracyclines that have been studied, with response rates ranging from 10% to 25% (8-10). Single agent capecitabine, gemcitabine, irinotecan, and others have been used, but the responses were minimal and none provided a survival advantage (10-13) (see *Table 1*).

Combination therapy

Combination chemotherapy regimens have been used with some success. The most well published regimen consists of cisplatin, interferon alpha, doxorubicin, and infusional 5-FU, otherwise known as the PIAF regimen. A phase III randomized, open-label trial included 188 previously untreated patients with histologically confirmed unresectable or metastatic HCC who were randomized to doxorubicin versus PIAF (17). Overall response rate in the doxorubicin group was 10.5% as opposed to 20.9% in the PIAF group ($P=0.058$). The overall survival in the PIAF group was approximately two months longer (8.67 *vs.* 6.83 months), but this also was not statistically significant ($P=0.83$). The toxicity of this regimen is important to note. PIAF produced much more neutropenia (82% *vs.* 63%, $P=0.003$), thrombocytopenia (57% *vs.* 24%, $P<0.001$), and hypokalemia (7% *vs.* 0%, $P=0.007$). Generally, this regimen is not recommended unless the patient has an excellent performance status and can tolerate a rigorous combination regimen.

Combination capecitabine and oxaliplatin (CapeOX) was studied in a single arm phase II trial of 50 previously untreated patients with histologically proven HCC who were not suitable for surgical resection, liver transplantation, or local ablation techniques. As with other agents, the objective response rate was low at 7%, but the

disease control rate was 72% with a median duration of 5.4 months (range, 2.2 to 20.5 months). Median overall survival was 9.3 months (18).

Oxaliplatin has also been combined with 5-FU and leucovorin (FOLFOX) in an open label phase III trial randomizing 371 previously untreated advanced HCC patients to FOLFOX versus doxorubicin (19). Initially presented at ASCO 2010, FOLFOX was associated with an increased progression free survival (3 *vs.* 1.8 months, $P<0.01$) and median overall survival (6.5 *vs.* 4.9 months, $P=0.07$) compared to patients treated with single agent doxorubicin. A 7-month ad-hoc followup analysis showed persistent overall survival trend, however, the study did not achieve its primary overall survival endpoint. Median overall survival for FOLFOX was much lower than reported for sorafenib (Nexavar[®], Bayer Pharmaceuticals) in the pivotal SHARP trial (see "sorafenib" section). The authors noted that this trial was designed before definitive sorafenib data was published. Cross study comparison is inherently flawed, but it is important to recognize that SHARP only included 20% of patients with hepatitis B virus (HBV) while this trial had more than 90% of patients with HBV. It is interesting to consider that in the Asian sorafenib trial (see "sorafenib" section), with approximately 70% hepatitis B positive patients, the median OS was exactly the same as this FOLFOX study. Conceivably, this combination is a viable option for patients who may not have ready access to sorafenib.

Finally, combination oxaliplatin and gemcitabine (GEMOX) was studied in advanced HCC with an overall response rate of 19% with 58% having disease stabilization in a phase II trial of 21 HCC patients (20). Other combination cytotoxic regimens include cisplatin and doxorubicin, cisplatin and capecitabine, gemcitabine and cisplatin, and gemcitabine and pegylated liposomal

Table 2 Combination chemotherapy

Study	Regimen	No. of patients	PFS/TTP	Response rate (%)	OS
Yeo <i>et al.</i> (17)	PIAF	188	N/A	20.9	8.67 months
Taieb <i>et al.</i> (20)	GEMOX	21	5 months	19.0	12 months
Louafi <i>et al.</i> (25)	GEMOX	32	6.3 months	18.0	11.5 months
Lee <i>et al.</i> (21)	Cisplatin/Dox	42	6.6 months (TTP)	18.9	7.3 months
Qin <i>et al.</i> (19)	FOLFOX	371	3 months	8.2	6.5 months
Lombardi <i>et al.</i> (24)	Gem/Doxil	41	5.8 months (TTP)	24.0	22.5 months
Parikh <i>et al.</i> (23)	Gem/Cisplatin	30	18 wks (TTP)	20.0	21 weeks
Boige <i>et al.</i> (18)	CapeOx	50	4.1 months	7.0	9.3 months

doxorubicin, although it is not clear if any of these regimens confers a survival benefit (21-24) (See *Table 2*).

Targeted therapy

Hepatocarcinogenesis is a complex system of pathways and alterations that has yet to be completely elucidated. What is known about these pathways is that they include growth factors such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin like growth factor (IGF). Although these growth factors activate multiple downstream pathways, the RAS/MAPK pathway is important for each one. Activation of RAS/MAPK may lead to HCC growth and proliferation. EGF binds to its cognate receptor, the extracellular domain of epidermal growth factor receptor (EGFR), triggering signal transduction through the RAS/MAPK pathway. VEGF binds to its cognate receptor, VEGFR, promoting HCC angiogenesis. HGF binds to the c-MET receptor, also upstream of the RAS/MAPK pathway. In one particular study, forty percent of patients with HCC were found to express MET and MET inhibition is a promising therapeutic target (26-30). Discussion of all potential pathways is beyond the scope of this review, but we will discuss relevant literature for these important HCC targets.

Anti-VEGF agents

Sorafenib

Elevated expressions of VEGF ligand and receptor have been found in plasma and liver biopsy samples of patients with HCC (31,32). In addition, elevated levels of serum VEGF levels are associated with a worse prognosis (33).

For these reasons, targeted VEGF therapies have been a key area of drug development. Sorafenib (Nexavar[®], Bayer Pharmaceuticals) changed practice as the first HCC therapy to show a statistically significant and clinically meaningful overall survival benefit. Sorafenib inhibits multiple tyrosine kinases, including VEGFR 1, 2, and 3, targeting angiogenesis pathways. In a phase II trial, 137 patients with advanced HCC treated with sorafenib had a median overall survival of 9.2 months (34). Based on this, Llovet *et al.* proceeded with the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, a phase III study that randomized 602 patients with advanced HCC with preserved liver function and no prior systemic treatment to sorafenib versus placebo (35). Patients in the sorafenib arm had a median overall survival of 10.7 *vs.* 7.9 months in the placebo arm ($P < 0.001$). Although only seven patients (2%) in the sorafenib group experienced a partial response, 204 patients (67%) had disease stability. Patients were primarily from Western countries with Child Pugh A cirrhosis. Approximately 30% of patients had hepatitis C virus (HCV) infection, 20% had HBV infection, and 25% had alcoholic liver disease. While this does not reflect the demographics of HCC worldwide, this is the first agent to consistently show a survival benefit in 30 years of trials. Approved by the Food and Drug Administration in November 2007, sorafenib is now the standard of care for first line systemic treatment in advanced HCC.

To confirm the results of the SHARP trial in a different patient population, sorafenib was studied in a predominantly Asian population. In a phase III trial with inclusion criteria that mirrored the SHARP trial, 229 patients with Child Pugh A cirrhosis were randomized to sorafenib versus placebo (36). The median overall survival in the sorafenib cohort was 6.5 *vs.* 4.2 months in the placebo arm [hazard

ratio (HR) 0.68; 95% CI, 0.50-0.93; P=0.014]. While a statistical significant survival benefit was achieved, the numerical benefit was less than that reported in the SHARP trial despite identical entry criteria and risk stratification. Possible explanations for this include a study population with poorer performance status, more prior therapies, more severe liver disease despite Child Pugh A cirrhosis status, or different disease characteristics (more patients with Hepatitis B) compared to the SHARP trial population.

In both the SHARP trial and the trial by Cheng *et al.* (36), the entry criteria were limited to patients with Child Pugh A cirrhosis (only about 5% of both trials had Child Pugh B cirrhosis). This excluded a large portion of patients who concomitantly have HCC and more advanced liver disease. Presented at ASCO 2013, the results from the Global Investigation of therapeutic Decisions in HCC and of its treatment with sorafenib (GIDEON) trial (37), suggested that sorafenib can be safely used in patients with Child Pugh Class B cirrhosis. GIDEON was a non-interventional, surveillance trial that observed over 3,000 patients treated with sorafenib and followed for response and adverse events. Interestingly, the rate of drug related adverse events were comparable between Child Pugh A and Child Pugh B liver disease. However, those with more advanced disease as indicated by a worse Child Pugh score had a lower median overall survival.

Sorafenib has been studied in combination with other known active agents. In a randomized phase II trial, patients with inoperable HCC without prior systemic treatment were administered doxorubicin with or without sorafenib (38). Combination doxorubicin and sorafenib improved median time to progression (6.4 *vs.* 2.8 months, P=0.02) and median overall survival (13.7 *vs.* 6.4 months; P=0.006) compared to single agent doxorubicin. With the positive results of SHARP, an interim analysis of this trial was conducted, prompting its premature closure due to lack of benefit in the single agent arm. A phase III trial is currently ongoing with combination doxorubicin and sorafenib more appropriately being compared to single agent sorafenib (39).

Sunitinib

With the success of sorafenib, the focus of HCC drug development has now shifted to other molecularly targeted agents. Sunitinib (Sutent[®], Pfizer) is a multi-targeted tyrosine kinase inhibitor (TKI) to VEGF 1, 2, and 3. Sunitinib's antiangiogenic properties suggested activity in HCC and it was evaluated in a single arm phase II study

with 37 previously untreated patients with only a partial response in one patient. Its primary endpoint of objective response was not met, but there was a stable disease rate of 35% (40). A phase III study that randomized over 1,000 patients to sunitinib versus sorafenib was stopped early due to concerns for fertility and safety. At followup, the study actually showed a statistical improvement in median overall survival favoring sorafenib over sunitinib (10 *vs.* 8.1 months, P=0.0019). Sunitinib was noted to cause more grade 3 and 4 adverse events, occurring in 82% and 73% of patients, respectively (41). Another phase II study was recently reported confirming these phase III results. In 24 patients with advanced HCC without prior systemic therapy, there was a significant worsening of liver functional reserve after sunitinib. Despite a partial response in four patients (12%), grade 3 and 4 adverse events occurred in 80% of patients (42).

Bevacizumab

Bevacizumab (Avastin[®], Genentech/Roche), a recombinant humanized monoclonal antibody targeting soluble VEGF-A, was evaluated in 46 HCC patients with Child Pugh A or B cirrhosis and one or less prior systemic therapy who received single agent bevacizumab using doses of 5 and 10 mg/kg every 2 weeks. Of these patients, six had an objective response (13%), including one complete response and five partial responses (43). The median PFS was 6.9 months, median overall survival was 12.4 months, and 53% of the patients were alive at one year. Circulating VEGF levels were decreased from baseline in all patients in the study. With this data, GEMOX and bevacizumab were combined in a phase II trial of 33 patients with unresectable or metastatic HCC who had two or fewer systemic therapies and CLIP score less than three. No patients had a complete response, but six patients had a partial response (20%) and eight patients had stable disease (27%). Median PFS was 5.3 months and overall survival was 9.6 months (44).

Thalidomide

Thalidomide's (Thalomid[®]; Celgene Corporation, Warren, NJ) antiangiogenic properties were also explored in HCC, but with disappointing results. In a phase II study of 27 previously treated and untreated patients, one patient had normalization of alpha fetal protein (AFP) and a partial response noted on imaging while two other patients experienced stable disease (45). Another phase II trial enrolled 37 patients, including 13 who had progression

after prior therapy, and had similar results with about a 30% stable disease rate while one patient had a partial response (3%) and one patient had a minor response (3%) (46). A phase III trial was opened in 2005, but terminated in 2011 due to lack of patient accrual (47).

EGFR blockade

Erlotinib

Epidermal growth factor receptor (EGFR1) overexpression has been identified in HCC, suggesting that EGFR activation is a potential pathway to HCC development (48). Erlotinib (Tarceva[®], Genentech/OSI Pharmaceuticals) is an oral selective TKI of EGFR1, approved for use in non-small-cell lung cancer and advanced pancreatic adenocarcinoma. In a multi-institutional phase II study, erlotinib was administered to 38 patients with surgically unresectable or metastatic HCC, one or fewer prior systemic therapies, and mainly Child Pugh A cirrhosis. Of 34 evaluable patients, 3 (9%) experienced a partial response and 17 (50%) had disease stability. The median overall survival was 13 months, which is superior to historic controls. Grade 3 and 4 adverse events, however, were greater than 60%. Although one of the intended aims of the trial was to stratify response according to the EGFR status, the samples were incomplete and EGFR status was not known in many of these patients (49). Another phase II trial combined erlotinib with bevacizumab for dual EGFR and VEGF blockade. Forty patients with unresectable advanced HCC who had one or fewer prior systemic therapy at a single institution were enrolled, most of whom had Child-Pugh A cirrhosis (85%). Of these patients, 10 (25%) had a partial response and 17 (43%) had stable disease or minor response. The median PFS was nine months and the median overall survival was 15.7 months. For unclear reasons, and in contradiction to the single agent erlotinib data, very few grade 3 or 4 toxicities occurred (50). Combination erlotinib plus bevacizumab has not been compared to sorafenib.

Cetuximab

Cetuximab (Erbix[®], Bristol Meyers Squibb) is a chimeric monoclonal antibody targeting EGFR1 that blocks EGFR dimerization and phosphorylation. It is approved for use in patients with advanced colorectal carcinoma and head and neck tumors. A phase II study examined cetuximab in advanced HCC among 30 patients who had up to two prior

systemic therapies (51). No patients achieved an objective response, but five patients (17%) had stable disease with a median duration of 4.2 months. Median PFS was 1.4 months and median overall survival was 9.6 months. EGFR protein expression by immunohistochemistry (IHC) could not be correlated to clinical benefit from cetuximab.

Cetuximab was further investigated in combination with CapOX (52) in 29 patients with Child-Pugh A or B cirrhosis with advanced HCC and no prior systemic therapy. Of 24 evaluable patients, 3 (12.5%) had partial response while 17 (71%) had stable disease, for a disease control rate of 83%. The median progression free survival was 3.3 months, and the median overall survival was 4.4 months, which was quite a bit shorter than using either single agent cetuximab or FOLFOX alone. The reasons for the short TTP, PFS, and OS were not clear.

Lapatinib

Since EGFR1 heterodimerizes with HER2 (EGFR2), dual blockade of these targets was postulated to have efficacy in treating HCC. Lapatinib (Tykerb[®], GSK) is an oral irreversible dual inhibitor of EGFR and HER2, currently approved for use in metastatic breast cancer. In a phase II trial, this drug was evaluated in 27 patients with unresectable HCC who had one or less prior systemic therapies (19% had 1 prior therapy). As with many of other EGFR inhibitor trials, lapatinib did not produce any objective responses. However, 10 (40%) patients had stable disease that lasted for over three months in six patients and over one year in two patients. The median PFS was 1.9 months and the median overall survival was 12.6 months. HER2/neu was not overexpressed per fluorescence *in situ* hybridization (FISH), consistent with other reports that HER2 overexpression in HCC is varied (53).

c-MET blockade and other targeted agents

Tivantinib

Tivantinib is a TKI of c-MET, which can be overexpressed or mutated in many tumor cell types and plays a key role in cell proliferation, survival and metastasis. The c-MET protein is a receptor tyrosine kinase also known as HGF. Overexpression of c-MET portends a worse prognosis in patients with HCC. A randomized phase II trial evaluated 107 previously treated patients and showed a benefit for patients with HCC and a high c-MET expression

treated with tivantinib versus placebo in the second line setting. Patients in the treatment arm with high c-MET expression had a significantly increased time to progression (2.9 *vs.* 1.5 months), progression free survival (2.4 *vs.* 1.5 months, $P=0.01$) and disease control rate (50% *vs.* 20%) (54). Despite a crossover design, a survival benefit trend favored tivantinib. Based on this data, a phase III trial (55) is currently underway, assigning 303 patients to receive tivantinib versus placebo in the second line setting (NCT01755767).

Cabozantinib

Cabozantinib is another promising c-MET inhibitor. It is an oral inhibitor of c-MET and VEGFR2, currently being studied in multiple solid tumors. At ASCO 2012, a phase II trial was presented using cabozantinib in 41 patients with advanced HCC who had no more than one prior systemic treatment. Three patients had a partial response, but 28 patients (78%) had evidence of tumor regression on imaging. As of September 2013, a phase III trial has been opened to further explore the role of this drug in treating HCC (56).

Axitinib

Axitinib (Inlyta[®], Pfizer) is a multi-TKI targeting VEGFR 1, 2, 3, PDGFR, and c-Kit. At ASCO GI 2012, interim data from an open-label phase II trial was presented using axitinib in the second-line setting. Data on 15 of the 29 enrolled patients who progressed on prior TKI or anti-VEGF therapy were presented. Of nine patients evaluable for response, there was one partial response with three other patients having tumor shrinkage. Side effects included hypertension, diarrhea, hand foot syndrome, and fatigue. Adverse events required dose reductions in 60% of patients. The full report on this study is pending (57).

Regorafenib

Regorafenib (Stivarga[®], Bayer) is a promiscuous multikinase inhibitor with targets including VEGFR2 and 3, Ret, Kit, PDGFR and Raf kinases, approved for metastatic colorectal cancer and metastatic gastrointestinal stromal tumors (GIST). In an open-label phase II trial enrolling 36 patients who progressed on first line sorafenib, the disease control rate was 72% (26 patients), median time to progression was 4.3 months, and median overall survival was 13.8 months.

The main toxicities were hand foot syndrome, fatigue, diarrhea, hypothyroidism, and hypertension, with rare grade 3 or 4 adverse events (58). A phase III trial using regorafenib versus placebo in patients who have progressed on sorafenib is ongoing (59).

Linifanib

Linifanib, a TKI of VEGF and PDGFR was studied in a phase II trial involving 44 predominantly Asian patients had up to one prior therapy and demonstrated an objective response rate that was greater than 10% with only mild toxicities (11). In an open-label phase III study, over 1,000 patients were randomized to linifanib versus sorafenib in the first line setting. Patients had advanced HCC, Child Pugh A cirrhosis, and were predominantly Asian. The primary endpoint was overall survival, evaluating both noninferiority and superiority. The median overall survival was 9.1 months compared to 9.8 months on sorafenib, although linifanib had a longer TTP of 5.4 *vs.* 4.0 months ($P=0.001$). The overall response rate was 13% in the linifanib arm, however more patients in this arm had dose interruptions and reductions. Thus far, this study has not met its endpoint goals (12).

Brivanib

VEGF and fibroblast growth factor receptor signaling are both implicated in HCC. Brivanib is a selective dual receptor inhibitor of both (13). In a phase III trial of patients who progressed after sorafenib, 395 patients with advanced HCC were randomly assigned in a 2:1 fashion to receive brivanib versus placebo. All patients had previously received sorafenib and the primary endpoint was overall survival. Time to progression (4.2 *vs.* 2.7 months, $P<0.001$) and overall response rate (10% *vs.* 2%, $P=0.003$) both favored brivanib. However, no difference was found for overall survival (9.4 *vs.* 8.2 months, $P=0.3307$), missing the study's primary endpoint (60).

Brivanib was also studied in the first line setting in a phase III noninferiority trial comparing it to sorafenib among 1,155 patients with advanced HCC who were not eligible for surgical and/or locoregional therapies. The primary endpoint was overall survival, which the study did not meet. Overall median survival was 9.5 months in the brivanib arm versus 9.9 months in the sorafenib arm (HR 1.07, $P=0.312$). Patients receiving brivanib had a marginally higher objective response rate of 12% *vs.* 9% compared

Table 3 Promising targeted agents

Study	Agent	No. of pts	PFS/TTP (months)	OS (months)	Response rate, %	Phase
Bekaii-Saab <i>et al.</i> (53)	Lapatinib	27	1.9	12.6	0	II
McNamara <i>et al.</i> (57)	Axitinib	15	N/A	N/A	33 (3/9)	II
Rimassa <i>et al.</i> (54)	Tivantinib	107	2.4	6.6	1 (1/107)	II
Bruix <i>et al.</i> (58)	Regorafenib	36	4.3	13.8	3 (1/36)	II
Verslype <i>et al.</i> (56)	Carbozantinib	41	4.2	N/A	8	II
Cainap <i>et al.</i> (12)	Linifanib	1,035	5.4	9.1	13	III
Llovet <i>et al.</i> (60)	Brivanib	395	4.2 (TTP)	9.4	10	III
Johnson <i>et al.</i> (61)	Brivanib	1,155	4.2 (TTP)	9.5	12	III

to the sorafenib arm. Adverse events of any grade were higher in the sorafenib arm, while there were more grade 3 hyponatremia, hypertension, and fatigue in patients receiving brivanib. Unfortunately, brivanib appeared to be less well tolerated than sorafenib with treatment discontinuation due to side effects in 43% of the patients compared to 33% of patients on sorafenib (61). (See *Table 3* for targeted agents).

Discussion

HCC drug development has been marked by a series of disappointing study results. Initial signals of doxorubicin activity over 30 years ago were shattered by the reality of subsequent poor trial outcomes. Since then, therapeutic focus has shifted to targeted therapies that block transduction through the RAS/MAPK pathway known to drive tumorigenesis, including for HCC. Sorafenib, a multi-targeted kinase inhibitor, was the first agent that has consistently demonstrated an overall survival advantage over placebo and other investigational agents, and remains the front-line standard of care for advanced HCC. A variety of reasons can be offered to explain the intransigent nature of HCC. HCC is notorious for tumor heterogeneity introducing the likelihood of resistance. Pathways leading to HCC are also varied, including viral hepatitis, alcohol, and inflammation. In fact, even among patients with viral hepatitis, sorafenib appears to confer a more salutary effect on those without HBV. As has been true with many other historically resistant tumors, enhanced understanding of HCC tumorigenesis pathways holds the promise for finally altering the natural history of this terrible disease. Targeted agents against angiogenesis, and EGFR and c-MET signaling are encouraging first steps. Future research will focus on continued understanding of HCC drivers and

combination therapies.

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Footnote

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Current status of bevacizumab for advanced hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide, with at least 550,000 deaths each year, predominantly in Southeast Asia (1). The incidence of HCC has tripled in the last three decades in the United States, and is on the rise worldwide (2). HCC can be treated curatively with surgical resection, liver transplantation, or radiofrequency ablation, but only 15% of patients are diagnosed at a stage where curative treatment is possible (3). When patients are diagnosed at an advanced stage of HCC, as are 60% of all cases, median survival times are less than 1 year. Systemic therapies have largely been unsuccessful, until the approval of sorafenib in 2007, which improved survival by 2.7 months compared to placebo (4). There have been many ongoing studies since that time looking for further targeted therapies to offer patients with advanced HCC.

HCC is a hypervascular tumor, and several proangiogenic factors play a role in HCC pathogenesis. Vascular endothelial growth factor (VEGF) has been shown to play an important role in many cases of HCC, allowing for development of new vascular supply to allow tumor growth, as well as having an important role in metastasis of tumor cells. In HCC, VEGF levels correlate with vascular invasion and metastasis, and the magnitude of VEGF changes after locoregional therapy is inversely proportional to therapeutic response (5,6). Therefore, targeting VEGF as a therapeutic intervention in patients with advanced HCC may result in prolonged survival.

Bevacizumab is an anti-VEGF monoclonal antibody that was the first angiogenesis inhibitor to be approved as an anti-neoplastic agent. It is currently indicated in metastatic colon cancer, non-squamous non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma (7). In the

treatment of advanced HCC, there were initial concerns regarding safety, especially gastrointestinal bleeding and thrombosis, however Phase II trials have shown toxicities to be manageable. It has been studied both as monotherapy, as well as in combination with the epidermal growth factor receptor inhibitor erlotinib and with cytotoxic chemotherapy. Most trials have been small, Phase II trials, and median progression free survival (3.6-7.2 months) and overall survival (4.37-13.7 months) has been variable (8-15). *Table 1* summarizes the current published literature with bevacizumab.

Boige *et al.* performed a phase II trial of bevacizumab in patients with advanced HCC, and looked at circulating endothelial cells and plasma cytokines and angiogenic factors at baseline and throughout treatment (15). Bevacizumab was given at 5 mg/kg every 2 weeks in 25 patients, and then dose was increased to 10 mg/kg in the remaining patients because disease control was seen in less than 11 patients, per their statistical design. Treatment seemed to be fairly well tolerated, and consistent with other studies, with 12% of patients having asthenia, 7% with elevation of serum transaminases and 9% with gastrointestinal (GI) hemorrhage. Notably, as in other studies, the GI hemorrhage occurred despite upper GI endoscopy and primary prophylaxis with either propranolol or variceal banding in all patients with significant gastroesophageal varices.

The patients included in this study had advanced disease, with 91% having BCLC stage C disease and 53% with metastatic disease. 65% of patients had cirrhosis, which is less than many of the other studies with bevacizumab. This may have resulted in less adverse events due to bevacizumab in this study, given that many HCC patients

Table 1 Summary of publications of bevacizumab and hepatocellular carcinoma

Author	# enrolled	Presence of cirrhosis	HCC stage	Dosage	Median PFS	Median OS	Grade 3-4 Toxicity
Siegel <i>et al.</i> J Clin Oncol 2008 (8)	46	NR	No EHS Median CLIP score = 2	5 mg/kg (N=12) 10 mg/kg (N=34)	6.9 months	12.4 months	HTN 15% Thrombosis 6% Hemorrhage 11%
Hsu <i>et al.</i> Brit J Cancer 2010 (9)	45	NR	96% EHS/MVI 98% BCLC C	BEV 7.5 mg/kg + capecitabine 800 mg/m ²	3.6 months	8.2 months	Diarrhea 4% N/V 2% GI bleed 9% Hand foot syndrome 9%
Sun <i>et al.</i> Cancer 2011 (10)	40	100%	97.5% EHS	BEV 5 mg/kg + oxaliplatin 130 mg/m ² + capecitabine 825 mg/m ²	6.8 months	9.8 months	Sensory Neuropathy 12.5% Fatigue 7.5% Diarrhea 5% GI Bleed 5% Anemia 5%
Yau <i>et al.</i> Invest New Drugs 2012 (11)	10, prior sorafenib failures	100%	100% EHS 90% BCLC C	BEV 10 mg/kg + erlotinib 150 mg	TTP 1.81 months	4.37 months	Diarrhea 10% Rash 10% Mucositis 10% Vomiting 10% Elevated LFTs 10%
Kaseb <i>et al.</i> Oncology 2012 (12)	51	NR	BCLC C 76%	BEV 10 mg/kg + erlotinib 150 mg	7.2 months	13.7 months	Fatigue 30% Diarrhea 17% HTN 14% Elevated LFTs 12% GI Bleed 10%
Philip <i>et al.</i> Cancer 2012 (13)	27	56%	70% EHS	BEV 10 mg/kg + erlotinib 150 mg	TTP 3.0 months	9.5 months	Rash 22% HTN 4% Fatigue 7% Diarrhea 15%
Govindarajan <i>et al.</i> Am J Clin Oncol 2012 (14)	21	85%	48% EHS 76% BCLC C	BEV 10 mg/kg + erlotinib 150 mg	TTP 2.57 months	8.33 months	Fatigue 19% Dehydration 10% GI bleed 5% Nausea 5% Dyspnea 5% Diarrhea 5%
Boige <i>et al.</i> The Oncologist 2012 (15)	43	65%	53% EHS 91% BCLC C	5 mg/kg (N=25) 10 mg /kg (N=18)	3 months	8 months	Asthenia 12% GI bleed 9% Elevated LFTs 7%

HCC hepatocellular carcinoma; PFS progression free survival; OS overall survival; NR not reported; EHS extrahepatic spread; MVI macrovascular invasion; BCLC Barcelona Clinic Liver Cancer Staging System; CLIP Cancer of the Liver Italian Program; BEV bevacizumab; TTP time to progression; HTN hypertension; N/V nausea and vomiting; GI gastrointestinal; LFTs liver function tests

have underlying liver disease that will decrease tolerability to systemic agents. The response rate seen in this study is consistent with previously published data, with a progression free survival of 3 months, and overall survival of 8 months. Disease control rate at 16 weeks was 39% in patients treated with 5 mg/kg, and 45% in patients treated with 10 mg/kg, which is higher than expected, especially given the short progression free and overall survival times. 6 and 12-month overall survival was 63% and 30% respectively, which is similar to historically what is expected for patients with advanced HCC.

Biomarker analysis has recently been an area of interest, to attempt to predict response to therapy both preemptively and during treatment. This paper looks at an interesting idea of circulating endothelial cells (CEC) and plasma cytokines and angiogenic factors (CAF), both of which may be altered in patients with advanced hypervascular malignancies such as HCC. In this study, the most significant changes were seen in VEGF-A levels at all time points, which is not surprising given the mechanism of action of bevacizumab. Interestingly, change in CEC level during the first 15 days was associated with better response to therapy, and elevated baseline IL-8 and IL-6 levels were correlated with poorer prognosis. If these findings are confirmed in larger trials, measurements of these biomarkers could be helpful in clinical practice.

Overall, it appears that bevacizumab may have a role in systemic treatment of advanced HCC, but appears to have a relatively low rate of response. This will need to be confirmed in larger phase III randomized double-blind placebo-controlled trials before it can be incorporated into standard of care treatment for hepatocellular carcinoma. Gastrointestinal bleeding, including variceal bleeding, continues to be a problem, and the need to perform pre-treatment endoscopic evaluation and treatment for all patients could delay therapy in some cases, especially if multiple banding procedures are required to completely eradicate varices. The most important part of this study is the biomarker exploration, and this needs further clarification with larger studies to elucidate the clinical implications.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Efficacy of combination treatment modalities for intermediate and advanced hepatocellular carcinoma: intra-arterial therapies, sorafenib and novel small molecules

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Abstract: Hepatocellular carcinoma (HCC) is a growing epidemic with a high mortality rate and clear need for improved therapies. In patients with Barcelona–Clinic Liver Cancer (BCLC) B and C, treatment with transarterial chemoembolization (TACE) has been the gold standard in therapy as it delays progression; however, recurrence proves common. In the US, transarterial bead embolization (TABE) has uniformly replaced TACE. With this limited armamentarium, there is need for a shift to novel strategies combining different modalities to further improve patient outcomes. Historically, HCC drug discovery concentrated on common features of HCC including its highly vascular nature and dependence on growth factors (GFs). The multikinase inhibitor sorafenib acts on angiogenesis via modulation of vascular endothelial GF expression and was the first step toward systemic targeted therapy against HCC. Sorafenib has provided clinicians with a tool to modestly improve survival by 2–6 months or longer. Despite the progress in survival provided by TACE, TABE and sorafenib independently, rigorous combination clinical trials do not consistently show significant improvement over TACE/TABE monotherapy. Other novel small molecules targeting angiogenesis such as brivanib, linifanib and everolimus have failed or are in development. Anti-HCV treatment became more feasible with the novel direct-acting antiviral agents; with the much higher and more durable treatment responses that they provide, the risk of HCC progression may be reduced. The most effective strategies in developing combination therapies are hampered by the complexities of FDA testing along with intellectual property and economic issues. To achieve significant progress, more basic science studies are necessary to help understand which novel molecules demonstrate the greatest synergy. Individual patient genomic profiling and biomarkers may help guide therapy and improve the clinician's ability to tailor treatment and to know when it could be appropriate to combine systemic therapy with transarterial embolization. Most importantly, partnerships that facilitate testing of novel therapies in intelligently designed trials based on preclinical pharmacokinetics must be established.

Keywords: Hepatocellular carcinoma (HCC); sorafenib; transarterial chemoembolization (TACE); transarterial bead embolization (TABE); transarterial radioembolization (TARE); combination therapy

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Introduction

Hepatocellular carcinoma (HCC) is a rising source of global morbidity and mortality. According to the World Health

Organization, it is now second in producing cancer deaths in men (1). In nations showing the highest HCC prevalence, diagnosis of patients occurs at younger ages, though

treatment may not be available (2). With no intervention, survival after diagnosis of intermediate to advanced HCC is approximately eight months (3); with expert care, prognosis can be extended beyond four years (4).

Treatment decisions are complex and dependent upon tumor staging, presence of portal hypertension, and the underlying degree of liver dysfunction, as well as local expertise. When HCC is confined to the liver with preserved hepatic reserve and no or minimal portal hypertension, a partial hepatectomy can be curative; however, recurrence, or *de novo* (metachronous) HCC is common. In patients with unresectable disease and tumor staging that falls within criteria, liver transplantation can be curative in a great majority of patients. Unfortunately, most patients will not be candidates for either surgery or transplant; clinicians also struggle with already cirrhotic patients with unresectable HCC who are not candidates for transplant. The use of combination therapy with surgical resection, as a pre-operative bridge to transplant, and with inpatients found to have lymphovascular invasion after transplant is an area of growing interest.

Locoregional treatments such as transarterial chemoembolization (TACE) or transarterial bead embolization (TABE) are generally used for intermediate disease, or Barcelona Clinic Liver Cancer B (BCLC B). Embolization of the vessels that supply HCC leads to a dense inflammatory response and necrosis of the lesion, although it often leaves a viable tumor along the periphery with documented vascular endothelial growth factor (VEGF) rebound (5). With these therapies, a partial response is common, as well as a high recurrence rate; combination with other modalities does not consistently yield survival rates greater than monotherapy (6).

The sequences that lead to the development of HCC are still incompletely understood, although the process likely begins with somatic mutations responsible for small tumor formation. The malignant hepatocytes release angiogenic growth factors (GFs) and tumor vascularization occurs allowing for expansion. In the pivotal phase III study, sorafenib, a small molecule multikinase inhibitor, was shown to extend overall survival by almost three months (7). Thus, current guidelines suggest its use in patients with advanced HCC (BCLC C) (8). Despite this critical step forward, poor outcomes continue to be the norm. The dominant molecular mechanistic aspect of sorafenib remains unclear. Which patients may benefit most from monotherapy is also not yet known. Although sorafenib was initially developed as a b-raf inhibitor for melanoma, it demonstrated little

activity (9). It is likely that it inhibits c-raf that in turn decreases VEGF expression and cellular proliferation via MAPK, and induces apoptosis. VEGF is a central mediator of angiogenesis (10). It also appears to activate phosphatases, inhibit stat-3, and alter IL-6 signaling (11). Although sorafenib yields improvement in survival, adverse events are common which limit its use. The acceptable threshold of side effects may vary by clinician and patient; those providers with a greater comfort in dealing with common adverse effects such as hand-foot syndrome may ultimately have improved outcomes. Studies of sorafenib show that dose duration and amount of drug exposure are key to response (7).

Currently, most clinical trials for intermediate stage HCC pair an already established modality such as TACE or sorafenib with a novel drug. Although there are signs that these may offer small improvements over standard care, the results of this strategy are generally equivocal to date. Drug discovery and clinical trials should aim at tactical combinations of new agents that can continue in tandem with procedures like TACE. Drug resistance may be avoided through use of two or more small molecules sharing the same target, such as the molecules that inhibit the tyrosine kinase receptors. Horizontal or vertical targeting to signal pathways may also lead to synergistic anti-tumor effects. Unfortunately, there remain significant hurdles to overcome when attempting to combine drug therapies in early clinical development. Despite these challenges, combination therapy offers the opportunity for significant progress to be made. In this review, the rationale and obstacles for combination therapy in unresectable HCC will be discussed.

Obstacles in developing effective therapies: heterogeneity of HCC

Rationale for combined therapy: does one plus one equal two?

The Institute of Medicine recently summarized the rationale and need for combination treatments to accelerate cancer therapy development (12). The hope is that an appropriate combination of agents may be found that will allow for the best treatment effects with the least side effects (13). Single agent therapies may induce drug resistance, or only partially inhibit the molecular pathways involved. Combination therapy may produce more effective outcomes by targeting multiple pathways critical for cancer progression. This approach has proved highly effective in

producing results against infectious diseases such as HIV and, more recently, HCV.

The development of novel combination therapies in HCC presents unique challenges. The most conspicuously obvious challenge is the diversity of conditions that lead to malignant transformation including chronic infection with hepatitis viruses, nonalcoholic steatohepatitis (NASH), hereditary diseases (hemochromatosis), toxins (alcohol and aflatoxin), and immune-mediated diseases (primary biliary cirrhosis and autoimmune hepatitis). Even within the various causes of HCC, the aberrance in the molecular pathways can be different (14). Patients may even have heterogeneity within a single tumor as well as synchronous and metachronous lesions. Genomic profiling of HCC highlights the diverse changes that can occur in HCC, although several discrete patterns can be recognized (15). Functional biological studies and biomarkers can guide clinical care to inform the selection of agents to improve these outcomes; however, many of these are lacking or are still in the early stages of development.

There is also concern from the FDA that novel-novel drug combinations may pose a greater risk to patients, although they may be supportive provided there is sufficient pre-clinical data. Additionally, combination therapy clinical trial design can prove complex; success may require significant pre-clinical data and planning (16). Drugs in combination have the potential to interact synergistically; this effect is lost when they are administered independently. In some cases, a single drug may have no direct effect on a disease, but when used in combination it may affect the metabolism of a second agent in a way that increases the overall effect. Careful consideration of the pharmacokinetics are required for successful phase I testing.

Potential drug trials combining novel agents are often complicated by economic and intellectual property considerations. Perception of considerable additional cost and risk to those in the private sector funding drug development also complicates matters. Furthermore, legal issues surrounding possible inventions derived from the collaboration can be a major sticking point from both academic and private institutions and may require lengthy negotiations. The development of trastuzumab emtansine (in the US, ado-trastuzumab emtansine), consisting of Genentech's anti-HER2 monoclonal antibody trastuzumab conjugated to Immunogen's anti-mitotic agent mertansine, which is now approved for metastatic breast cancer, is a model to overcome these obstacles through use of a collaborative and successful approach (17). The irreversible

binding of trastuzumab to the HER-2 receptor leads to internalization of mertansine by the tumor cell. The use of this chimeric small molecule showed improved efficacy in patients who had already received trastuzumab (18). Strategies such as these in HCC may decrease the toxicity and increase the efficacy of novel therapeutics.

Targeted therapy today: duck hunting with a bow and arrow

Complex cellular biology with a set of heterogeneous causes is responsible for challenging drug development in HCC. The hallmark of HCC is its dense hypervascular arterial blood supply; consequently, angiogenesis pathways are of pronounced interest. HCC's can be linked to genetic mutations and epigenetic alterations in the cell cycle, proliferation of cells, and production of GFs. Although the exact sequence of hepatocarcinogenesis is not known, good evidence exists that at least three distinct molecular pathways are dysregulated: the mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3-kinase (PI3K), and β -catenin (See *Figure 1*). Thus, therapy targeting a single aspect of HCC's molecular biology will likely be met with limited success. A cocktail of small molecules targeting the overlapping and alternate pathways may help overcome the limitations encountered thus far.

Sorafenib appears to have multiple effects *in vitro*. Most prominently, it inhibits the Raf family kinases through the MAPK pathway activated by VEGF (19). This is believed to alter cellular proliferation, reduce angiogenesis, and increase apoptosis in tumor cells (20). Sorafenib decreases mRNA expression of VEGF via inhibition of the PI3K pathways in tumor cells, and inhibits the VEGF receptor kinase in the endothelial cell (21). Wnt signaling is identified as a key player in many solid tumors, including HCC. Activating mutation in the β -catenin gene (CTNNB1) represents the second highest frequency of known mutations in HCC (22). In HepG2 cells, which harbor this mutation, sorafenib attenuates Wnt-pathway activation (23). Historically, developments of agents that target Wnt directly are complicated by toxicity; however, there are some Wnt antagonists such as LGK974 in early development (24). Levels of C-Kit and HGF may predict higher or lower responses to sorafenib (25).

Although oncogenic mutations are responsible for the initiation of tumor growth, GFs are the major regulators of all subsequent steps of tumor progression. Tumors that produce excessive GF can manipulate their own further growth through autocrine regulation, as well as support

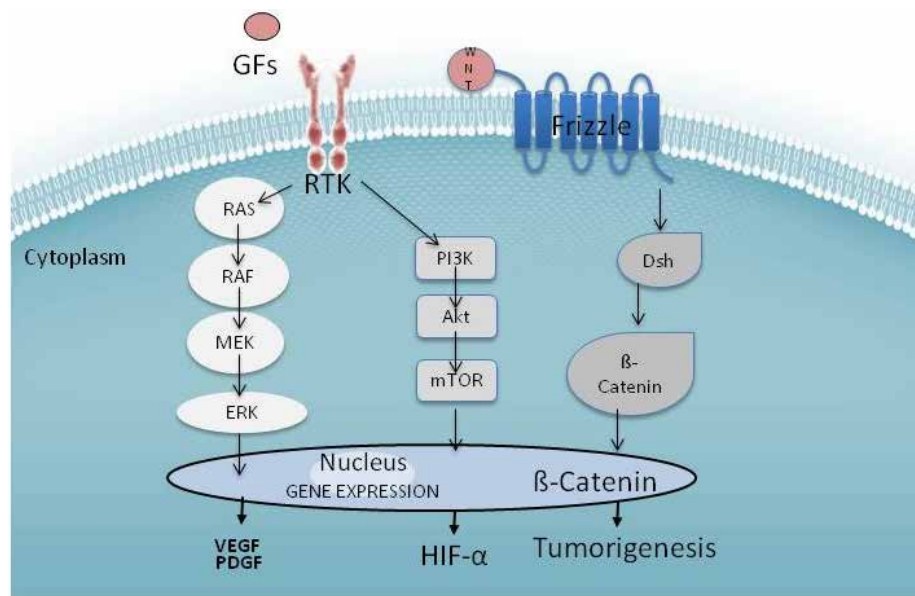


Figure 1 Key signaling cascades in HCC. The MAPK pathway is stimulated by growth factors (GFs), such as VEGF, that activate receptor tyrosine kinase (RTK), followed by Ras-Raf-MEK-ERK activation. The genes linked to this pathway lead to further expression of GF production. GFs in setting have both autocrine and paracrine functions. Stimulation of RTK also activates the PI3K-Akt-mTOR cascade which eventually leads to hypoxia inducible factors (HIF- α). Wnt activates the frizzles trans-membrane receptor leading to dishevelled (Dsh) to the membrane allowing β -catenin to accumulate in the cytosol and eventually the nucleus. Once in the nucleus β -catenin interacts with transcription factors and facilitates tumorigenesis.

metastatic growth in a paracrine manner. Platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) also lead to activation of the Ras-Raf-MAP-ERK pathway and expansion mediators of mutation-bearing clones. Sunitinib inhibits both VEGF and PDGF signaling cascades (26), although early clinical trials were stopped as survival in patients treated with sorafenib alone was superior (27). Linifanib is another VEGFR/PDGFR multikinase inhibitor in clinical trials for HCC. Some data suggest that resistance to tyrosine kinase inhibitors is mediated through FGFR; thus the use of brivanib, which targets FGF in addition to the VEGF cascade, has a theoretical role in sorafenib-resistant HCC (28). The monoclonal antibody bevacizumab offers a different approach: irreversibly binding systemic VEGF in a protein complex, thus blocking it from binding to the receptor (29). Ramucirumab works by binding to VEGF receptor 2 (VEGFR2), thus blocking the binding of VEGF to VEGFR2 (30).

Hepatocyte growth factor (HGF) is a ligand that appears crucial for HCC progression (31). It binds to the c-Met receptor, another tyrosine kinase receptor linked to the effector pathways of HCC. C-met leads to downstream

activation of MAPK and PI3K. The PI3K/Akt/mTOR pathway leads to activation of a number of nuclear transcription factors, including nuclear factor kappa from B cells (NF- κ B). The mTor inhibitors everolimus, sirolimus and temsirolimus are drugs that have the potential to alter this pathway. There are several drugs in development that target c-Met, including tivantinib, cabozantinib, and foretinib. As evidenced by tumor immunohistochemistry, use of tivantinib in high c-Met expresser patients appears to improve the drug's effectiveness (32), although serious adverse events, including death, were reported in the initial trials (33). Future studies of tivantinib should be accompanied by tumor sampling to determine c-Met expression since it appears to predict response.

HCC drug combination therapy could involve two small molecules with the same target, different targets on the same pathway (vertical), or inhibition of different pathways (horizontal). For example, dual treatment with tyrosine multikinase inhibitors like sorafenib and brivanib could potentially further reduce VEGF signaling and resistance. Using oral therapies with radiation therapy, surgery, transarterial therapy, or thermal ablation are all potential

combinations for our patients in the clinic setting.

HCC model systems

Model systems for HCC allow researchers to understand the effects of small molecules *in vitro*, and identify which may perform synergistically. A number of different model systems exist to study HCC in the laboratory; each has certain limitations. Immortalized human hepatocytes can be obtained by *in vitro* transfection of SV-40 T antigen (34), and by overexpression of the HCV core protein (35). Most studies are currently performed with cells extracted from primary tumors suitable for maintaining characteristics after multiple passages such as HepG, Hep3B and Huh7. These cell lines are derived from human tumors and, thus, reflect the genomic defects and pathophysiology of a single individual. For example, Huh7 cells were established in 1982 from a 57-year-old Japanese male (36). Despite the inherent difficulty in interpreting the results of these studies, they can provide useful preclinical data for evaluating the synergy of combination therapy. Furthermore, many studies have shown favorable results with combinations of several anti-HCC small molecules, validating the performance of dual inhibition of HCC-related biomarkers such as VEGF or Akt phosphorylation (37). Subcutaneous xenograft models using implanted tumor tissue in mice are used to characterize the performance of various molecules in HCC. Although they are labor intensive, expensive, and technically challenging, they can be useful in predicting therapies that may perform synergistically in clinical trials.

Hepatitis viruses

The most common causes of HCC are the hepatitis B virus (HBV) and the hepatitis C virus (HCV) which account for 80% of all cases (38). HBV is a DNA virus that can integrate into host DNA and has the oncogenic potential to transform hepatocytes in the absence of cirrhosis or even significant fibrosis (39); the HBx protein also shows oncogenic potential. HCV is almost exclusively linked to HCC in cirrhosis and may exert its oncogenesis through viral proteins such as the core (40). Among patients with NASH, HBV and HCV, risk of HCC varies by viral genotype, presence of core and precore mutations and other risk factors such as gender and concurrent alcohol use. In the key study by Liaw, suppression of HBV with antivirals was shown to decrease the risk of HCC in patients with cirrhosis (41). In this study, patients with HBV cirrhosis

were treated with lamivudine or placebo. The data and safety monitoring board (DSMB) terminated the study at 32 months because the lamivudine group fared better, showing a modest reduction of HCC. Recent studies with tenofovir and entecavir have shown similar results (42).

In HCV, only durable cures from infection are linked to a reduction in HCC risk (43). Much enthusiasm was generated in recent years as HCV direct-acting antivirals arrived in the market. At the time of publication of this manuscript, interferon remains the backbone of treatment. Due to adverse events and continued poor response to therapy, most clinicians avoid treating patients with HCC. In the HALT-C trial, there was no reduced risk of HCC after prolonged IFN therapy (44). Thus, a partial response is not protective. There is a universal consensus that patients who achieve an SVR have a reduced risk of HCC (45). Antiviral therapy may turn off inflammation and decrease the risk of HCC. Whether treatment with antivirals can decrease progression of already present HCC remains unanswered. Since HCV's viral proteins are known to modulate important pathways related to HCC, removal of these instigators may slow progression in the same way as other inhibitors. Currently, sofosbuvir is being tested in patients with HCC awaiting liver transplant; however, progression of HCC is not a viable endpoint as patients will be transplanted throughout the study. Clinical trials examining anti-HCV treatment in patients with HCC who are not transplant candidates will be valuable.

HCC therapies in development

Most small molecules currently in phase Ib, II and III trials in combination have failed to show non-inferiority or superiority to sorafenib monotherapy. The vast majority of the upcoming or ongoing trials with these agents seek to pair them with sorafenib or TACE (See *Table 1*); however, there may also be a role for small molecules as adjuvant therapy with resection or around time of liver transplant.

Adjuvant therapy for resection and liver transplant

No studies have been performed using small molecules as neoadjuvant therapy before resection. Resection is generally considered curative and thus the use of drugs like sorafenib would be aimed at decreasing the chance of recurrence. In this setting, treatment of viral hepatitis would appear to be the most important therapy to decrease risk of HCC recurrence. Interferon therapy has been shown to

Table 1 Selected small molecule agents currently being tested in combination with other agents in US phase Ib, II or III studies

Class	Compound	Target	Combination agent
Receptor tyrosine kinase inhibitors	Sorafenib	VEGFR, PDGFR, Raf	See below
	Erlotinib	EGFR	Sorafenib, bevacizumab
	Brivanib	VEGFR-2, FGFR	TACE
	Orantinib	VEGFR-2, FGFR	TACE
	Sunitinib	VEGFR, PDGFR	TACE
	Golvatinib	VEGFR-2, c-Met	Sorafenib
Angiogenesis inhibitors	Bevacizumab	VEGF-A	Temsirolimus, erlotinib, lenalidomide
	Trebananib (AMG 386)	Ang-1, Ang-2	Sorafenib
	Tigatuzumab	TRAIL-R2	Sorafenib
	Mapatumumab	TRAIL-1	Sorafenib
	Selumetinib	MEK	Sorafenib
	Thalidomide	bFGF, VEGF	TACE
	Lenalidomide	bFGF, VEGF	Bevacizumab, sorafenib, temsirolimus, or 5-Fluorouracil, leucovorin, oxaliplatin (FOLFOX)
Poly ADP ribose polymerase inhibitor	Veliparib	PARP1, PARP2	Temozolomide
Antiviral agents	Adefovir	HBV	TACE
mTOR inhibitor	Temsirolimus	mTOR	Sorafenib, TACE, bevacizumab, lenalidomide
	Everolimus	mTOR	Pasireotide, TACE,
Glypican inhibitor	GC33	GPC3	Sorafenib
Insulin growth factor inhibitor	Cixutumumab	IGF-1R	Sorafenib
	MEDI-573	IGF-1R	Sorafenib

decrease recurrence and mortality in patients with HBV/HCV-related HCC in meta-analyses (46,47). Whether sorafenib has benefit in patients after curative resection is the topic of the phase III trial STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) which has completed recruitment, with results expected soon. Many in clinical practice may use sorafenib in patients who were found to be beyond Milan criteria on the basis of the explanted liver, but no prospective data exists to support this practice. Two small retrospective studies showed increased overall survival in patients treated with sorafenib when transplanted beyond Milan criteria, and suggest a benefit of such practice (48,49).

Sorafenib and TACE: one + one = one

Historically, there was insufficient data for an evidenced-based guideline on the combined use of TACE and sorafenib. Thus, clinicians who incorporated this into their practice did so empirically. The theoretical combination

approach of embolization techniques with sorafenib was aimed at the possibility that sorafenib could slow the revascularization that occurs after embolization. Once these two modalities were placed in the hands of clinicians, adverse events were common. Additionally, some experts felt that pretreatment with sorafenib made embolization more difficult, and that larger chemo particles (>400 microns) were not adequately permitted to enter the tumor due to anti-VEGF therapy. These reports were attributed to the continuous anti-angiogenesis therapy with sorafenib. Additionally, use of TACE and sorafenib concurrently could possibly worsen adverse events related to variceal bleeding, hand foot syndrome (HFS), and hypertension. Due to the theoretical reasons mentioned, approaches were developed to temporally separate the two treatments.

As a result, sequential and interrupted strategies were advanced clinically and used in trials (50). Sequential therapy involves only starting sorafenib after TACE sessions are complete. The interrupted strategy starts sorafenib after the TACE session, and stops when more TACE is planned.

The Space Study had sorafenib started before TACE, but therapy was halted for one week before and at least three days afterward, thus decreasing the possibility that sorafenib would interrupt VEGF signaling or cause other signaling changes. The main benefit of the interrupted approach as opposed to the continuous approach is the possible decreased risk of variceal bleeding. Unfortunately, no randomized data is available using the interrupted strategy, and conflicting data exists on the safety of continuous treatment (51). Sequential therapy may offer strategic opportunities to alter angiogenesis, although there is no clear evidence to recommend this as a strategy. Additionally, the agents and concentrations of chemotherapy used vary by center, as does the use of doxorubicin bead-TACE (DEB-TACE). Most experts agree that the key intervention performed is the embolization of the vessel, with less importance assigned to the chemotherapy used. Three high-quality studies (randomized, double-blind, and placebo-controlled) were performed, and the comparative analysis of these studies shows the heterogeneity of patients, study designs, variability of endpoints, and TACE protocols in recent HCC trials. Additionally, the dosing reductions and sequence of sorafenib varied from study to study.

In a Japanese and Korean phase III study of patients with unresectable HCC, Kudo *et al.* reported on 458 patients with intermediate HCC randomized to receive 400 mg b.i.d. of sorafenib or placebo after TACE (52). The primary endpoint was time to progression (TTP). Most patients started on sorafenib/placebo nine weeks after TACE using a sequential strategy; the median dose of sorafenib administered was 386 mg per day. High rates of dose reduction (73%) and interruption (91%) were seen in this study. Median TTP in the sorafenib and placebo groups was 5.4 and 3.7 months, respectively [hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.70-1.09; $P=0.252$]. Despite the lack of efficacy, some suggest that this was related to significant reductions in sorafenib and high rates of adverse events compared with other studies. In the subgroup analysis of this study, Korean patients underwent longer sorafenib treatment duration and achieved significantly prolonged TTP (HR 0.38; 95% CI, 0.18-0.81).

Although the SHARP trial was not designed to assess the performance in sorafenib specific to certain liver diseases (7), post-hoc sub-group analysis showed HCV patients treated with sorafenib had significantly longer overall survival compared to those treated with placebo (14 *vs.* 7.9 months; HR 0.50; 95% CI, 0.32-0.77) (53). In a single-center study conducted in 2007 prior to knowledge of

the SHARP results, 62 HCV-positive patients with BCLC B HCC sequentially received either sorafenib (400 mg b.i.d.) or placebo 30 days after TACE (54). The primary endpoints were TTP and safety. The median TTP was 9.2 months in the sorafenib group and 4.9 months in the placebo group (HR 2.5; 95% CI, 1.66-7.56).

In the Sorafenib or Placebo in combination with TACE (SPACE) trial, 307 patients with intermediate-stage HCC received sorafenib, 400 mg b.i.d., or placebo continuously in combination with DEB-TACE. The primary endpoint was TTP in this phase II study. A trend toward prolonged TTP emerged with the sorafenib group compared to the placebo group (HR 0.79; 95% CI, 0.58-1.08); although median TTP was slightly better in the placebo group (5.6 *vs.* 5.5 months) (55). The dose interruption of sorafenib may explain the lack of response.

Although there continues to be significant interest in the combination of TACE and sorafenib, probably because of the general familiarity with each modality, efficacy has not been clearly shown, and data are currently inconclusive. The side effects with combined use of TACE and sorafenib are acceptable. Combined toxicity profiles are similar to those seen with either drug alone although there may be a potential additive toxicity in regards to HFS and hypertension. Further data is needed in regards to BCLC B and C. Randomized controlled trials are lacking; currently the combination of TACE and sorafenib does not appear additive.

Combination of sorafenib and chemotherapeutic agents

Theoretically, the combined use of sorafenib with chemotherapeutic agents that inhibit the MAPK pathway may reduce resistance to sorafenib (56). In a randomized trial comparing doxorubicin alone *vs.* in combination with sorafenib, patients receiving sorafenib fared significantly better in regards to TTP (6.4 *vs.* 2.8 months, $P=0.02$) (57). As there was no arm with sorafenib monotherapy, the authors could not conclude that the combination of doxorubicin and sorafenib proved better than sorafenib alone. The combination of sorafenib, capecitabine, and oxaliplatin compared to sorafenib monotherapy is currently being tested in a phase III trial based on early data showing favorable response rates (58).

Potential use of transarterial embolization

Transarterial radioembolization (TARE) with Yttrium-90

loaded microspheres is a form of brachytherapy. The procedure appears to be safe and efficacious in patients with unresectable HCC, although it does not appear superior to TACE based on preliminary data from non-randomized studies (59). TACE is associated with increased risk of ischemic-related necrosis in patients with portal vein thrombosis (PVT) (60) whereas TARE causes only minimal alteration in vascularity (microembolization) (61). In retrospective and non-randomized prospective studies TACE and TARE have generally shown similar performance although there seems to be reduced toxicity in TARE patients (59,62-65). Again, these trials suffer from inferior design and lack of uniformity in the TACE and TARE procedures making comparisons between studies difficult. Studies of TABE combination therapy with sorafenib are in progress as well. To date, no data exists on the combination of TARE and systemic therapy. Intriguingly, *in vitro* studies suggest that treatment with sorafenib re-sensitized radiation induces resistance via effects on Raf-1 (66). Given TARE's favorable side effect profile and potential mechanistic advantage of dual use, a well-designed trial testing the combination of TARE and sorafenib (or other systemic agents) would be worthwhile (67).

Failure of other tyrosine kinase inhibitors therapies: sunitinib, brivanib, and linifanib

Two other tyrosine kinase inhibitors, sunitinib and brivanib, were compared to sorafenib; neither demonstrated superiority. In the case of sunitinib, the trial stopped early due to statistically significant reduced survival in the sunitinib arm (27). Brivanib is another multikinase inhibitor that inhibits VEGF and FGF. In the phase III BRISK-FL trial, sorafenib and brivanib monotherapy were compared. Overall survival was similar so the trial did not meet its primary endpoint of non-inferiority to sorafenib. The side effect profile of sorafenib was slightly more favorable, making brivanib even less desirable as monotherapy (68). The disappointing results of these promising agents demonstrate the need for novel trial design. Whether these drugs might have improved outcomes if used sequentially or in combination with sorafenib or each other remains unknown. Linifanib is another potent inhibitor of the tyrosine kinase receptor that failed to show non-inferiority in comparison to sorafenib (69). As discussed earlier, dual tyrosine kinase inhibitor use has the potential to reduce resistance although to date these combinations have not been explored. Phase III trials to evaluate the combination

of TACE and sunitinib or TACE and brivanib have been proposed; however, there is no rationale to believe these combinations would perform better in this regard than sorafenib and these studies may ultimately not be completed.

Diversifying targets in HCC to attempt success

A number of other small molecules that target other aspects of HCC molecular pathogenesis are in development. A small phase II trial of erlotinib, an epithelial growth factor receptor (EGFR) inhibitor, showed an impressive 13-month survival in a patient with advanced HCC (70). The SEARCH (Sorafenib and Erlotinib, a rAnDomized tRIal protoCol for the treatment of patients with HCC) showed no advantage of combined treatment with sorafenib. Studies of erlotinib and bevacizumab combined therapy did not show improved outcomes to the historical controls from SEARCH (71). Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) which is a key driver of angiogenesis. In a phase II clinical trial it showed a favorable response but there are no further studies evaluating efficacy (72). In a recent single center study of TACE and bevacizumab compared to TACE alone, patients who received bevacizumab showed increased progression-free survival ($P=0.021$), although there was no difference in overall survival between the two groups (73).

The mTOR pathway has been identified as a target in a number of malignancies. In early phase I/II studies, everolimus monotherapy shows antitumor effects along with a reasonable safety profile (74). Combination studies of everolimus and sorafenib are ongoing. Rapamycin and temsirolimus also have the potential to be used against HCC. Other novel molecules such as trebananib are currently in early development. Trebananib targets angiopoietin signaling at later stages of vessel maturation and demonstrates synergy when combined with VEGF inhibitors in pre-clinical studies (75). This molecule will be tested in combination with sorafenib in an upcoming phase II trial.

Trial design for combination therapies

Review of the available literature demonstrates the paucity of combination therapy clinical trials undertaken outside of those attempting to add sorafenib or TACE to an agent. The principal benefits of combination therapy are to exploit synergy and differential susceptibility of tumors

to agents, and to utilize non-overlapping toxicities (76). Although there would appear to be much benefit from this approach, investigators cannot automatically assume that two safe drugs will remain as such when used in combination. Traditionally, in phase I testing of two agents in combination, the maximum tolerated dose (MTD) must be determined without regard to efficacy. Most experts now consider that an adaptive approach to combination therapy is beneficial due to the multiple variables involved in trial design. The main aim of these trials is to establish safety while dose escalating and maximizing the anti-tumor response (77). By their nature, these types of trials are much more complex to analyze statistically; as such, careful design consideration is needed.

Conclusions and future directions

Combination therapy for HCC is a promising avenue for patients with advanced HCC. There are many potential modalities and agents to explore as possible therapies; however, these need to be approached uniformly to enable appropriate data interpretation. As a community, we must move beyond sorafenib and TACE. Upcoming clinical trials should focus on inhibition of multiple targets based on preclinical data from basic scientists. The approach taken with HIV and HCV (in which multiple pathways for inhibition of viral replication are undertaken) could prove beneficial if applied to cancer pathogenesis. Furthermore, academic and industry leaders must establish new partnerships to facilitate testing of these new therapies in tandem. More research on individual therapy for patients is necessary. Fine needle aspiration of HCC and the tumor microenvironment along with genomic profiling may lead to more targeted therapy, thereby improving outcomes in clinical trials. Sampling of tumors may also allow for stratifying patients by biomarkers like c-Met.

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Footnote

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Transcatheter embolization therapy in liver cancer: an update of clinical evidences

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Abstract: Transarterial chemoembolization (TACE) is a form of intra-arterial catheter-based chemotherapy that selectively delivers high doses of cytotoxic drug to the tumor bed combining with the effect of ischemic necrosis induced by arterial embolization. Chemoembolization and radioembolization are at the core of the treatment of liver hepatocellular carcinoma (HCC) patients who cannot receive potentially curative therapies such as transplantation, resection or percutaneous ablation. TACE for liver cancer has been proven to be useful in local tumor control, to prevent tumor progression, prolong patients' life and control patient symptoms. Recent evidence showed in patients with single-nodule HCC of 3 cm or smaller without vascular invasion, the 5-year overall survival (OS) with TACE was similar to that with hepatic resection and radiofrequency ablation. Although being used for decades, Lipiodol® (Lipiodol® Ultra Fluid®, Guerbet, France) remains important as a tumor-seeking and radio-opaque drug delivery vector in interventional oncology. There have been efforts to improve the delivery of chemotherapeutic agents to tumors. Drug-eluting bead (DEB) is a relatively novel drug delivery embolization system which allows for fixed dosing and the ability to release the anticancer agents in a sustained manner. Three DEBs are available, i.e., Tandem® (CeloNova Biosciences Inc., USA), DC-Beads® (BTG, UK) and HepaSphere® (BioSphere Medical, Inc., USA). Transarterial radioembolization (TARE) technique has been developed, and proven to be efficient and safe in advanced liver cancers and those with vascular complications. Two types of radioembolization microspheres are available i.e., SIR-Spheres® (Sirtex Medical Limited, Australia) and TheraSphere® (BTG, UK). This review describes the basic procedure of TACE, properties and efficacy of some chemoembolization systems and radioembolization agents which are commercially available and/or currently under clinical evaluation. The key clinical trials of transcatheter arterial therapy for liver cancer are summarized.

Keywords: Transarterial; chemoembolization; hepatocellular carcinoma (HCC); drug-eluting particles; microspheres; Lipiodol®; radioembolization; yttrium-90

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third most common cause of cancer-related death (1). With improved surveillance of patients with chronic liver disease and advances in imaging, more patients are diagnosed with early-stage

HCC (2-4). For the treatment of early stage HCC, curative therapies including liver transplantation, hepatic resection, and radiofrequency ablation (RFA) are recommended. Liver transplantation is the treatment option especially for patients with decompensated cirrhosis, but potential recipients outnumber donors. Hepatic resection is widely used as the main choice of treatment for resectable HCC.

However, the risk of postoperative hepatic dysfunction often precludes surgery (5).

Intrahepatic cholangiocarcinoma (IHC) is the second most common primary hepatic neoplasm after HCC (6), with the highest incidence in Asia. At the time of diagnosis, patients with IHC usually present with advanced stage disease and only 30% among them are candidates for surgical treatment (7). Intravenous regimens including gemcitabine and various combinations of 5-fluorouracil (FU) with cisplatin provide low response rate (8).

Liver metastases can be found in 40% to 70% of patients with colorectal cancer (CRC) (9). Surgical resection is usually the standard treatment modality. However, resection can only be performed in a minority of patients due to the presence of multifocal tumors or limited hepatic reserve at the time of diagnosis (10). In the past, 5-FU and leucovorin (LV) constituted the foundation of most chemotherapy regimens. Recent years have seen important results in the treatment of advanced CRC, particularly in the use of new chemotherapy approaches and their combination with targeted therapies (bevacizumab, cetuximab and panitumumab). Modern regimens such as combined 5-FU/LV with oxaliplatin or camptothecin (CPT)-11 and monoclonal antibodies have achieved response rates of approximately 80%, and median survival of patients with non-resectable liver metastases has increased to 20-26 months. Nevertheless, the new systemic chemotherapeutic regimens have been associated with skin reactions, high costs and impaired liver functions. A further goal is therefore how to successfully achieve local control and increase the proportion of patients able to undergo liver resection, reduce recurrences, and prolong survival and quality of life of patients who remain unsuitable for resection.

Gastroenteropancreatic (GEP) neuroendocrine neoplasms, also called GEP neuroendocrine tumours (NETs), were previously regarded as rare, but in fact are increasing in incidence (11). Liver metastases represent the most crucial prognostic factor, irrespective of the primary NET site. In historical series, 5-year survival is 13-54% compared with 75-99% for patients without hepatic metastases (12). Despite various complex management strategies for neuroendocrine liver metastases, surgery is the only treatment that offers potential for cure.

Percutaneous ablations, including percutaneous ethanol injection (PEI) and RFA, represent the recommended curative modalities for patients with early-stage liver cancer who are not candidates for surgical resection or liver transplantation. Conventional transarterial

chemoembolization (TACE) is the gold standard for the treatment of patients with HCC who cannot receive curative therapies and radioembolization is an interesting alternative therapy for HCC patients who are poor candidates for TACE. Chemoembolization might offer long-term survival rates comparable to those of hepatic resection and RFA for small single-nodule HCC if underlying liver function was similar among the patients receiving each treatment (13,14).

Choice of minimally invasive treatment for HCC

PEI and RFA are widely used in clinical practice. With PEI, the distribution of ethanol may be blocked by the intratumoral fibrotic septa and/or the tumor capsule, resulting in a heterogeneous distribution. As a result, curative capacity of PEI, particularly in tumors greater than 2 cm in diameter is limited, and frequently requires multiple injections over multiple sessions. In contrast, RFA results in coagulative necrosis of both the tumor and a rim of surrounding parenchymal tissue producing a margin of ablated non-tumoral tissue, which might eliminate small-undetected satellites. RFA has been shown to be as effective as hepatic resection in the treatment of small single-nodule HCC (15,16). However, RFA of lesions located close to major organs or the liver capsule is often contraindicated (17). Giorgio *et al.* (18) compared the 5-year survival of patients with a single HCC ≤ 3 cm, who were randomly assigned to receive either PEI or RFA. No differences were observed in terms of overall survival (OS) or local recurrence rate. Oeda *et al.* (19) evaluated the association of treatment method with OS in 98 patients treated with PEI and 92 subjects who received with RFA. The 5-year survival rate in the PEI group was 40%, whereas it was 51% in the RFA group ($P=0.04$). When stratifying patients according to tumor stage, a significant advantage in survival was observed for RFA in individuals with stage II disease (5-year survival: 48 vs. 28% with PEI, $P=0.03$). However, RFA resulted in more severe complications and was more expensive than PEI. A recent meta-analysis of about 8,500 patients, with a 10-year perspective, showed that in patients with very early HCC and Child-Pugh class A, RFA provides similar life-expectancy and quality adjusted life-year at a lower cost compared with resection (20). While RFA is usually considered a front-line treatment choice in patients eligible for percutaneous techniques, with low cost and low complication rate PEI should be considered with suitable candidates with small HCC, particularly for HCC at difficult-to-treat location for RFA (21,22).

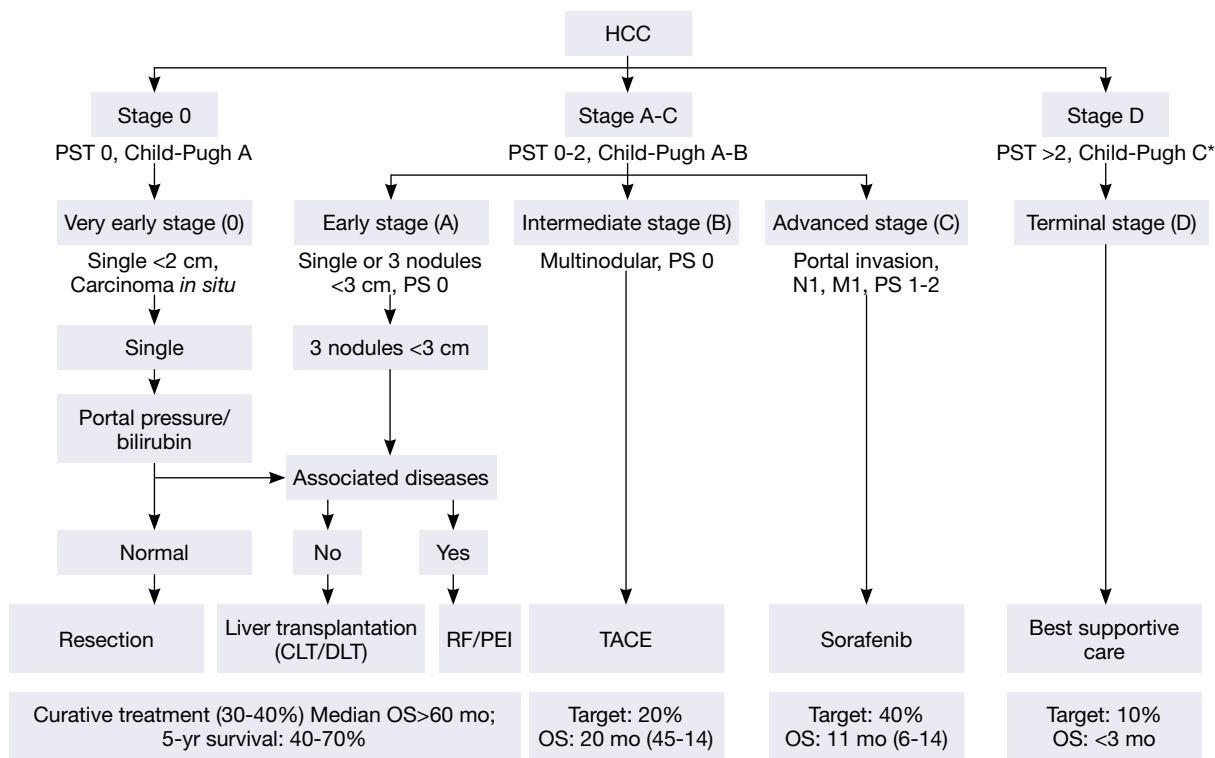


Figure 1 EASL-EORTC (European Association For The Study Of The Liver- European Organisation For Research And Treatment Of Cancer) clinical practice guidelines: management of hepatocellular carcinoma. Updated Barcelona Clinic Liver Cancer (BCLC) staging system and treatment strategy, 2011. Reproduced with the permission from ref. (23).

The Barcelona Clinic Liver Cancer (BCLC) algorithm (23) is widely used for the management of HCC in Europe and the USA (Figure 1). The European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines approved the BCLC classification system as a favorable staging system for prognosis allocation and treatment schedule which were validated from cohort studies and randomized controlled trials (RCTs). However, this classification also has limitations, such as absence of consideration of nodule location and etiology of cirrhosis (non-cirrhotic patients are not manageable with this classification). It does not consider treatment sequences or combination therapies which could lead to indications for selected patients with specific approaches that are not recommended to date. This comes from a too heterogeneous population, notably in the intermediate stage (BCLC stage B) in respect to tumor burden and liver function. In clinical practice, guidelines do not systematically reflect the best therapeutic approach for each patient. In selected patients treatment allocation should be determined on an individualized rather

than a guideline-based medicine by a multidisciplinary board. In Asia, resection of tumors in advanced stages and in patients with less than perfect liver function is more aggressively pursued. Consensus-Based Clinical Practice Guidelines Proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version is shown in Figure 2 (2). A recent staging and treatment allocation system issued by The Hong Kong Liver Cancer (HKLC) identified subsets of BCLC intermediate- and advanced-stage patients for more aggressive treatments than those were recommended by the BCLC system (Figure 3) (24). Very recently, a retrospective and single-center study (Johns Hopkins Hospital, Baltimore) on 968 North American patients showed that HKLC staging outperformed BCLC staging as a prognostic classification system in patients treated with intra-arterial therapy (presented at the Society of Interventional Radiology Congress, Feb 2015 by Sohn S & Geschwind JH). However, this HKLC staging system will require extra validation both in Asia and elsewhere, and it should also be tested in patients with liver disease other than hepatitis B (25).

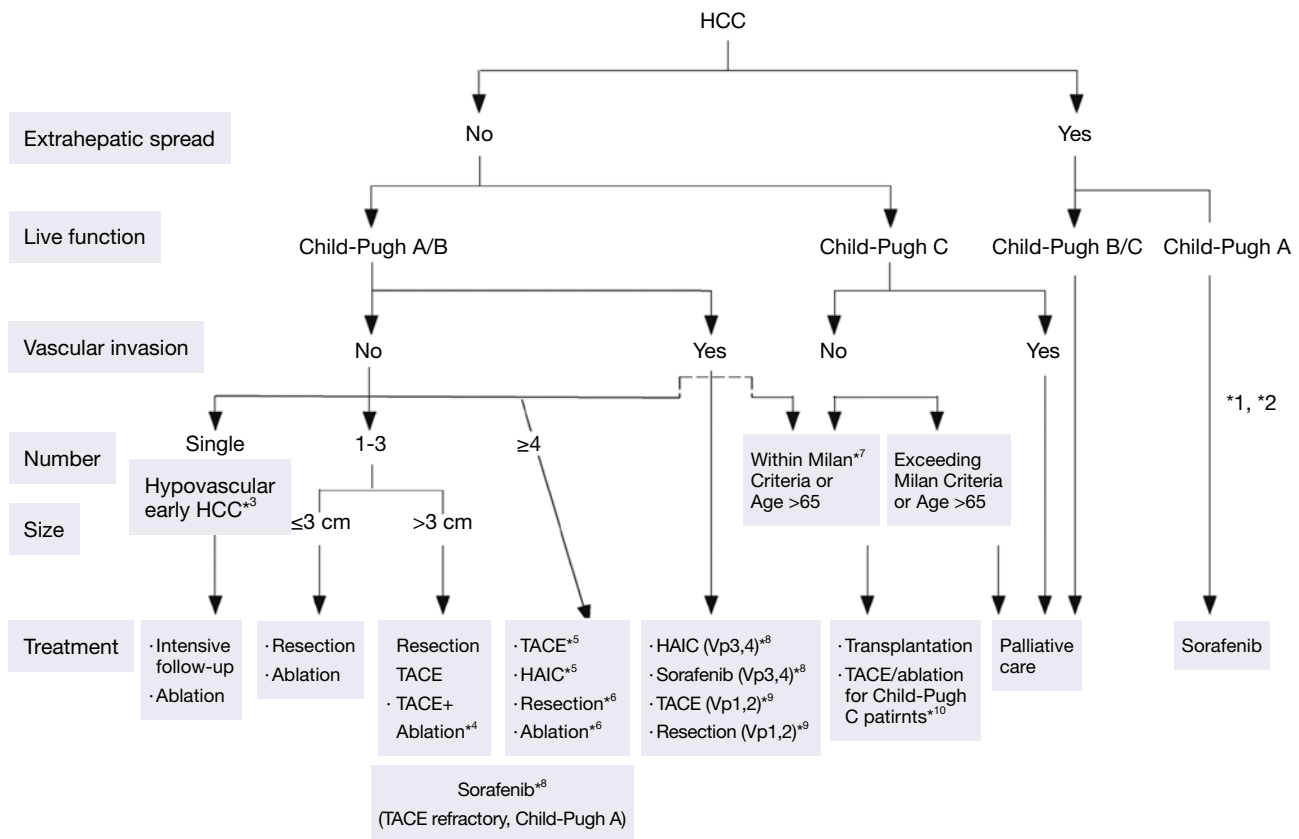


Figure 2 Consensus-based treatment algorithm for HCC proposed by JSH revised in 2010. Footnotes: *1, Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor; *2, Sorafenib is the first choice of treatment in this setting as a standard of care; *3, Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (I) when the nodule is diagnosed pathologically as early HCC; (II) when the nodules show decreased uptake on Gd-EOB-DPTA MRI; (III) when the nodules show decreased portal flow by CTAP, since these nodules are known to frequently progress to the typical advanced HCC; *4, Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated; *5, TACE is the first choice of treatment in this setting. HAIC using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5-FU + CDDP) or intra-arterial 5-FU infusion combined with systemic IFN therapy. Sorafenib is also a treatment of choice for TACE refractory patients with Child-Pugh A liver function; *6, Resection is sometimes performed even when numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE; *7, Milan criteria: tumor size ≤ 3 cm and tumor number ≤ 3 ; or solitary tumor ≤ 5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients; *8, Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal venous invasion at the first portal branch) or Vp4 (portal invasion at the main portal trunk); *9, Resection and TACE is frequently performed when portal invasion is minimum such as Vp1 (portal invasion at the third or more peripheral portal branch) or Vp2 (portal invasion at the second portal branch); *10, Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (<3.0 mg/dL). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue. Even in Child-Pugh A/B patients, transplantation is sometimes performed for relatively younger patients with frequently or early recurring HCC after curative treatments. HCC, hepatocellular carcinoma; JSH, Japan Society of Hepatology; CTAP, computed tomography arterial portography; TACE, transarterial chemoembolization; FU, fluorouracil; HAIC, hepatic arterial infusion chemotherapy. Reproduced with the permission from ref. (2).

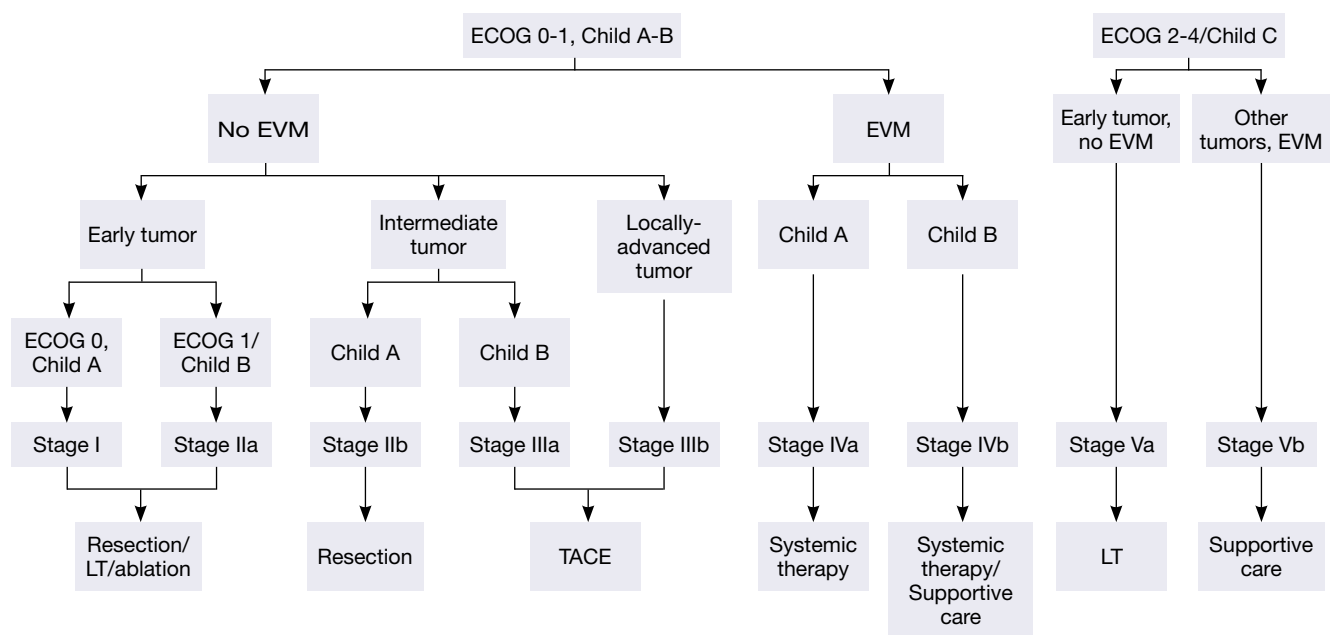


Figure 3 The Hong Kong Liver Cancer (HKLC) prognostic classification scheme. Early tumor: ≤ 5 cm, ≤ 3 tumor nodules and no intrahepatic venous invasion. Intermediate tumor: (I) ≤ 5 cm, either >3 tumor nodules or with intrahepatic venous invasion, or (II) >5 cm, ≤ 3 tumor nodules and no intrahepatic venous invasion. Locally-advanced tumor: (I) ≤ 5 cm, ≤ 3 tumor nodules and with intrahepatic venous invasion, or (II) >5 cm, >3 tumor nodules or/and with intrahepatic venous invasion, or (III) diffuse tumor. Abbreviation: EVM, extrahepatic vascular invasion/metastasis. Reproduced with the permission from ref. (24).

Recently, Yang *et al.* (26) compared the treatment effects of hepatic resection, RFA, and conventional TACE on long-term survival. It was found that 5-year OS with conventional TACE (c-TACE) was similar to that with hepatic resection and RFA in patients with single-nodule HCC of 3 cm or smaller without vascular invasion when the underlying liver status was balanced among the patients receiving each treatment. In addition, most of the patients initially treated with c-TACE achieved a complete response, which was one of the independent prognostic factors of survival, although some should receive repeated treatments. However, when c-TACE is used as an initial treatment, special care should be taken to obtain a complete response, and surveillance for tumor recurrence should be undertaken. These results are consistent with those of cohort studies demonstrating that TACE provided OS similar to hepatic resection in early-stage HCC (27,28).

Procedure for transarterial chemoembolization (TACE)

TACE with use of anticancer drugs followed with gelatin sponge (Gelfoam[®]) was introduced by Yamada *et al.* in the

late 1970s (29,30). The liver has a unique dual blood supply from both the portal vein and the hepatic artery. The normal parenchyma of the liver receives two-thirds of its necessary blood supply from the portal vein and receives the remaining one-third from the hepatic artery. Hepatic tumors receive their blood supply mainly from the hepatic artery. TACE is able to offer highly concentrated doses of chemotherapeutic agents to the tumor tissues, while the surrounding normal hepatic parenchyma is preserved. The embolic agent(s) causes ischemia and necrosis of the tumor, and slows anticancer drug washout (Figure 4). On the other hand, the blood supply to the normal liver tissue is maintained by the dominant blood supply from the portal vein system.

Chemoembolization is the infusion of a mixture of chemotherapeutic agents with or without iodized oil, associated with embolisation (32). According to the guidelines published by AASLD (33) and EASL (23), c-TACE is recommended as first-line therapy for patients who are not candidates for surgery, transplantation or ablation, i.e., HCC who do not have vascular invasion or extrahepatic spread.

TACE should be distinguished from three other interventional procedures: (I) transarterial oily chemoembolization (TOCE, or “chemo-lipiodolization”) where the anticancer

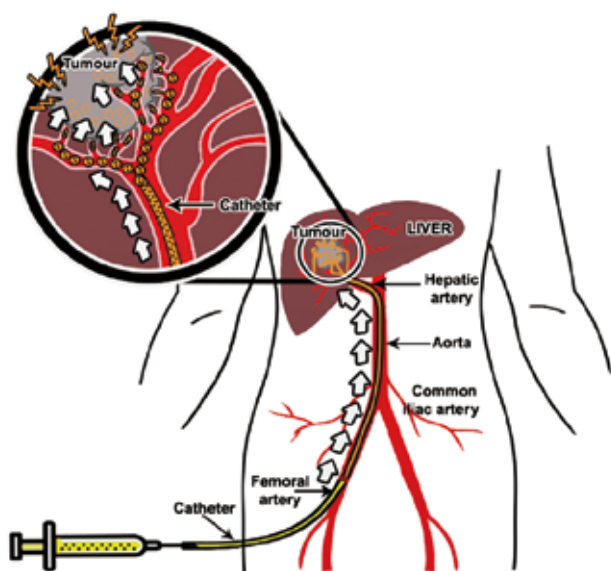


Figure 4 Principle of conventional transarterial chemoembolization. Reproduced with the permission from ref. (31).

agent is mixed with Lipiodol® without any other embolizing agent; (II) bland transarterial embolization (TAE) where no anticancer drug is given; (III) transarterial chemotherapy (TAC) where the anticancer drug is infused without Lipiodol or embolization particles.

TACE for liver tumors involves the following steps:

- I. Evaluation of portal vein patency;
- II. Angiographic evaluation of hepatic arterial anatomy and potential variations;
- III. Determination of the tumor arterial feeders;
- IV. Identification of the arteries that should be avoided during treatment delivery, e.g., right gastric and supraduodenal arteries;
- V. Identification of the patency of the portal vein or the presence of hepatopedal flow through collaterals to the liver in case of portal vein tumor thrombosis.

Prior to TACE, a thorough angiography is performed to locate all the feeding arteries of a tumor including any possible extrahepatic arteries that may feed the tumor. Once the arterial anatomy is clearly understood, a catheter is advanced superselectively into the feeding artery of the tumor. A 4F hydrophilic cobra catheter used with a hydrophilic guide-wire suffices for about half of cases. Use of a standard lumen catheter allows rapid injection of the viscous chemoembolic emulsion and is less likely to clog with particles. However, the catheter should not be used in vessels less than twice its diameter, as the catheter will

cause a partial occlusion of the vessel lumen, resulting in a pseudo-stasis. Withdrawal of the catheter then results in a reflow to the tumor. Small vessels and branches which cannot be accessed with a standard angiographic catheter can usually be catheterized with micro-catheters with a catheter diameter in between 2.0 and 2.4 French and 0.018- or 0.025-inch glide wires (34). The recent Surefire® Infusion System (Surefire Medical, Westminster, USA) is an 0.027-inch lumen microcatheter with an expandable tip at the distal end. This device is intended for use in angiographic procedures to increase targeted delivery, to minimize reflux and to dynamically collapse in forward flow. It is designed to deliver radiopaque contrast media and therapeutic agents (chemotherapeutic agents and solid and liquid embolic agents) to selected sites during TACE procedure (35,36).

When the catheter is positioned for treatment, it is important to perform an arteriography to confirm the anatomy before injecting any chemotherapy agents. This superselective injection may reveal findings not depicted in the celiac or superior mesenteric artery injection, such as cystic, right gastric or falciform arteries arising from the target hepatic artery, or guide-wire induced spasm in the target artery. The end point of the TACE procedure is visualization of the complete blockage of the tumor-feeding branch. It is essential to check for extrahepatic collateral arterial supply to the tumor lesion. An extra-hepatic collateral artery supplying a tumor is more frequent for subcapsular location or exophytic tumor. CT findings of a peripherally located portion of viable tumor on a follow-up CT scan should induce investigation of such arteries because of a close contact between the liver and the diaphragm, the blood supply to the diaphragm can reach the liver by direct adherence. Thus, the right inferior phrenic artery is the most common collateral pathway. Modification of TACE in patients with hepatic arteriovenous shunt (AV shunt) can be performed by either embolization with gelfoam or using balloon occlusion of the hepatic vein draining the shunt (37).

The most common sole-agent anticancer drug used in published TACE studies has been doxorubicin (36%), followed by cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin C (8%), and SMANCS (5%) (38). The administered dose of the anticancer agent should depend on the size of the tumor, the position of the catheter, the patient's liver function, and the response to previous courses of TACE, if any. It is worth mentioning that RCTs failed to show significant differences in survival between doxorubicin and other drugs such as cisplatin

or epirubicin, and till now, there is no evidence of the superiority of any single chemotherapeutic agent over other drugs or for mono-drug chemotherapy versus combination chemotherapy (38).

TACE is not recommended in early stages as a first option. At very early stage the HCC is not highly vascularized and its main blood supply comes from the portal vein, but as the HCC grows its blood supply increasingly comes from the hepatic artery, notably when the lesions are histologically well/moderately differentiated (39).

Liver functional reserve is the key to an optimal selection of candidates. Conventional TACE should be contraindicated in patients with decompensated cirrhosis. A panel of experts has recommended a series of absolute and relative contraindications for TACE that include hepatic encephalopathy, reduced or absent portal vein flow, biliary obstruction and large/massive tumors (40). TACE is generally contraindicated in patients with branch or main portal vein thrombosis (PVT), since occlusion of arterial blood flow may induce liver failure, although superselective TACE may not be harmful in selected patients with segmental PVT. Super-selective TACE, i.e., the catheter is selectively placed in a medium-small branch of hepatic artery, can be used in a patient with compromised liver function. There are recent uncontrolled trials and cohort studies that suggest a treatment benefit in selected patients with preserved liver function (41,42). A recent meta-analysis including 8 studies with 1,601 patients, concluded that TACE in patients with PVT improved the 6-months and 1-year survival compared with conservative treatment (43). If the patient has a diffuse or massive HCC or an HCC involving the major portal veins, TACE procedure cannot be safely performed.

TACE can cause a number of complications resulting from underlying factors of the patient or inadvertent techniques. Post-embolization syndrome that consists of transient abdominal pain and fever is common. It is not a complication of TACE per se. 60-80% of the patients after liver TACE experience this syndrome. It is usually self-limiting within 3-4 days (44).

A transient decline in liver function is common but acute liver decompensation (ascites, encephalopathy or jaundice) is reported in only 0.1-3% of procedures. Biliary and gastrointestinal complications have been reported in 2-10% and 1-5% of patients, respectively. Other complications include liver abscesses in patients with incompetent ampulla, vascular injury from repeated intraarterial chemotherapy, and tumor rupture. The most serious

complication is treatment-induced liver failure. TACE benefits should be balanced with the risk of this liver failure, thus the best candidates are patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread. Compromised liver function, main portal vein obstruction, biliary tract obstruction, a previous history of bile duct surgery, over dose of embolic agents, hepatic artery occlusion due to repeated TACE and nonselective TACE increase the chance for complications. The presence of these factors should be identified prior to TACE procedure, and an adjustment of the cytotoxic drug dosage, and a more selective procedure should be performed. The most morphologic contraindications for TACE also include hepatofugal flow or portosystemic anastomosis. Patients with Child-Pugh C and some with B, patients with a BCLC stage D, and patients with clinical symptoms of end-stage cancer should be excluded since the ischemic insult can lead to severe and even fatal adverse events.

Complete responses are rarely seen after a single session of conventional TACE and repeated sessions can be scheduled at fixed pre-planned intervals or depending on the observed response (40). Most of the recurrent tumors are supplied by feeders from the adjacent segmental arteries (45). Patients are thus evaluated every 3-8 weeks and additional TACE sessions are performed if contrast-enhanced areas revealing tumor activity are observed in cross-sectional imaging. Depending on the arterial anatomy, two to four procedures are required to treat the entire liver. Thereafter, response is assessed by repeated imaging studies and follow-up of tumor biomarkers.

Clinical evidence for transarterial embolization (TACE)

The most reliable way to confirm a survival benefit is large RCTs; however, initial small RCTs had failed to show a survival benefit of TACE treatment for HCC patients. In 2002, two RCTs from Spain and Hong Kong investigated the survival benefits of conventional TACE compared to the best conservative treatment (46,47). These RCTs were followed by cumulative meta-analyses (48,49), showing that c-TACE significantly reduced the overall 2-year mortality rate compared to control patients who received conservative treatments. In 2003, Llovet *et al.* (49) reported a meta-analysis, constructed from 7 RCTs including 545 HCC patients, comparing c-TACE or bland transarterial embolisation (TAE) *vs.* conservative

management or other therapies (systemic chemotherapy or tamoxifen). Most patients had cirrhosis, with Okuda stages I-II, and lacked evidence of PVT. Doxorubicin was used in one study and cisplatin in three; Gelfoam[®] was used as the embolic agent in all the trials. Mean number of treatment ranged between 1 and 5 sessions. Survival benefits were identified in two studies. The two-year survival rate in the treated group was 41% (range, 19-63%) *vs.* 27% (range, 11-50%) in the control group ($P=0.017$). The significant survival benefit was for c-TACE with doxorubicin or cisplatin, but not for bland TAE alone. In 2007, Marelli *et al.* (38) also found similar results in a meta-analysis. In a recent Asian prospective cooperative study including 99 HCC patients, however, conventional TACE was associated with median OS of 3.1 years with 2-year OS of 75% (95% CI: 65.2-82.8%) (50). O'Suilleabhain *et al.* (51) evaluated the long-term survival of TACE in patients with unresectable HCC and suggested that a cure for unresectable HCC may be possible with TACE, although this is rare. TACE after radical excision of HCC can also destroy remnant cancer cells, decrease recurrence rate, and increase survival rate. A possible survival advantage has also been reported in patients treated with TACE before resection of HCC when compared with resection alone (52).

TACE has shown to be effective in the treatment of CRC metastases for unresectable patients. In one article, nineteen trials were reviewed. In these studies, TACE has been applied in 324 patients with CRC metastases with conventional method or its variants (53), with response rates varying from 25-100%. In a prospective study, 463 patients with unresectable liver metastases of CRC that did not respond to systemic chemotherapy were repeatedly treated with TACE in 4-week intervals. The anticancer drug was mixed with Lipiodol[®] and consisted of mitomycin C alone, mitomycin C with gemcitabine, or mitomycin C with irinotecan. Embolization was performed with starch microspheres. Partial response was achieved in 68 patients (14.7%), stable disease in 223 patients (48.2%), and progressive disease in 172 patients (37.1%). The 1-year survival rate after TACE was 62% and the 2-year survival rate was 28% (54).

In addition to HCC and liver CRC metastases, TACE is also performed for cholangiocarcinoma (55), and hepatic metastases from neuroendocrine tumors (56), breast cancer (57), and other tumors including sarcoma (58), pancreas (59), and gastric cancer (60). There are also a few series supporting the use of TACE as a palliative option for metastatic neuroendocrine liver metastases. In a

retrospective analysis, the combination of mitomycin C with gemcitabine was found more effective in controlling local tumor growth than mitomycin C alone, with an improved 5-year survival of 46.7% *vs.* 11.1% with monotherapy (61). Liapi *et al.* retrospectively evaluated tumor response in 26 patients with decreased tumor size after treatment but with partial response in only 27% (WHO criteria) and 23% (RECIST criteria). Mean OS was 78 months (62). In cholangiocarcinoma, a single-center study with 115 patients confirmed excellent tumor response rates (57.4% with stable disease). The safety profile and tolerability was also good for the entire cohort with only 15 patients showing adverse effects. Finally the mean OS was 20.8 months with a 3-year survival of 10% (63). The data on the utility of TACE in cholangiocarcinoma is growing, especially in view of TACE ability to elicit a strong tumor response and disease control. As a result, and because the patients are living longer, there is a strong interest in designing studies—notably with DEBs—that would combine TACE with systemic therapies (such as gemcitabine and cisplatin).

Till now, several important issues remain to be clarified including what is the best chemotherapeutic drug, what is the best embolization agent and what is the most appropriate retreatment schedule. Centers differ in the characteristics of the patients treated, the choice of the embolizing agent used, the choice and/or dose of the anticancer agents used, the anticancer/Lipiodol[®] mixture preparation, embolization end-points, and the schedule and/or interval of retreatment. In the next sections, we will discuss some of the commonly used materials in conventional TACE and discuss some examples used clinically. Then, drug-eluting beads (DEBs) in TACE and radioembolization agents will be discussed. Results from the relevant key RCTs will also be highlighted.

Embolic agents

Transcatheter vascular occlusion can be achieved by using embolization agents such as gelatin sponge, starch microspheres, polyvinyl alcohol (PVA) beads, or collagen particles. Some embolization agents such as PVA polymer are not biodegradable. To allow repeated transcatheter therapy, biodegradable agents, such as gelatin sponge and starch microspheres are used. In general, small embolization agents (less than 100 μm) that embolize end-branches of the hepatic artery are favored as these agents can prevent the development of collateral arterial flow to a tumor. However, embolic agents too small in size such as gelatin powder that

are able to reach far smaller vessels can damage extratumoral liver tissue, including biliary duct system.

An early study on an *in vivo* rat model revealed that a mean particle diameter of at least 40 μm is required for embolization. Microparticles less than 40 μm in diameter can distribute to non-targeted organs, such as the lungs (64). On the other hand, particle size much larger than 1,000 μm can induce catheter clogging. Embolization agents with following size ranges are currently available from various vendors: 40-120, 100-300, 500-700, 700-900 and 900-1,200 μm . The diameter of occluded arteries generally correlates well with the embolic particle size. In addition, slower infusion of more diluted suspension provides a more distal arterial occlusion (65). The elasticity and shape of the particles also play a role; embolization particles with irregular surfaces tend to lodge in larger diameter vessels compared with regularly surfaced particles, and particles with a high degree of elasticity are more likely to reach small vessels (66). One of the common issues during intra-arterial embolization procedure is particle reflux, which could lead to embolization of untargeted areas within an organ or even other vital organs. Generally, large particles occlude more proximal vascular areas more quickly, which increases the risk of reflux and nontarget embolization (67). If the total number of particles injected exceed the target area that can maximally fill, reflux is likely to occur. A reduction in injection rate can reduce the risk of reflux and non-targeted embolisation. The use of calibrated particles (PVA or acrylic copolymer gelatin particles) is increasing worldwide since they can be chosen by size according to the target vessel (68).

Gelatin sponge

Gelatin sponge is one of the most commonly used embolization agents. It is a hemostatic agent composed of purified porcine-derived gelatin, and marketed as Gelfoam[®]. To prepare the embolisation particles, the gelatin sheets are cut into small pieces, and softened in fluid. Particle sizes are typically in the range of 0.5-2 mm. The vessel occlusion is temporarily, and recanalization occurs within a few days to weeks. Temporary embolization facilitates repeated intra-arterial treatment. As Gelfoam[®] particle size tends to be of millimeters in size, they are likely to clump in the larger artery and may not penetrate into the targeted small vessels. Gelatin sponge is also available as a powder, and can reach smaller vessels to achieve more distal embolisation. However, as gelatin powder can get much deeper into tissues, it can be more likely to lead to nontargeted

embolisation than the Gelfoam[®] particles.

Polyvinyl alcohol (PVA)

PVA particles cause permanent or semi-permanent vessel occlusion. PVA has a good safety profile. However, because PVA particles can be quite varied in size and shape, the particles tend to clump up occasionally, which can cause catheter clogging. Several vendors developed PVA-based microspheres specifically for TACE, such as PVA (Cook, Bloomington, USA), Contour SE[®] particles (Boston Scientific, Natick, USA) and Bead Block[®] (BTG, Surrey UK). DC/LC Bead[®] (BTG, Surrey UK) is microsphere that consist of PVA with a hydrogel core. The size range of these products varies from 100-1,200 μm (69). PVA could also be used to occlude collaterals that form after repeated embolization with other agents. A comparative study showed little difference in patient survival between TACE performed using gelatin sponge particles and TACE using PVA particles (70).

Embosphere[®]

To overcome the issue generated with irregular particle size and shape, spherical particles have been developed. Embosphere[®] is a spherical embolic agent marketed by Merit Medical (Rockland, MA, USA). It is polymeric microsphere made of trisacryl cross-linked with gelatin. It is also a permanent agent, and comes in calibrated size ranges. Due to the lack of aggregation, the smooth and hydrophilic surface, and its deformability, Embosphere[®] can penetrate deeper and embolise smaller vessels than PVA particles (71). However, it is not yet clear where Embosphere[®] or PVA is the most clinically effective embolization agent.

Embozene[®]

Embozene[®] (CeloNova BioSciences Inc., Atlanta, GA, USA) is a recently developed long acting embolizing agent, composed of a hydrogel core of polymethylmethacrylate and an exterior shell of a proprietary flexible polymer of polyphosphazene: Polyzene[®]-F, which is shown to be anti-inflammatory and bacterial-resistant (72). Embozene[®] microspheres are the only microspheres offering tightly calibrated sizes, namely 100, 250, 400, 500, 700, and 900 μm , with each size calibrated to have 95% of the particles within 50 μm of the nominal size. However, it remains to be demonstrated whether Embozene[®] microsphere, with

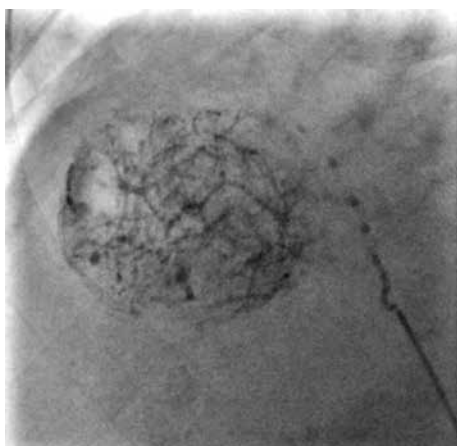


Figure 5 One patient with a giant hepatocellular carcinoma underwent TACE treatment. Radiographic image was obtained during the injection of the mixture drug/Lipiodol[®] through a micro-catheter. Note the typical aspect of lipid droplets progressing through arteries and filled the HCC tumorous vasculatures. TACE, transarterial chemoembolization; HCC, hepatocellular carcinoma.

such a tight controlled particle size, would bring additional clinical benefits for embolisation.

Degradable starch microsphere

Some studies suggested the post-embolization syndromes can be less pronounced using temporary embolizing agents (73). As discussed above, gelatin sponge can maintain occlusion up to several weeks. For shorter duration, Degradable Starch Microsphere (Spherex[®], Magle Life Science, Lund, Sweden; EmboCept[®], Pharmacept, Berlin, Germany) provides transient occlusion of small arteries. Spherex[®] consists of sterilized starch microspheres suspended in saline solution. The TACE procedure involves the co-injection of the anticancer drug with Spherex[®] (74). More recently, EmboCept S[®] (PharmaCept, Berlin, Germany) has been marketed (*in vitro* degradation half-life =35 min, only size available is 50 μm). In the blood stream, the starch microspheres are degraded by serum-amylases and the blood flow is restored within 60-80 minutes. Favorable response suggests that TACE using mixture with Spherex[®], Lipiodol[®] and anticancer drug could be a suitable palliative measure in patients who might not tolerate long acting embolic agents (74). Poly (ethylene glycol) methacrylate (PEGMA) hydrolyzable microspheres (ResMic[®], Occlugel, Jouy-en-Josas, France) is another calibrated and resorbable embolic agent (75).

Lipiodol[®]

Lipiodol[®] (Lipiodol[®] Ultra Fluid, Guerbet, Roissy, France), also known as ethiodized oil, is an oily contrast medium with an iodine content of 38 percent by weight. Its iodine concentration is 480 mg/mL. The viscosity of Lipiodol at 37 °C is approximately 25 mPa.s and its density is 1.28. It consists of a mixture of di-iodinated ethyl esters of fatty acids from poppy seed (*Papaver somniferum L.*) oil (31). Basically, Lipiodol[®] combines four characteristics that explain its wide use in TACE procedures: (I) it is opaque to X-rays; (II) it can be used for drug delivery purposes, with substantial versatility regarding the therapy that can be delivered (including immune or gene therapies); (III) it has tumor-seeking properties; (IV) it induces a transient and plastic embolization of tumor microvessels (Figure 5) (76-79). It is not designed to achieve complete and permanent arterial occlusion, as it is eventually washout from the target organ/area. When selectively injected into the hepatic artery, Lipiodol[®] selectively remains more in tumor nodules for several weeks to over a year due to a siphoning effect from hypervascularization of the tumor vessels and the absence of Kupffer cells inside tumor (Figures 6,7). Non-clinical studies with fluorescent tracer have shown that, in the case of exclusive arterial embolization, the drop in the peribiliary plexus blood pressure would allow portal perfusion of the liver tumor. Conversely, because of its oily nature, Lipiodol[®] distributes in both the tumor artery branches and the peritumor portal venules, thus allowing transient dual embolization (79).

Lipiodol[®] is used as a vehicle to carry and localize the anticancer drug inside the tumor. Broad-spectrum of anticancer drugs are used in conjunction with Lipiodol[®]. When the solubility of the anticancer drug in Lipiodol[®] is low, the so-called “lipiodolization” technique is used. In brief, the cytotoxic drug is first dissolved in saline. Then the drug dissolved in saline and Lipiodol[®] are vigorously mixed, and shaken to form an homogeneous mixture. It is recommended to start by pushing the syringe with the anticancer drug first into the Lipiodol[®] syringe. The mixture is to be prepared at the time of use and must be used promptly after preparation (within 3 hours). If necessary during the procedure, the mixture can be re-homogenized. When the Lipiodol[®] and drug mixture is injected into a tumor supplying vessels, the anticancer drug is slowly released from Lipiodol[®] and remains in high concentrations within the tumor for a prolonged period.

Generally, embolic agent is applied immediately after

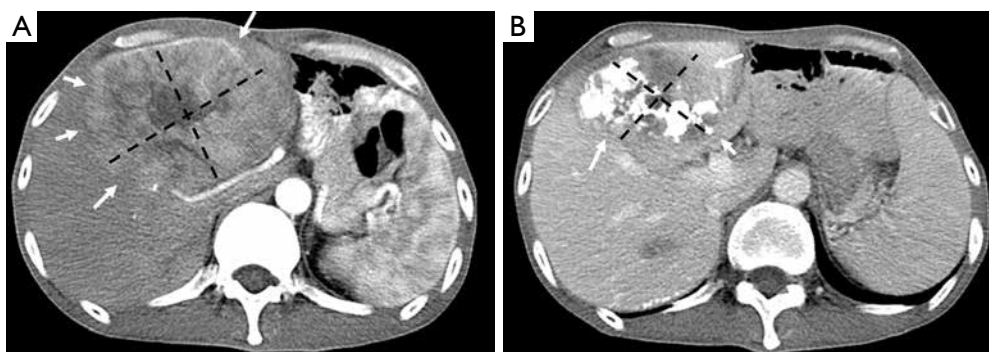


Figure 6 One patient with a giant hepatocellular carcinoma underwent TACE treatment composed of a mixture of pirarubicin 10 mg, cisplatin 30 mg, bleomycin 8 mg, and 20 mL Lipiodol®. (A) contrast-enhanced X-ray computed tomographic (CT) images show the giant tumor (arrows); (B) follow-up contrast-enhanced X-ray CT 3 months post-TACE, the tumor appears smaller and Lipiodol® continues to deposit within the tumor.



Figure 7 One patient with a hepatocellular carcinoma underwent TACE treatment. (A) Plain X-ray computed tomographic (CT) images show the tumor (arrows). Two courses of chemoembolization mixture composed of cisplatin 40 mg, mitomycin 6 mg, pirarubicin 30 mg, 10 mL Lipiodol®, and of cisplatin 20 mg, pirarubicin 20 mg, 5 mL Lipiodol® were administered with an interval of 2 months; (B) follow-up contrast-enhanced X-ray CT 2 months after the first-TACE; (C) follow-up contrast-enhanced X-ray CT 4 months after the second TACE. The tumor appears smaller and Lipiodol® continues to deposit within the tumor.

the injection of the Lipiodol® formulation into the hepatic artery. Further embolization procedures may be necessary if blood supply to the tumor has been unexpectedly developed via various extrahepatic collateral pathways. Studies have shown that Gelfoam® embolization facilitates the slow release of doxorubicin from Lipiodol®, hence further increasing the drug concentration inside the tumor by preventing washout of the mixture (80). Recent studies have tried to develop new formulations. A Lipiodol®–pirarubicin mixture may be more effective and more stable *in vitro* than the classical doxorubicin-Lipiodol® mixture (81). A novel lipophilic platinum complex (SM-11355), which is a derivative of cisplatin, developed for Lipiodol® suspension, has been shown in clinical studies to lead to a lower plasma

platinum concentration but a longer half-life, reflecting the sustained release properties of this formulation (82).

Patients with heterogeneous Lipiodol® uptake on CT scan have higher tendency of recurrences during the follow-up period than those with homogeneous uptake. The degree of Lipiodol® labeling has been found to be an independent prognostic factor (83,84). While Lipiodol® has been widely adopted in TACE protocols, it may also mask assessment of residual vascularity on CT imaging following therapy, thereby requiring routine follow-up with contrast enhanced MRI.

Drug-eluting beads (DEBs)

DEB is a relatively novel drug delivery embolization system,

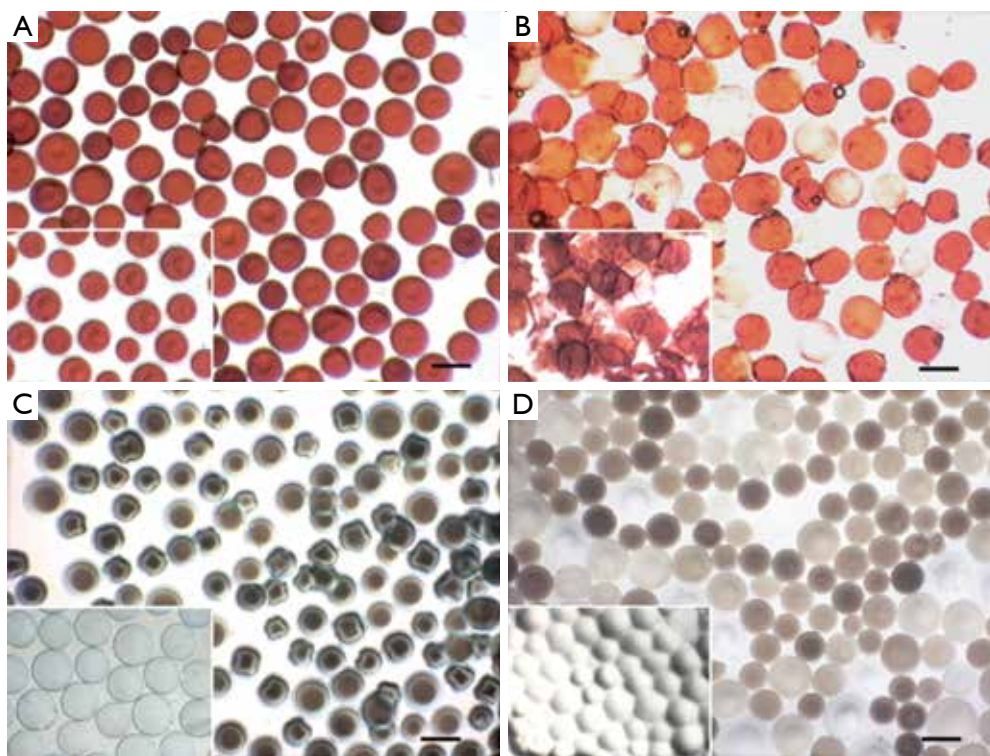


Figure 8 Photomicrographs of doxorubicin-loaded DC Beads[®] (A) and Hepaspheres[®] (B) microspheres and irinotecan-loaded DC Bead (C) and Hepasphere (D) microspheres. In the lower left corners, insets show the aspect of the beads retrieved after the release experiment (1-week exposure to 5 mL/min NaCl 0.9% flow). Scale bars indicate 500 μ m. Reproduced with the permission from ref. (85).

comprising biocompatible, nonresorbable PVA polymeric microspheres doped with sulfonyl groups resulting in a static charge leading to reversible ionic binding with polar molecules such as doxorubicin (Figure 8). These beads allow for fixed dosing and the ability to release the anticancer agents in a sustained and controlled manner. Significant reductions of peak plasma concentrations have been observed with DEBs when compared with conventional chemoembolization in a limited number of patients (86,87). Two particles are commercially available, i.e., DC/LC-Beads[®] (Biocompatibles, UK) and HepaSphere[®] (BioSphere Medical, Inc., USA) that can be loaded with doxorubicin for the treatment of HCC.

DC/LC-Beads[®]

The DC/LC Bead[®] has undergone clinical investigations (88,89). The product is indicated for the treatment of treating a variety of malignant hypervascularised tumours, including HCC. It is a PVA based microspherical embolization agent, prepared from N-acrylamidoacetaldehyde derivatized

PVA copolymerized with 2-acrylamido-2-methylpropane sulfonate. The presence of the anionic sulphonate group enables the sequestering of positively charged drugs, such as doxorubicin, epirubicin or irinotecan, by Coulomb charge interactions. The drug is slowly but incompletely released from the beads in the targeted site (85). The transcatheter drug delivery is simplified as the drug (e.g., doxorubicin) and the embolic particles (the sulfonate modified PVA bead) are administered at the same time.

The sizes of the bead are available in different size ranges: 100-300, 300-500, 500-700, and 700-900 μ m, with drug loadings varying from 5 to 45 mg/mL hydrated beads (90). Patients could receive three or four chemoembolization treatments within 6 months. It has been demonstrated that DC Bead[®] spheres could be loaded with doxorubicin to a recommended level of 25 mg/mL hydrated beads, whereas other commercial embolic microspheres such as Contour SE[®], Embosphere[®], and Bead Block[®] were shown not to load doxorubicin to the same extent or release it in the same fashion (91). *In vitro* study showed doxorubicin does not release from the beads when the elution medium was

pure water, while when the elution medium contained ions and phosphate-buffered saline solution, reproducible and sustained release profiles were demonstrated (89). With a drug load of 25 mg/mL bead, the rate of drug release from the 700-900 μm beads was slower than that from the 100-300 μm beads, with a half-life of 1,730 and 150 hours, respectively (91). These half-life data translate to a less than 1% and 20% of drug released over 24 hours from the total available drug loaded to the 700-900 and 100-300 μm beads, respectively. In a subsequent study (85), it was shown that the loading and release of doxorubicin followed a dose-response relationship. Using the 500-700 μm beads, it was found that the half-life increased from 381 to 3,658 hours as the concentration of doxorubicin load increased from 6.25 to 37.5 mg/mL. For a fixed drug load of 37.5 mg/mL, the half life was only weakly dependent on bead size, with a minimum of 1,505 hours for the 100-300 μm beads. One study on a rabbit liver VX-2 tumor model confirmed a high level of doxorubicin in the tumor over the entire period of study of 14 days and associated widespread necrosis of the tumor tissue (86). The *in vitro* elution data of doxorubicin have been shown to correlate well with the areas under the curve of 15 patients treated with DC/LC Bead[®] loaded with doxorubicin in the PRECISION V clinical study (92). This covered all doses used in the study: 6.25, 12.5, 18.75, 25, and 37.5 mg/mL in 24 hours.

The size of the DC/LC Bead[®] used is usually selected based on the anatomy of the feeding vessels. It is recommended to choose smaller (100-300 or 300-500 μm) particles first, followed by larger (500-700 μm) particles. Other groups used small (40-120 μm) particles until stasis in the target vessel was achieved. In the case of diffuse tumors, lobar or segmental embolization is performed, and if hepatic vein shunting is identified, larger particles are used to minimize the risk of non-targeted pulmonary embolization. While the DEB relies on passive release/diffusion of drug from the carrier, a delivery system with the ability to actively release the drug payload (e.g., via heat/magnetic triggered release) would enhance the flexibility of the dosing regimen and potentially improve the efficacy of the treatment.

HepaSphere[®]

HepaSphere[®] (Merit Medical, Rockland, MA, USA) is biocompatible, hydrophilic (absorbent), nonresorbable, and expandable microsphere. HepaSphere[®] is conformable and swells upon exposure to aqueous solution. It was made

with sodium acrylate and vinyl alcohol copolymer. The particle size is precisely calibrated in the dry state. The dry microsphere absorbs fluid and swells within several minutes when exposed to aqueous-based media. The swollen particle is soft, deformable, and easily delivered through the majority of the currently available microcatheters.

In vitro doxorubicin release has been investigated for DC-Beads[®] and Hepaspheres[®]. While doxorubicin-loaded DC Beads[®] maintained their spherical shape throughout the release, Hepaspheres showed less homogeneous drug loading and, after release, some fractured microspheres were found. Interestingly, incomplete doxorubicin release was observed in saline over 1 week for both DEBs (27 \pm 2% for DC Beads[®] and 18 \pm 7% for Hepaspheres[®]; $P < 0.013$). This effect was attributed to strong doxorubicin-bead ionic interactions. With irinotecan, drug release was found to be faster, an effect which may be explained to weaker interactions (92).

The dry HepaSphere[®] DEBs are supplied in a range of sizes, namely, 50-100, 100-150 and 150-200 μm . *In vitro* studies demonstrated that particle diameters in ionic contrast media are approximately 2 and 3.5 times larger than the original diameters in the dry state and 4 times larger in human serum. The polymer contained within HepaSphere[®] is anionic, which allows the sequestering of cationic drug molecule, such as doxorubicin or epirubicin by Coulomb charge attraction (as in the case of DC Bead[®]). This enables cationic chemotherapeutic agent to be carried within the microsphere. Moreover, these particles, because of the slightly larger expansion in human serum, are able to mold to the morphology of the vessel lumen.

HepaSphere[®] has been evaluated in an initial clinical study which comprised of 50 patients in four centers (93). The microspheres were either loaded with doxorubicin (mean dose 43.6 \pm 8.7 mg) or with epirubicin (mean dose 41.7 \pm 14.6 mg). It has been shown that TACE using HepaSphere[®] is feasible, well-tolerated, and is associated with good tumor response. Repeated TACE procedures can be carried out without difficulties. The objective response rate of the initial HepaSphere[®] study was comparable to that of DC Bead[®] obtained in initial clinical studies (93). However, it is currently unclear of the clinical benefit of using HepaSphere[®] over DC Bead[®], other DEBs or conventional TACE.

Irinotecan-eluting beads

5-FU has been the standard treatment for CRC metastases

for more than 40 years. Irinotecan, a topoisomerase inhibitor, has recently been developed as a chemotherapy agent for the treatment of CRC metastases. With the combined use of 5-FU and irinotecan the survival rate of CRC patients has been shown to improve significantly comparing with those given 5-FU alone. Based on the interest of DC Bead[®], the same vendor (BTG, Surrey, UK) has developed irinotecan-eluting bead for the treatment of liver CRC metastases (94). The system consists in combining embolisation beads (DEBIRI[®]) with irinotecan hydrochloride solution. It has been shown that the DEB of sizes ranging from 100-900 µm can load irinotecan up to a maximum capacity of 50 mg/mL of beads. The *in vitro* release profile of irinotecan was shown to be sustained and dependent on the presence of ions in the elution medium, drug loading, and bead size (95). Irinotecan-eluting bead is currently undergoing several RCTs in the treatment of liver metastases of CRC (96,97).

Conventional TACE (c-TACE) versus DEB-TACE for hepatocellular carcinoma management: a comparison

In a small and non-comparative study, TACE performed using DEBs loaded with doxorubicin has been shown to reduce the drug-related side effects while maintaining the same therapeutic efficacy (87). A prospective randomized comparison of chemoembolization with doxorubicin-eluting DC/LC Beads[®] and arterial bland embolization with Bead Block[®] PVA microspheres (BTG, UK) for HCC concluded that there is an additional benefit from the addition of doxorubicin (98). In this study, there was a complete response in 26.8% of patients in the DEB group and 14% in the arterial bland embolisation group at 6 months. Time to progression was longer for the DEB group than in the group with bland embolisation (42.4±9.5 *vs.* 36.2±9.0 weeks, *P*=0.008). The prospective randomized PRECISION V phase II study compared TACE doxorubicin loaded DC Beads[®] to conventional TACE procedure (intra-arterial injection of doxorubicin emulsified in Lipiodol[®] followed by particle embolization with Gelfoam[®] or PVA particles). The primary endpoint was tumor response according to the amended EASL criteria (99). This study included 212 HCC patients with large or multinodular HCC. At six months, both groups had similar tumor response rate (complete response in the DC/LC Beads[®] group: 27%, in the conventional TACE group: 22%, objective response rate: 57% and 44% respectively and disease control rate: 63% *vs.* 53%, *P*=0.11). Treatment-related serious adverse events

within 30 days of the procedure were similar. However, secondary safety outcomes, including incidence and severity of adverse events, liver function parameters, and cardiac function, were significantly better in the DC Beads[®] group (100). A sub-analysis of this trial showed that liver toxicity and cardiac toxicity were significantly lower in DC/LC Beads[®] group (101). Subsequently, a RCT compared TACE doxorubicin loaded DC Beads[®] to conventional TACE followed by selective embolization with gelatin sponge particles, in 67 patients with unresectable HCC. The one-month complete response rates were 51.5 and 70.6% after DEB-TACE and conventional TACE respectively. No difference between groups was found with respect to time to recurrence, local recurrence, radiological progression and survival. The increase in alanine aminotransferase was higher in the conventional TACE than in the DEB-TACE at 24 hours (102). A recent randomized clinical trial (PRECISION Italia study) compared the clinical efficacy and safety of DC-Beads[®] and conventional TACE in 177 patients. The 1- and 2-year survival rates were similar: 86.2% and 56.8% after DC/LC-Bead[®]-based TACE and 83.5% and 55.4% after conventional TACE (*P*=0.949). There were no differences in terms of adverse events incidence and severity, except less post-procedural pain with DEBs (103). Two recent meta-analyses (both concerning 7 RCTs and around 700 patients) comparing DEB-TACE with conventional TACE concluded that both techniques lead to similar clinical response and tolerance (104,105).

In a retrospective study of patients treated for a well-differentiated metastatic neuroendocrine tumors or HCC, the occurrence of biloma and parenchymal infarct was significantly associated with DEB-TACE, irrespectively of the tumor type (106). Similar results were subsequently reported in patients treated for neuroendocrine liver metastases (107).

In a recent retrospective study of 164 patients receiving 374 TACE, multivariate analysis revealed that DEBs of size >300 µm induced more non-tumoral liver necrosis compared to Lipiodol[®]-based TACE or DEBs <300 µm, and pretreatment bile duct dilatation and PVT were predictive of liver necrosis (108). As with conventional TACE, DEB-TACE is generally well tolerated and not surprisingly the spectrum of adverse events is similar to conventional TACE. It has a more favourable pharmacokinetic profile than conventional TACE that translated into less doxorubicin-related systemic adverse events in one RCT (100). With DEBs launching, physicians hoped to standardize TACE procedure in comparison with conventional practice (109),

Table 1 Important features of conventional and drug-eluting beads-based TACE

	Conventional TACE	DEB-based TACE	References
Proven benefit on overall survival (vs. best standard care)	Yes	Yes	(23)
Real-time fluoroscopy-guided drug delivery	Yes	No	(62)
Tumor labeling on CT (prognostic value)	Yes	No	(83)
Duration of embolization effect	Transient	Permanent	(62)
Selectivity for the tumor	Yes (depends on vessel size)	Yes, if small particle size (<300 µm)	(77) (78) Namur 2010
Local release of anticancer drug	Fast	Low	Namur 2010*
Systemic release of anticancer drug	Moderate	Low	(40) (87)
Versatility of drug delivery	Yes	No	(31)
Allows simultaneous local delivery of several therapies	Yes	No	(62)
Risk of liver infarct and biloma	Low	High (beads >300 µm)	(106) (107) (108)
Cost (mean overall procedure included hospitalization, consumables, medical acts)	€2,869	€3,960	Clouet 2014** (French study)

TACE, transarterial chemoembolization. *, Namur J, *et al.* J Vasc Interv Radiol 2010;21:259-67. **, Clouet J, *et al.* Diagn Interv Imaging 2014;95:427-34.

aimed at defining standards for an appropriate and consistent use DC/LC-Beads[®]. These general guidelines are related to pretreatment imaging, peri-procedure medication, loading dose of doxorubicin, planned dose of doxorubicin, choice of beads size, beads dilution, catheter positioning, injection rate and embolization end-point. However, given the many patient- and tumor-related variables that play a role in the decision-making process and given the complexity of HCC, individual patient and tumor characteristics may require a different approach with DEBs which often require a customized/non-standardized approach.

The most important features of conventional and drug-eluting beads-based TACE are summarized in *Table 1*.

Transarterial radioembolization (TARE)

External beam irradiation has historically played a limited role in the treatment of HCC due to the radiosensitive nature of normal hepatic tissue. Radiation exposure limit in the liver is rather 70 Gy in non-cirrhotic liver and 50 Gy in cirrhotic liver. Liver exposure to greater radiation doses may result in a clinico-pathological syndrome characterized by ascites, anicteric hepatomegaly, and elevated liver enzymes, developing weeks to months following therapy. Given these limitations, minimally invasive transarterial radioembolization (TARE) has emerged. Radioembolization is defined as the injection of micron-sized embolic

particles loaded with a radioisotope by using percutaneous transarterial techniques. Yttrium-90 (⁹⁰Y) is commonly used for this purpose. ⁹⁰Y is a pure beta emitter that decays to stable zirconium. Its physical half-life is 64.2 hours. The emissions generated have a mean tissue penetration of 2.5 mm, with a maximum reach of 11 mm. This limited tissue penetration allows for local high dose radiation with less risk of radiation induced hepatic necrosis than may be seen with external beam therapy. Two types of microspheres are commercially available, i.e., SIR-Spheres[®] (Sirtex Medical Limited, Australia) and TheraSphere[®] (Biocompatibles, UK). These two devices are different in a number of important respects. TheraSphere[®] has higher specific activity (2,500 Bq) and lower number of spheres (1.2 million microspheres/3 GBq). Conversely, SIR-Sphere[®] has lower specific activity (50 Bq), and greater number of spheres (approximately 40-80 million spheres/3 GBq).

TheraSphere[®] was approved in 1999 by the Food and Drug Administration under humanitarian device exemption for the treatment of unresectable HCC in patients who can have appropriately positioned hepatic arterial catheters. TheraSphere[®] is composed of non-biodegradable glass microspheres ranging from 20 to 30 µm in diameter, in which ⁹⁰Y is an integral constituent of the glass. One gigabecquerel (27 mCi) of ⁹⁰Y per kilogram of tissue provides a dose of 50 Gy. The microspheres are supplied in 0.5 mL of sterile, pyrogen-free water contained in a 0.3-mL V-bottom vial secured within a 12-mm clear acrylic shield.

The specific activity is 2,500 Bq at the time of calibration.

SIR-Sphere[®] was granted premarketing approval in 2002 from the Food and Drug Administration for the treatment of colorectal metastases in conjunction with intrahepatic floxuridine, an analog of 5-FU. SIR-Sphere[®] consists of biodegradable resin-based microspheres containing ⁹⁰Y. The average size of a sphere is 35 µm (range, 20–60 µm) in diameter. Each vial contains 3 GBq of ⁹⁰Y in a 5 mL vial. Each vial contains 40–80 million spheres. The activity per microsphere is 50 Bq at the time of calibration.

Rhenium-188 radioconjugate can be available through the use of a Rhenium-188 generator. The half-life of Rhenium-188 is 16.9 hours. The isotope delivers high-energy beta emission (2.1 MeV max) and a low energy gamma emission (155 keV) permitting SPECT/PET imaging for dosimetry step and follow-up post-TARE. Usually, this radioconjugate is in the form of Rhenium-188 4-hexadecyl 1, 2, 9, 9-tetramethyl-4, 7 diaza-1, 10-decaethanilol labeled with Lipiodol[®] (110). Dosimetry is based on the safe and tolerable dose to organs at risk including the liver, lungs and bone.

In contrast with the larger than 100 microns particles used in TACE to occlude tumor feeding vessels, much smaller particles (25–35 microns) are used in TARE to reach the tumor microvasculature. Clinical experience with TARE has shown a low incidence of post-embolisation syndrome, supporting its minimally embolic effect (110–123). Gulec *et al.* (117) retrospectively analyzed the data from a heterogeneous cohort of 40 patients with primary and metastatic liver malignancies who underwent treatments using ⁹⁰Y resin microspheres (SIR-Sphere[®]). The average administered activity was 1.2 GBq and tumor absorbed doses ranged from 40.1 to 494.8 Gy. The authors concluded that doses up to 100 Gy to the uninvolved liver were tolerated by this procedure without the development of veno-occlusive disease or liver failure. The authors further noted that lowest tumor dose necessary to generate a detectable response was 40 Gy.

Broadly equivalent survivals after TACE and TARE have been reported in retrospective analyses of single institutions. A comparative analysis was reported including 463 patients treated with either TACE or TARE (118). Fatigue and fever were more common following TARE; while abdominal pain, diarrhea and aminotransferases elevations were more frequent following TACE. Response rate was in favor of TARE over TACE (49% *vs.* 36%, *P*=0.052). Overall, although TARE time to progression was significantly better than TACE (13.3 *vs.* 8.4 months, *P*=0.0232), median

5-year survival was not significantly different. In the largest comparative study, all-type adverse events, response rate and time to progression were better in TARE than in conventional TACE but OS was no different (119).

Most patients currently treated by TARE are poor candidates to TACE because of a high tumor burden, presence of vascular invasion or lack of response to previous TACE. Radioembolization is one of the more technically challenging transcatheter embolisation procedures because of the risk of non-target embolisation. Two absolute contraindications exist for the use of ⁹⁰Y microsphere treatment in any patient (116,123). The first is a pretreatment ^{99m}Tc macro-aggregated albumin (MAA) scan demonstrating significant hepato-pulmonary shunting (>20%) that would result in >30 Gy being delivered to the lungs with a single infusion or as much as 50 Gy for multiple infusions. The second is the inability to prevent deposition of microspheres to the gastrointestinal tract with modern catheterization techniques. Patients can only be considered for TARE is the degree of arterio-venous shunting to the lung is limited (usually less than 20%) and there is no possibility that microspheres may reach the gastrointestinal tract.

Evidence supporting the use of TARE in the treatment of HCC patients comes from consistent, large cohort series involving patients with more advanced HCC, not suitable for other locoregional therapies or who have failed to TACE. Radioembolization can be used in HCC patients who progressed to TACE and for those in the advanced stage because of portal vein invasion.

Many clinical studies (total of 25 in USA and Europe) with TheraSphere[®] and SIR-Sphere[®] are on-going to evaluate feasibility, efficacy and tolerance in primary and secondary liver cancer (HCC, ICH, mCRC and NET) management. Ongoing trials will also answer the question of whether radioembolization is any better than sorafenib in prolonging the survival of poor TACE candidates. Altogether treatment with intra-arterial therapies (TACE+TARE) procedures of all primary and secondary liver cancer lesions is estimated higher than half a million in the world per year based on market studies of intra-arterial devices/products.

Response assessment of TACE in HCC patients

The range of patients treated by TACE in clinical practice largely exceeds the boundaries of the intermediate stage and reported survivals widely range from 8–26% at five

years (13). Among 4,966 Japanese patients without vascular invasion, extrahepatic metastases or prior treatment that received superselective conventional TACE, median survival was 3.3 years (124). However, when median survival is reported by tumor stage, it ranges from 16 to 45 months in the early stage, from 15.6 to 18.2 months in intermediate stage, and from 6.8 to 13.6 months in the advanced stage (13).

Radiologic parameters by CT and MRI may be useful in biological characterization of tumors and predictive efficacy for HCC treated with chemoembolization. OS was significantly longer for patients with completely encapsulated HCC versus patients with incompletely or nonencapsulated tumors (125). Kim *et al.* (126) reported that gross vascular invasion, bile duct invasion, irregular tumor margin, peripheral ragged enhancement, and satellite nodules on CT or MRI were associated with less favorable response after chemoembolization. After adjusting tumor size, tumor number, and alpha-fetoprotein (AFP) level, these CT and MRI scores were independently associated with OS. MRI-specific parameters such as signal intensity on T2- or T1-weighted images, fat signal, or hyperintensity on diffusion-weighted images did not have prognostic value. Kawamura *et al.* (127) reported that the arterial- and portal-phase dynamic CT images obtained preoperatively were classified into four enhancement patterns: Type-1 and Type-2 are homogeneous enhancement patterns without or with increased arterial blood flow, respectively; Type-3, heterogeneous enhancement pattern with septum-like structure; and Type-4, heterogeneous enhancement pattern with irregular ring-like structures. The percentages of poorly-differentiated HCC according to the enhancement pattern were 6% of Type-1 and -2, 13% of Type-3, and 73% of Type-4. Type-4 pattern was a significant and independent predictor of poorly-differentiated HCC while Type-3 pattern was a significant predictor of simple nodular type with extranodular growth or confluent multi-nodule.

Assessment of tumor response is of extreme importance in patients undergoing locoregional treatments of liver cancer. The Clinical Practice Guidelines jointly issued by the EASL and the European Organization for Research and Treatment of cancer (EORTC) state that assessment of response in HCC should be based on mRECIST criteria by performing contrast-enhanced CT or MRI 4 weeks after treatment. Conventional methods, such as classical Response Evaluation Criteria in Solid Tumors (RECIST) criteria, have no predictive value in HCC patients treated with TACE or TARE (128). These criteria only rely

on tumor shrinkage as a measure of antitumor activity, an assumption that is only valid with cytotoxic drugs. TACE and TARE induce direct tumor necrosis and their anticancer activity is not predictive to a reduction in overall tumor load but rather to a reduction in viable tumor, as identified by contrast-enhanced radiologic imaging. Thus, a modification of the RECIST criteria, named modified RECIST (mRECIST), for HCC based on the fact that diameter of the target lesions with viable tumor, should guide all measurements. Treatment response after TACE is assessed with identification of intra-tumoral necrotic areas and reduction of tumor burden in dynamic studies in regular intervals utilizing cross sectional modalities, such as triphasic CT or MRI. In addition, specific modifications of the original criteria regarding assessment of vascular invasion, lymph nodes, ascites, pleural effusion and new lesions have been introduced (129). Tumor response measured by EASL or mRECIST after TACE has been shown to correlate with survival outcomes (130,131).

Pre-procedural AFP has not been demonstrated to be a prognostic marker of post procedural clinical response. In patients with high AFP before treatment, subsequent decrease after treatment is indicative of response; however, this is not reliable, and monitoring of AFP should not substitute dynamic imaging studies. Immediate post procedural elevations in tumor markers may be reflective of cellular lysis, not disease progression, and should not be used to assess response in the acute setting.

Patients that show no tumor response shortly after TACE is completed have a worse prognosis. If complete tumor necrosis is not achieved after the first session of TACE, a second attempt is warranted because feeding arteries may have been missed. However, patients that do not respond to two consecutive sessions of TACE should be considered for alternative therapies (13).

Recently Wang *et al.* (132) showed evidence of an association between intraprocedural tumor perfusion reduction during chemoembolization and transplant-free survival and suggests the utility of transcatheter intraarterial perfusion magnetic resonance (MR) imaging measured tumor perfusion reduction as an intraprocedural imaging biomarker during chemoembolization. Loffroy and colleagues (133) proposed the use of intraprocedural C-arm dual phase- cone-beam computed tomography immediately after TACE with doxorubicin-eluting beads to predict HCC tumor response at 1-month MR imaging follow-up. They reported a significant relationship between tumor enhancement seen at DP-CBCT after TACE and objective

MR imaging response at 1-month follow-up, suggesting that DP-CBCT can be used to predict tumor response after TACE. Sahani *et al.* suggested that perfusion MRI may be a more sensitive biomarker in predicting early response than RECIST and mRECIST (134,135). Other functional imaging methods, such as ¹⁸F-fluorodeoxyglucose PET, contrast-enhanced ultrasound have been used to assess post-treatment evaluation (136-141). However, Xu *et al.* recently suggested that contrast enhanced ultrasound may occasionally miss small residual tumorous nodule (142).

Current and future developments

Combined therapies

There are several theoretical reasons to combine TACE and other recommended therapies such as RFA or sorafenib. RFA is an excellent therapeutic approach of small (<3 cm) lesions. As the size of lesions increases, its local efficacy is reduced, due to a maximum volume of ablation in the range of 4 cm, and in heat loss due to perfusion mediated tissue cooling. It has been demonstrated in animal model that performing TACE before RFA increase volume of ablation (143), thus making this approach of interest in large tumors (144). TACE may also allow down-staging of 3-5 cm lesions to permit subsequent RFA treatment. A RCT in 189 patients with HCC <7 cm showed that patients assigned to conventional TACE+RFA had better OS and recurrence-free survival than patients on RFA only (145). A recent meta-analysis compares the effectiveness of combination of RFA and TACE with that of RFA alone in HCC patients (7 trials comprising 571 patients). The combination of RFA and TACE was associated with a significantly higher OS rates and recurrence-free survival rate compared with RFA alone (146).

Combining TACE and sorafenib has also a strong theoretical rationale. Tumor hypoxia intentionally caused by TACE can induce upregulation of circulating vascular endothelial growth factor (VEGF), which is essential for HCC growth, invasion, and metastasis. Recent studies have reported a significant association between VEGF upregulation after TACE and poor prognosis (147,148). Sorafenib is an oral multitargeted receptor tyrosine kinase inhibitor with, notably, VEGFR-2/3 inhibitory properties. Sorafenib (Nexavar[®], Bayer and Onyx Pharmaceuticals Inc., USA) was approved from the United States Food and Drugs Administration (FDA), the European Medicines Agency (EMA), Chinese Health Authorities, etc. for the treatment

of advanced HCC (149,150). The addition of sorafenib to TACE compared to TACE alone in patients with advanced or intermediate unresectable HCC and good liver function is feasible with a rate of adverse events predictable and manageable with dose reduction (149,150). In the SPACE trial, the safety and efficacy of sorafenib *vs.* placebo associated with DEB-TACE (DEBDOX[®]) was investigated in 304 patients with intermediate-stage HCC. Addition of sorafenib to DEB-TACE improved time-to radiological progression (TTP). Median TTP was 169 and 166 days in the sorafenib and placebo groups respectively (HR 0.797, 95% CI: 0.588-1.080, P=0.07). TTP at the 25th and 75th percentiles (preplanned) was 112/88 and 285/224 days in the sorafenib and placebo groups, respectively (151). Several clinical trials are currently evaluating this combined effect on the outcome of patients with unresectable HCC [e.g., on the site ClinicalTrials.gov, studies number NCT01833299; NCT01906216 (the SELECT trial); NCT01829035; etc.]

The risk exists of early rebound with VEGF release leading to tumor relapse. Several important questions remain open, such as the best sequential timing of targeted therapy and TACE to prevent such rebound effect, the best imaging technique to evaluate clinical response, the best targeted drug to use in combination with TACE, and the most reliable primary endpoints.

Immune therapy

Second generation immune therapy of tumors is attracting widespread attention, including for HCC (152,153). The liver is permanently exposed to food-derived dietary and microbial antigens from the gastro-intestinal tract, as well as antigens from apoptotic tumour cells, thus leading to liver being an inherent tolerogenic microenvironment (154). Local immune therapy is an interesting option for the treatment of HCC or liver metastases. Promising results on survival have been reported in patients with liver metastases from primary uveal melanoma after immunoembolization with granulocyte-macrophage colony-stimulating factor (GM-CSF) mixed with Lipiodol[®] (associated with Gelfoam[®]) and administered into the hepatic artery (155). Local administration of dendritic cells (DCs) stimulated with OK432, a streptococcus-derived anti-cancer immunotherapeutic agent, in the presence of interleukin (IL)-4 and GM-CSF, during TACE procedure in HCC patients has been found to be safe and prolonged recurrence-free survival of patients compared with the historical controls treated with transcatheter hepatic arterial

embolization without DC transfer (156). Minimally invasive thermal ablation techniques (cryoablation or hyperthermic ablations) are associated with the local release of tumour antigens (157) which may lead to innovative techniques of immune therapy, possibly involving Lipiodol® as a drug-delivery system. However, many challenges remain as individual cancers have their own pattern of cancer antigen expressions, thus making the development of universally applicable therapy difficult. Indeed, safety issue is crucial. The involvement of large number of tumor-associated antigens is another challenging issue.

Conclusions

In patients diagnosed with HCC, a survival benefit has been observed in patients that meet the rigorous criteria for curative resection or transplantation (158). TACE has been proven to be useful in local tumor control, to prevent tumor progression, prolong patients' life and control patient symptoms. TACE alone or combined with other minimally invasive procedures can also be used as a neoadjuvant therapy or as a bridging therapy to liver transplantation or resection. In the latter condition it prevents tumor progression and patient drop-out from the waiting list of liver transplantation. Multimodal treatment may be the best way to optimize TACE/TARE outcomes in HCC. So far, there is no significant evidence of the clinical superiority of DEB-TACE over conventional TACE in terms of clinical efficacy. TARE may be safe in advanced disease, including portal vein invasion and larger tumors. With introduction of sorafenib as standard treatment for advanced HCC, phase II and III studies are ongoing to explore safety and efficacy of RFA, TACE or TARE in combination with sorafenib or targeted drugs under clinical development. With these and other studies, the clinical indications and specific patients ideally suited for these palliative interventions will continue to be refined.

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None.

Footnote

Conflicts of Interest: Jean-Marc Idée and Sébastien Ballet are employees of Guerbet (France). Guerbet markets contrast agents and specifically Lipiodol® mentioned in this review. Other authors declare no conflict of interest.

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Management of liver cirrhosis in patients with hepatocellular carcinoma

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Abstract: Management of hepatocellular carcinoma (HCC) is challenging compared to other common malignancies because of the nature of the associated background of chronic liver dysfunction. Most of the patients with HCC have underlying cirrhosis. While progression of the tumor is a major contributor to mortality, cirrhosis and its complications often accounts for a significant portion of the morbidity and mortality seen in this group of patients. Severity of underlying liver disease and degree of decompensation predicts prognosis and dictates the tumor treatment options and responses. A multidisciplinary approach is considered the standard of care and paramount to optimal patient outcomes. This review provides information on the general management of cirrhosis, cirrhosis-related complications and commonly associated symptoms, mainly focusing when available on high-level evidence and guidelines.

Keywords: Cirrhosis; ascites; encephalopathy; varices; peritonitis

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Introduction

Cirrhosis is a common problem worldwide, accounting for significant mortality and hospital admission rate. Estimated prevalence of cirrhosis in the United States is 0.15% of the population and it is estimated that up to 1% have histological cirrhosis that is not yet clinically detected (1). Similar numbers have been reported from European countries and even higher numbers are estimated in most Asian and African countries. Main underlying etiology varies geographically; Alcohol consumption and chronic hepatitis C are the leading causes of cirrhosis in western countries. Chronic hepatitis B is highly endemic in the Asian Pacific region and appears to be the commonest cause of liver cirrhosis, with few exceptions. For example hepatitis C is common in Japan accounting for the most common cause of cirrhosis and liver cancer, while alcohol related cirrhosis is more common in China and Korea compared to other Asian countries (2).

Hepatocellular carcinoma (HCC) represents the main contributor to liver-related mortality (3) and tumor

progression is the main cause of death in HCC patients (4), however a significant percentage of them die from complications relates to cirrhosis. Therefore, managing cirrhosis to delay the advent of complications as well as appropriately treating these complications early in its course both during and after treatment of the HCC is paramount to improve morbidity and mortality.

Liver cirrhosis histologically represents an advanced stage of hepatic fibrosis associated with hepatic nodules that progressively disrupts the normal hepatic architecture and transforms the liver from a low-resistance to a high-resistance organ, this process elevates the sinusoidal pressure causing impaired hepatocyte function and increases the pressure in the portal vein leading to portal hypertension (5). Portal hypertension is defined as being 6 mmHg or greater as measured by the wedged hepatic vein gradient. As the portal pressure increases so does the risk for developing complications related to cirrhosis (5). This review summarizes the current management strategies that have been shown to be effective at decreasing the

morbidity and mortality associated with the development of complications from cirrhosis.

HCC in relation to cirrhosis

Most of the patients with HCC have underlying cirrhosis. Worldwide data show that prevalence of cirrhosis in persons with HCC is about 80-90% (6). Cirrhosis of all etiologies may be complicated by HCC, but persistent hepatitis B virus (HBV) or hepatitis C virus (HCV) infection account for over 80% of HCC cases worldwide (7). In Japan, the United States, Latin America, Egypt and Europe, hepatitis C is the major cause of HCC. The incidence of HCC is 2-8% per year in patients with chronic hepatitis C and established cirrhosis. While in Asia, Africa, and in some eastern European countries, chronic hepatitis B is the prime cause of HCC, far outweighing the impact of chronic hepatitis C (8).

During the evaluation of patients with HCC without a clinical diagnosis of cirrhosis, a detailed examination is important to identify symptoms and signs indicating presence of cirrhosis such as abdominal enlargement and/or swelling, insomnia or sleep pattern reversal, vascular spiders, visible collaterals and palpable liver or spleen. Laboratory findings suggesting cirrhosis include abnormalities in one or more of synthetic function (serum albumin, prothrombin time, and serum bilirubin) and/or a low platelet count (platelet count $<160,000 \times 10^9/L$ is 80% sensitive in detecting portal hypertension from cirrhosis) (9). For patients having clinical features with suggestive laboratory and imaging findings, a biopsy is not necessary to confirm presence of cirrhosis.

The development of decompensated cirrhosis is signaled by the presence of the following: jaundice, ascites, portal hypertensive gastrointestinal (GI) bleeding, and/or encephalopathy. The rate of decompensation is estimated to be 3-5% per year (10). One-year mortality in compensated cirrhosis is 1-3.4%, but with decompensation the mortality increases to 20-57% (11). The severity of hepatic decompensation clearly affects outcome and thus, the treatment choice for HCC as well as the response to treatment. Assessment of the severity of cirrhosis is usually done using the Child-Pugh classification as it reflects functional hepatic reserve. An example is surgical resection of HCC which can be safely done only in patient with well-preserved liver function (Child-Pugh A), while liver transplantation is the best option for patients with decompensation (Child-Pugh B and C cirrhosis) (12).

Similarly, patients with compromised hepatic reserve such as Child-Pugh B are well known to have poorer outcome and more adverse events with targeted therapy such as sorafenib when compared to Child-Pugh A patients (13,14).

General management of cirrhosis includes

Identification and treatment of underlying etiology can slow progression or partially reverse cirrhosis both histologically and clinically. This is well seen in alcoholic liver disease, where abstinence was associated with improvement in fibrosis (15,16), normalization of portal pressure (17), and resolution (or reduction) of ascites (18). Similar results are seen in patients with compensated or even decompensated cirrhosis due to autoimmune hepatitis treated with steroids (19), HBV treated with antiviral therapy (20) and in compensated cirrhosis due to HCV treated with combination therapy (21). However, the role of antiviral therapy in patients with HCC is not clear as most official guidelines consider active HCC as a contraindication to treatment. Prevention of second insults should be achieved by avoiding hepatotoxic medications, herbal preparations and for those patients with cirrhosis that are sero-negative immunization against hepatitis A and B.

Although presently not standard practice, a number of recent studies show a beneficial effect of commonly used drugs on progression of cirrhosis and its complications. These drugs include non-selective beta blockers, statins, antibiotics and anticoagulation (22). A detailed discussion of these studies is beyond the scope of this article but these early reports suggest a beneficial effect on fibrosis progression, development of varices and bacterial translocation. However, before these concepts are applied to daily practice further studies are needed. In addition, several animal studies inhibiting the TGF- β 1, renin angiotensin pathway and vascular endothelial growth factor pathways show promise in halting fibrosis progression (23).

Common complications of cirrhosis

Ascites

Cirrhosis is the most common cause of ascites (over 75%) (24) and the most common complication of cirrhosis that leads to hospital admissions (25). New onset ascites in patients with cirrhosis should be evaluated with imaging such as ultrasound with dopplers or a dynamic CT scan to

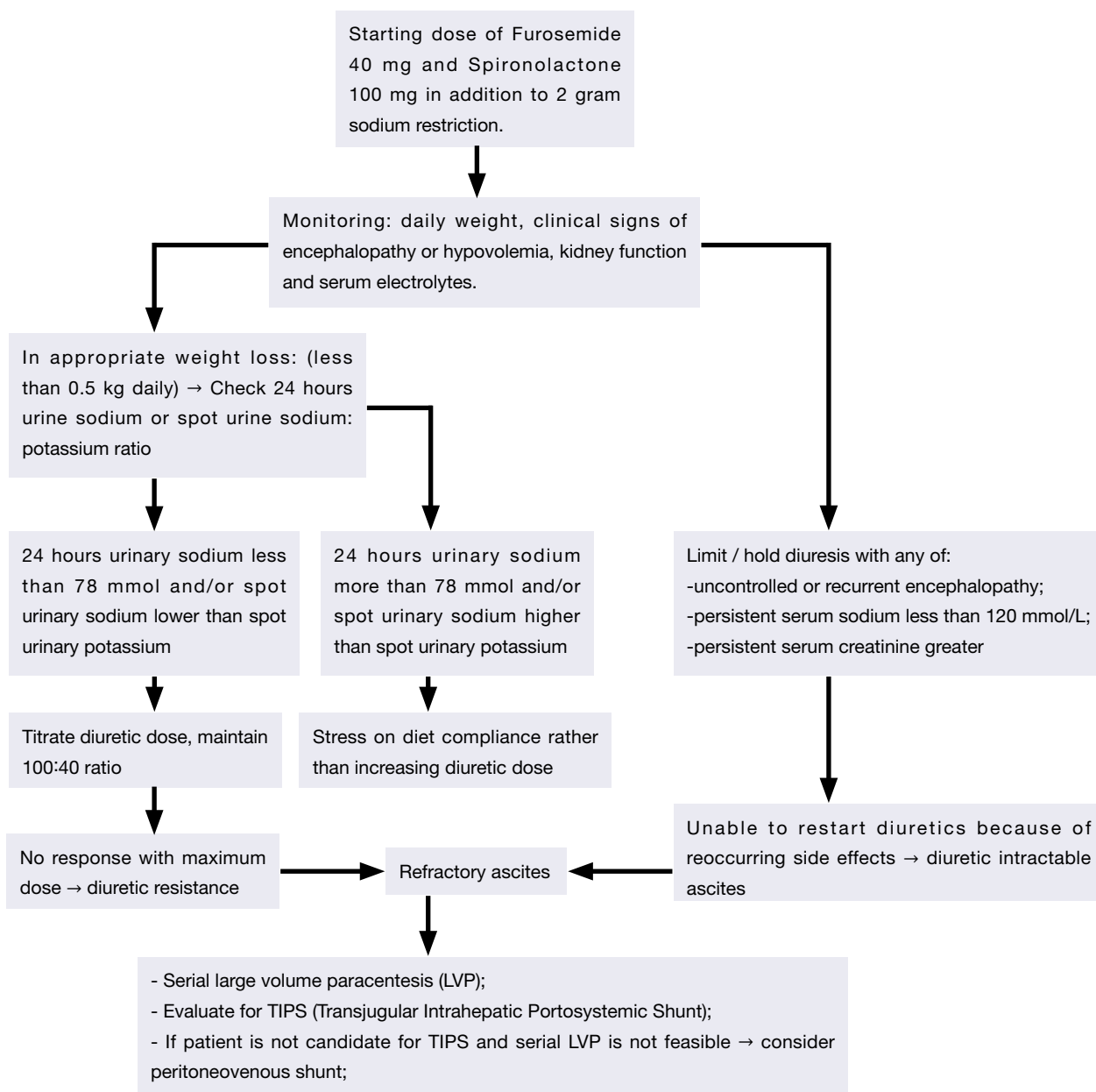


Figure 1 Approach to treatment of ascites in patients with liver cirrhosis.

document liver disease and rule out other causes of ascites. The ascitic fluid should be analyzed to document a high serum-ascites albumin gradient (SAAG) and low protein fluid. Additional testing should include a cell count with differential, cultures to rule out infection and cytology (26), which is usually negative in cirrhotic ascites even in the presence of HCC (27).

Figure 1 summarizes the treatment guidelines for

ascites. First line treatments for ascites are to restrict dietary salt intake to 2 grams per day and initiate diuretic therapy. A combination of spironolactone and furosemide is recommended over starting spironolactone alone as combination therapy leads to earlier mobilization of ascites and helps maintain normokalemia (28). Usually a daily dose of 40 mg of furosemide and 100 mg of spironolactone 100 mg is started, then the dose is titrated to response every

3-5 days to a maximum of 160 mg of furosemide and 400 mg of spironolactone. A ratio of 40:100 is maintained, unless there is an abnormal potassium level (26).

A number of side effects can occur with diuretic therapy. Gynecomastia can occur with spironolactone. In cases of severe gynecomastia, other potassium sparing diuretics that can be tried are amiloride or triamterene (29). Worsening of kidney function and electrolyte disturbances is common with diuretics. As a general rule, oral diuretic therapy is preferred over intravenous loop diuretics because of good oral bioavailability and the higher potential to worsen kidney function with intravenous diuretics (30). Diuretics are often temporarily held for: uncontrolled or recurrent encephalopathy, serum sodium less than 120 mmol/L with no response to fluid restriction, or serum creatinine greater than 2.0 mg/dL (26). Daily weight monitoring is an excellent way to objectively monitor response and avoid over diuresis. While aggressive weight loss can be safely achieved in patients with significant edema, in patients with only ascites, a loss of 0.5 kg daily is preferred as more rapid mobilization of fluid increases risk of intravascular volume depletion.

Bed rest, fluid restriction in the absence of severe hyponatremia and frequent albumin infusions are not indicated in treatment of ascites due to liver cirrhosis (26). In the patient presenting with tense ascites, a single large volume paracentesis can rapidly improve symptoms and this can be followed up by titrating diuretics dose and counseling on diet modification (31). For patients who lack a response to diuretic therapy, diet adherence should be discussed since it is an extremely common problem and can be evaluated with a 24 hours urinary sodium (>78 mmol) or spot urinary sodium higher than spot urinary potassium (32). When salt indiscretion is found, stress the importance of a sodium restriction diet prior to increasing the diuretic dose. Additional common causes of lack of response to diuretics are insufficient doses, NSAID use, severe hyponatremia, underlying kidney disease, local cause of ascites (such as malignancy or chronic infection specially tuberculosis or fungal infection) and true diuretic resistant ascites which is seen in advanced stages of liver disease (33).

The inability to initiate or continue diuretics because of persistent development of diuretic-induced complications is called diuretic intractable ascites. Both diuretic resistant and diuretic intractable ascites represent refractory ascites, which can be seen in 10-15% of patients (34). In refractory ascites, diuretics are discontinued and ascites managed with serial large volume paracentesis or transjugular intrahepatic

portosystemic shunt (TIPS). Both strategies can be effective for ascites control (35). Surgical peritoneo-venous shunt is rarely used and limited to patient with abdominal scars (33).

Hepatic hydrothorax is seen in 5% of patients with cirrhosis and ascites (36). Hepatic hydrothorax is usually right sided. Therefore, left-sided pleural effusions in this clinical setting, warrants work up for other causes such as malignancy or infection as tuberculosis. Similar to ascites, first line treatment is diuretic therapy and sodium restriction with thoracentesis done in cases of respiratory distress. TIPS is a reasonable second line option for symptomatic plural effusion not responding to diuretics (26) but chest tube placement is contra-indicated because of the associated increased morbidity and mortality (37).

Spontaneous bacterial peritonitis (SBP)

SBP is a common and potentially fatal complication that develops in patients with cirrhosis and ascites. The overall prevalence of SBP in patients with cirrhosis and ascites admitted to the hospital is estimated to be 10-30% with the recent diagnostic techniques (38). However, the true prevalence of SBP in the setting of cirrhosis with ascites and HCC is poorly defined. A study on Korean patients with cirrhosis presenting with SBP showed that 41.5% had HCC at time of diagnosis and the presence of HCC was an independent predictive factor of higher mortality (39). Patients with SBP typically present with fever, abdominal pain and leukocytosis. However, SBP should also be suspected in unexplained encephalopathy, acute kidney injury (AKI), ileus, and a clinical picture suggestive of sepsis (hypotension, hypothermia, acidosis) (40). A definite diagnosis requires a paracentesis with ascitic fluid showing a PMN count ≥ 250 cells/mm³ and, although not required for diagnosis, positive ascitic fluid cultures. Bed side blood culture bottles inoculated with ascitic fluid should be obtained before antibiotics are started (41). Classic findings of SBP are ascitic fluid PMN counts ≥ 250 cells/mm³ and a positive ascitic fluid culture with monomicrobial infection [usually with gram negative gut (as *Escherichia coli* or *Klebsiella*) or less likely gram positive cocci (streptococcus or staphylococcus)] (42).

In patients who lack a response to appropriate antibiotics within 48 hours (as documented by rising PMNL on repeat paracentesis or less than 25% drop of the pre-treatment value), culture growing polymicrobial or "atypical" microbe that is usually associated with bowel perforation (anaerobes, enterococci or fungal) suspect secondary peritonitis (43,44).

High morbidity and mortality are expected if secondary peritonitis is missed, as it requires broader antibiotic coverage compared to SBP and even urgent surgical intervention in most cases (43). Helpful tests are ascitic fluid for LDH, protein, and glucose, at least two out of three of the following are highly suspicious for secondary peritonitis (total protein greater than 1 g/dL, lactate dehydrogenase greater than the upper limit of normal for serum, and glucose less than 50 mg/dL). However, these criteria have only 50% sensitivity in secondary peritonitis without perforation (41). Therefore, a CT scan may still be needed in patients with a suspicious history or localized abdominal examination signs.

Treatment should be started based on clinical manifestations and ascitic fluid PMN count ≥ 250 . Antibiotics are started once cultures are obtained and should not be delayed based on the availability of culture results. Importantly, a subset of patients only have a neutrocytic response with negative cultures (culture-negative neutrocytic ascites), and these patients should be treated as SBP because of the similar prognosis and mortality (45). Another group of patients may have an initial neutrocytic response with a PMN < 250 but cultures come back positive with one organism (mono microbial bacterascites), and the decision to treat is based on the presence of symptoms as well as a repeat ascitic fluid cell count to show if they have cleared the "colonization" or developed SBP (46).

Duration of treatment is generally 5 days in patients with a typical response (47). The preferred antibiotic therapy is an intravenous third generation cephalosporin like cefotaxime 2 grams every 8 hours or intravenous ceftriaxone 2 grams a day (48). Cultures are used to tailor the antibiotic therapy according to sensitivity and a negative culture is never an indication to stop treatment. Patients at risk of multiresistant infections should be monitored closely for their clinical response and culture results (patients with nosocomial infections, previous multiresistant infection or recent/chronic antibiotic use) (49). Quinolone resistance is a growing problem so they are no longer recommended for empiric coverage, even though some studies showed similar efficacy in well selected patients (50-52). Repeat paracentesis is not routinely indicated and is usually reserved for those patients who do not show improvement within 48 hours of therapy, especially if they are at risk for secondary peritonitis or multidrug resistant infection based on history or culture results (40). In addition to antibiotics, albumin infusion has been shown to decrease the incidence of

type-1 HRS and mortality compared to antibiotics alone. The recommended dose is 1.5 g/kg body weight within 6 hours of diagnosis, followed by 1 g/kg on day 3 (53). Albumin infusions is of particular importance in patients with baseline kidney impairment (creatinine > 1 mg/dL or blood urea nitrogen > 30 mg) or severe liver disease (total bilirubin > 4 mg/dL) (54).

Prophylaxis is another important treatment. Patients who survive an episode of SBP are at high risk for recurrence (approximately 70% cumulative risk at 1 year) (55) and lifelong antibiotic prophylaxis or until a liver transplant is indicated with oral norfloxacin 400 mg per day. If not available, other options are ciprofloxacin (750 mg once weekly, orally) or co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim daily, orally) (40). Other populations in whom prophylaxis has shown to improve survival are patients with acute GI bleeding, antibiotic prophylaxis has shown to decrease incidence of SBP and also to reduce re-bleeding. In these setting, the recommended regimen is intravenous ceftriaxone for 7 days. In patients with less severe liver cirrhosis (i.e., without at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin > 3 mg/dL), prophylaxis can be switched to oral quinolones when oral intake is resumed (56). Prophylaxis should also be considered in patients with low ascitic fluid protein (< 15 g/L). Controversial evidence exist, however, the highest evidence for benefit was shown in patients with ascitic fluid protein < 15 g/L and severe liver disease (Child-Pugh score > 9 points with serum bilirubin level > 3 mg/dL or impaired renal function (serum creatinine level > 1.2 mg/dL, blood urea nitrogen level > 25 mg/dL, or serum sodium level < 130 mEq/L) (57). The regimen studied was norfloxacin (400 mg/day) and it showed improved survival and decreased incidence of SBP. In addition, unnecessary long-term use of PPI is prudent since they were shown to increase the risk of SBP (58).

Patients with hepatic hydrothorax are also at risk for spontaneous bacterial pleural empyema. This complication is less common than SBP and it is associated with SBP in more than 50% of cases (59). It should be suspected in patients with a hydrothorax who develop fever, pleuritic pain, unexplained encephalopathy or other general signs of SBP. Once suspected, diagnostic thoracentesis should be performed and a diagnosis is made with positive culture and more than 250 neutrophils/mm³ or a negative culture and more than 500 neutrophils/mm³, in the absence of lung infection. The treatment is similar to that of SBP and subsequent lifelong prophylaxis is also indicated (60).

Hepatic encephalopathy (HE)

HE is one of the common complications of chronic liver disease and it can occur with cirrhosis (Type C) and in patients with no hepatocellular dysfunction but presence of porto-systemic shunts (Type B) (61). In addition, it has been reported that HCC can rarely predispose to encephalopathy in patients without cirrhosis due to generation of ammonia from tumor breakdown and portosystemic shunting, a result of partial tumor occlusion of the hepatic veins (62).

The presentation of HE varies depending on the severity and the staging. Symptoms of HE are depression, irritability, insomnia, disturbances in the diurnal sleep pattern, lethargy, disorientation, inappropriate behavior and even coma. An underlying cause for HE should be sought, such as infection, SBP, worsening renal failure, GI bleed, electrolyte abnormalities (hypokalemia, alkalosis, hyponatremia), constipation, non-compliance and medication effect such as sedatives or narcotics. Worsening or increased frequency of encephalopathy without a clear precipitating factor indicates decompensation and can be seen in stable cirrhotic patient following progression of HCC or following treatments with liver directed therapies like TACE.

Diagnosis of HE is based on clinical grounds with a work-up that is used to prove the presence of chronic liver disease, and rule out other precipitating factors discussed above. A common finding on clinical exam is asterixis (bilateral flapping tremors). An elevated arterial ammonia level is not essential for the diagnosis (63). The role of psychometric tests is mainly for detecting mild degrees of encephalopathy (minimal HE), which may not be obvious on routine exam because of the normal mental status. However, minimal HE is important to recognize since it has an effect on long-term memory and complex intellectual tasks such as driving (64).

Treatment relies mainly on correction of underlying causes if any are found and reduction of ammonia levels. In general, sedatives should be avoided and electrolyte abnormalities corrected. Correction of hypokalemia is of particular importance since it increases renal ammonia production and the associated metabolic alkalosis may increase ammonia entry into the brain (65). For symptomatic treatment of agitation, haloperidol is a safer option compared to benzodiazepines (66).

Non-absorbable disaccharides such as lactulose are the first line treatments by acting as a laxative and also acidify the colon to limit absorption of ammonia. One

approach in the acute setting is an hourly oral dose of 45 mL until patient has a bowel movement then the dose can be adjusted to have 2-3 soft stools daily. Lactulose can also be used as retention enema (300 mL in 1 L of water) and has been shown to be more effective than tap water enema (67). Another oral agent for the treatment of HE is rifaximin that was approved by regulatory agencies for recurrent encephalopathy (68) and minimal HE. Other oral antibiotics such as metronidazole, neomycin and vancomycin have shown some effect (69). The evidence for flumazenil, acarbose and Zinc supplement is still developing. Rarely, surgical reduction or obliteration of shunts or large spontaneous porto-systemic anastomoses can be helpful (70).

Current evidence shows no added benefit for strict protein restriction compared to moderate protein intake (71). Vegetable protein may have slight benefit over animal protein in regard to nitrogen balance (72), and this can be an option in patients who are not improving with medical therapy or for patients who are noticed to have worse symptoms with protein intake.

AKI in patients with liver cirrhosis

Patients with advanced liver cirrhosis are more susceptible to AKI compared to the normal population due to the reduced effective circulating blood volume and mean arterial pressure secondary to splanchnic vasodilation leading to kidney hypoperfusion (73). Common etiologies in cirrhotic patients are hypovolemia (usually due to overdiuresis or acute GI bleeding), hepatitis virus-associated glomerulonephritis (74) and hepatorenal syndrome that is a diagnosis of exclusion observed in about 13-25% of patients (75,76).

The work-up is guided by the clinical setting, and generally includes ultrasound of the kidneys, urine electrolytes, urine analysis to assess for the presence of hematuria and proteinuria, and appropriate serological testing for antibodies against the glomerular basement membrane and for vasculitis. Occult sepsis should also be evaluated with ascitic fluid analysis for SBP. It should be noted that patients with chronic liver disease have a significantly lower baseline serum creatinine concentration than the general population and a slower rise in serum creatinine with a drop in GFR due to decreased production of creatinine (from wasted muscles and from the liver) and due to increased volume of distribution given the edema and ascites (77). Newer methods to assess renal function in

cirrhosis are being evaluated and includes urinary neutrophil gelatinase-associated lipocalin that was shown not only to accurately assess the degree of renal dysfunction, but also to identify the etiology (78,79).

Criteria for HRS diagnosis are based on presence of cirrhosis with ascites and a rise in serum creatinine to >1.5 mg/dL, in the absence of other causes of AKI such as absence of shock, hypovolemia, nephrotoxic drugs, abnormal renal US, proteinuria <0.5 g/day and microhaematuria (<50 red cells/high powered field) (40). Hypovolemia can be excluded by stopping diuretics for at least 2 days, volume expansion with albumin 1 g/kg/day up to a maximum of 100 g/day and documenting a CVP >3 cm water (80). Precipitating events of HRS should be identified and treated. SBP should be treated immediately with antibiotics and albumin infusion. Pentoxifylline has preventive effect in severe alcoholic hepatitis and may be in other patients with liver cirrhosis and baseline kidney dysfunction (81).

Definitive treatment for HRS is a liver transplant. Median survival of patients with untreated type 1 HRS is approximately 1 month, with survival rate substantially improving to approximately 65% after transplant (82). Pharmacologic agents including albumin infusion and vasoconstrictors are a bridge to transplant. A commonly used vasoconstrictor regimen is oral midodrine titrated to 12.5 mg 3 times per day and octreotide 100 μ g/8 h subcutaneously titrated to 200 μ g/8 h, to achieve an increase in mean blood pressure of 15 mmHg (83). Other options are noradrenaline continuous infusion that can be used in extremely hypotensive patients in ICU setting (84) and terlipressin which is not widely available (85). Few studies showed a beneficial effect for TIPS on kidney function in HRS type 1 and type 2, however this has not been compared to other treatment options (86) in randomized controlled trials.

Additionally, supportive management is directed towards managing electrolytes, acid base and volume status. Hemodialysis or continuous venovenous hemodialysis can be used before liver transplantation. Other alternatives to hemodialysis have been studied and showed improved survival, including molecular reabsorbent recirculating system (MARS) and another Prometheus extracorporeal liver support system, however, further studies are required (22). Kidney function is expected to recover after transplant and combined liver-kidney transplantation is generally not indicated except in patients who have been on prolonged dialysis form more than 12 weeks before

transplant (44).

HRS type 2 is usually seen in the setting of refractory ascites and diuretic resistance typically evolving over months. No treatment consensus exists in this setting; however, terlipressin plus albumin are probably the most studied treatment options (87) as a bridge to liver transplant.

GI bleeding

Variceal bleeding is a common complication of cirrhosis and is associated with high mortality. Gastroesophageal varices are present in up to 50% of patients at the time of diagnosis of cirrhosis (88) and without treatment, small varices progress to large varices at rates of 5% to 20% per year (89), which increases the risk of bleeding. Other factors to predict risk of bleeding are advanced liver disease and presence of red wale marks (90). Clearly, acute variceal bleeding is associated with high mortality; estimated 6week mortality following single bleeding is about 15% to 20% and reaches 30% in patients with Child class C (91).

Current guidelines recommend a screening endoscopy once a patient is diagnosed with cirrhosis even without decompensation or previous GI bleeding. Less invasive measures are being studied with limited accuracy such as transient elastography, platelet count/spleen diameter ratio, CT scanning for varices, and video capsule endoscopy (92,93). There is growing evidence on the role of measuring hepatic venous pressure gradient (HVPG) with a gradient more than 10 mmHg indicating clinically significant portal hypertension predicting the development of varices, decompensation and even HCC (94). In the setting of acute variceal bleed, HVPG more than 20 predicts poor outcome (95). Variceal pressure measurement was shown to be as effective as HVPG in prediction of bleeding risk and response to beta blockers with the advantage of being less invasive (96). The role of both studies among diagnosis and treatment algorithms is not yet clear.

Screening protocols include an esophagogastroduodenoscopy (EGD) once a diagnosis of cirrhosis is made. If there are no varices, no medical or endoscopic prophylaxis is recommended, and a repeat endoscopy is performed in 3 years in patients with compensated cirrhosis and earlier if hepatic decompensation occurs and then annually (97). If the screening EGD showed small varices (<5 mm), then medical prophylaxis with nonselective beta-blockers is indicated, with stronger evidence if patient has criteria for high-risk varices (Child B/C or presence of red

wale marks). In patients with small varices who receive beta-blockers, a follow-up EGD is not necessary (97). In cases of large varices with the high-risk criteria, nonselective beta-blockers or endoscopic variceal ligation should be used for prophylaxis. If no high risk criteria are present, then first line should be nonselective beta-blockers and variceal ligation should be used if there is a contraindication to beta blockers (98). Generally, for patients treated with variceal ligation, it should be repeated every 1-2 weeks until varices are completely obliterated, followed by repeat endoscopy in 1-3 months then every 6-12 months to evaluate for recurrence (97).

Starting doses of NSB are propranolol 20 mg twice daily or nadolol 40 mg once daily then titrated to maximally tolerated dose or until heart rate is approximately 55 beats/min. Although not a standard therapy, low dose carvedilol was associated with lower bleeding rates and better compliance compared to variceal ligation in one study (99). Additional benefit for NSBBs and improved survival was shown (100), mainly through reducing bacterial translocation and infections like SBP and slowing progression of collaterals through anti angiogenic effect probably by affecting gene expression of endothelial growth factors (101). However, in patients with refractory ascites, recent study showed worsened survival with NSBB (102), likely due to alteration of hemodynamics (paracentesis-induced circulatory dysfunction like picture) and reduction of renal perfusion (103). Further studies are needed to clarify this, meanwhile, it is probably safer to hold NSBB in this population and use band ligation. Heavy lifting (>40 pounds) should be avoided in patients with large varices as it can predispose to bleeding through increasing intra thoracic pressure (9).

Acute variceal bleeding is an emergency and patients should be admitted with close monitoring in intensive care unit or at least intermediate care level. Intravascular volume support and blood transfusions should be started with a goal to maintain hemoglobin around 8 g/dL, as more aggressive transfusion can lead to elevation in portal pressure that can worsen variceal bleeding (104). However, other factors such as cardiopulmonary comorbidities, patient age, hemodynamic status and ongoing bleeding should also be considered. Significant coagulopathy should be corrected using fresh frozen plasma and/or platelets, although no clear guidelines are available. As mentioned before antibiotic prophylaxis is indicated even in the absence of ascites as it improves survival not only by preventing infections but also decreases risk of early re-bleeding (97,104). Pharmacologic

therapy with vasoconstrictors including terlipressin, somatostatin or somatostatin analogs (octreotide) should be started once bleeding is suspected even before EGD. Once diagnosis is confirmed, it should be continued for 3-5 days. The EGD should be performed within 12 hours, after the patient is resuscitated with the aim being to confirm the diagnosis and control the bleeding using variceal ligation or sclerotherapy. Current evidence shows better control of the bleeding and less risk of re-bleeding when pharmacologic and endoscopic therapies are combined (105).

Treatment failure even with the measures mentioned above is seen in 10-20% of patients (97). Available options for these patients are temporary balloon tamponade (for <24 hours) or shunt therapy, through TIPS (or less commonly surgical shunt) in well-selected patients. Lower threshold for early TIPS (within 24-48 hours) may improve outcome in high-risk patients (those with Child class C or HVPG >20 mmHg) (106,107).

Up to 20% patients have gastric varices on endoscopy and a higher mortality is related to the fundal type of varices. Unfortunately, band ligation is usually not effective in these cases (108,109) and current evidence shows better results with endoscopic variceal obturation using cyanoacrylate. If this is not available, then TIPS should be used specially with high-risk patients who continue to bleed with pharmacologic therapy (110). Other options currently being studied are thrombin injection (111) or retrograde transvenous obliteration done by interventional radiology (112). Ectopic varices can be seen in the small bowel or rectum and are rarely discovered until they bleed. For these varices there are no clear guidelines for their management, however endoscopic therapy is usually not effective and definite treatment is either TIPS, embolization or surgical control of bleeding (113). Non-variceal portal hypertension related GI bleeding is commonly seen as portal hypertensive gastropathy (PHG), which usually manifests as chronic bleeding and anemia and can be treated with NSB, iron supplements and blood transfusion if needed. Patients, who require frequent transfusion, should be evaluated for TIPS. PHG rarely causes acute bleeding, in this case treatment is usually medical with octreotide or terlipressin with adequate response (114,115) and TIPS can be considered as a second line option (116). There is also no clear role for PPI (117). Gastric antral vascular ectasia is different from PHG, it does not usually correlate with portal hypertension but disappears after liver transplant. It is an uncommon cause of acute bleeding in cirrhotic patients and usual treatment in this case is endoscopic

therapy using laser or Argon plasma photocoagulation (118). Little information exists from case reports about portal hypertensive enteropathy and colopathy but usual treatment in cases of severe bleeding is aiming towards reduction of portal pressure using somatostatin analogues or TIPS, also endoscopic therapy and surgical resection in cases of localized lesions (119).

Hyponatremia

Hyponatremia in liver cirrhosis is a common slowly developing condition and seen in up to 50% of patients. However, severe hyponatremia characterized by a sodium level less than 125 is observed in about 5% (120). Severity of hyponatremia correlates with worse outcome before and even after liver transplant (121). Dilutional hyponatremia due to excess antidiuretic hormone (ADH) is the most common etiology, however other reversible causes should be ruled out as diarrhea, diuretic side effects and excess hypotonic fluids.

Treatment is usually not indicated unless there is severe hyponatremia less than 120 meq/L, symptomatic hyponatremia or before liver transplant. First treatment modality is free water restriction. Current AASLD guidelines recommend restriction for levels less than 125, to 1-1.5 liters per day. Generally, fluid intake should be less than urine output (26). One way to predict response to adequate fluid restriction is the urine to plasma electrolytes ratio (measured as urine sodium + potassium/plasma sodium). A ratio <0.5 predicts good response to free water restriction as it indicates the excretion of electrolyte free water in the urine (122).

Tolvaptan is the only oral Vasopressin 2 receptor antagonist available that is associated with a significant rise in serum sodium and improvement of mental status (123) as it induces selective water diuresis without affecting sodium and potassium excretion. However, a recent study showed significant hepatotoxicity with high doses of tolvaptan (124) prompting a safety alert on its use in patients with underlying liver disease by regulatory agencies until more information is available.

Hypertonic saline use can lead to permanent neurologic symptoms due to demyelination in cases of rapid correction, therefore, use in liver patients should be restricted to severe hyponatremia with neurologic symptoms (as seizures) or if patient is close to transplantation (within hours) to avoid rapid correction with fluids given during surgery or with correction of liver function during transplant (125).

Cardiopulmonary complications of liver cirrhosis

Hepatopulmonary syndrome (HPS)

HPS should be suspected in any patient with cirrhosis regardless degree of decompensation who develops dyspnea, specially exertional (as exercise increases the shunted fraction), platypnea and orthodexia (126,127). This respiratory complication is seen in 10-20% of cirrhotic patients and the median survival is 2 years from the time of diagnosis (128) and death is usually due to other complications of cirrhosis. Patients with HPS and severe hypoxia have increased mortality even after transplant.

Diagnosis is established with the triad of chronic liver disease, hypoxia (<96% on pulse oximetry or elevated Alveolar-arterial gradient) and evidence of intra pulmonary shunts (129) and other common causes of hypoxia have been ruled out. Initial diagnostic test is the contrast echocardiogram, where contrast is seen in the left side of the heart within 3-6 heart beats, compared to less than 3 beats with intra-cardiac shunts (130). Lung perfusion scans using 99m Technetium macroaggregated albumin can demonstrate intrapulmonary shunts through passage of more than 6% of the radioactive substance to the brain (130). However, this study does not differentiate between intrapulmonary and intracardiac shunts, so contrast echocardiogram is still needed.

Main treatment is liver transplant and listing using MELD exception points should be applied (130). Oxygen therapy improves exertional dyspnea and quality of life (131). In patients who fail to respond to 100% oxygen, pulmonary angiogram should be considered as it can differentiate type II HPS (intrapulmonary AV fistulae) from type I (precapillary pulmonary artery dilation), in type II, coil embolization done by interventional radiology can be helpful (132). Other treatment modalities that have been studied with controversial results include nitric oxide synthase inhibitors (as methylene blue), garlic and TIPS (130).

Portopulmonary hypertension (POPH)

POPH is seen in up to 10% of cirrhotic patients, particularly in more decompensated patients and those with refractory ascites (133). The outcome is very poor with a median survival of 6 months without liver transplant.

Screening should be performed in patients who present with unexplained dyspnea, fatigue or signs of right sided heart failure and as a part of the liver transplant evaluation as extremely high pressure >50 mmHg, carries

a high operative risk (134). Screening for POPH should be started with echocardiogram, which typically shows elevated right ventricular systolic pressure (RVSP) as well as pulmonary acceleration time (diagnostic if greater than 100 msec) and can rule out other cardiac causes of pulmonary hypertension such as valvular heart disease (130). Positive echocardiogram findings should be followed by right heart catheter as it is more accurate in documenting pulmonary artery pressure (135) and also allows evaluation of response to vasodilator administration.

Treatment includes oxygen supplementation in case of hypoxia and oral endothelin receptor antagonist such as bosentan that has shown to improve exercise tolerance and hemodynamics (136). Prostacyclin analogue, esoprostenol can also be used; however it requires continuous infusion (137). Sildenafil is used in other causes of pulmonary hypertension but in POPH it can worsen portal hypertension (130). Beta blockers are associated with worsening exercise capacity and pulmonary hemodynamics so they should be stopped in patients with POPH and variceal ligation should be used (138).

Cirrhotic cardiomyopathy represents the systolic and diastolic dysfunction and electrophysiological abnormalities (mainly a prolonged QT interval) that is seen in up to one third of cirrhotic patients (139) and it can be demonstrated on echocardiogram (specially using tissue Doppler) (140). However, clinical detection usually occurs only after a stressful condition as TIPS or after surgery as liver transplant. Unfortunately, no official guidelines on diagnosis or treatment are available, however, beta blockers (141) and aldosterone antagonists seem to be beneficial and fluid status should be managed with diuretics as needed. Liver transplant may revert some of the cardiac abnormalities (130). Cardiac glycosides as digoxin do not seem to be beneficial.

Arterial hypertension can still be seen in patients with cirrhosis especially patients with fatty liver disease because of the association with metabolic syndrome. Aggressive treatment in decompensated cirrhosis should be avoided because low mean arterial pressure (<82) has been shown to independently predict worse survival in this group of patients (142). Additionally, patients start to be hypotensive once decompensation develops so close monitoring of the blood pressure by both the physician and the patient are required to determine the need to adjust or stop the anti-hypertensive medications. ACE-inhibitors should be avoided or used with caution in the cirrhotic hypertensive patient as they can lead to worsening hemodynamics and

renal failure (143).

Other common problems of cirrhosis

In addition to management of complications of cirrhosis, other common issues are frequently encountered; targeting of these symptoms can improve quality of life.

Muscle cramps are common in cirrhosis (about 2/3 of patients) compared to general population, especially in advanced stages with hypoalbuminemia and water retention, and are associated with poor quality of life (144). Electrolyte imbalance should be looked for and corrected if present. However, according to one study occurrence of cramps was independent of abnormal serum electrolytes or diuretic consumption, suggesting an undiscovered underlying mechanism (145). One suggested treatment is quinine sulfate that is not approved as a drug for treatment of cramps any more but can be found in some brands of tonic water, and can help control cramps in cirrhotic patients (9).

Itching can be a problem in cirrhosis regardless the etiology and even cirrhotic patients without jaundice can complain of marked pruritus. Local dermatologic conditions should be ruled out, and then drug therapy in the form of cholestyramine can be tried. Other medications that have been studied and can be used as second line treatments include serteraline, naltrexone and rifampicin (146). Some of these medications are safer than bile acid binding agents because of less drug interactions.

Dyspepsia and nausea are common symptoms in cirrhosis affecting nutrition and quality of life. Usually due to an underlying organic cause, for which a clinical evaluation should be done looking for gastritis, gastric ulcer, gall stones, GERD or gastroparesis. For patients with functional dyspepsia (about ¼ of patients) (147), treatment is usually symptomatic with a serotonin 5-HT₃ receptor antagonist such as ondansetron (148), if failed, careful use of metoclopramide can be tried (9).

Pain control

Cirrhotic patients are subjected to higher risk with pain medications compared to general population. Nonsteroidal anti-inflammatory drugs (NSAIDs) should generally be avoided because of the associated GI toxicity (in a patient that may be coagulopathic with varices) and also reduction of renal function and diuretic response by inhibiting vasodilating prostaglandins release. Selective COX-2

inhibitors may have fewer side effects, but further studies are required to confirm this findings and evaluate long term side effects including cardiac ones (149).

Acetaminophen is not contraindicated in liver patients but should be used with caution. The suggested safe daily limit is 2-4 grams in the patient with cirrhosis and in case of active alcohol drinking, the daily limit should be 2 grams or even less, because of glutathione depletion (150). Most available studies evaluated only short-term use. Further studies evaluating long term use are needed.

Whenever possible, opioids should be avoided in decompensated cirrhotic patients (or limited to severe pain as malignancies) because of the altered elimination (hepatic and renal) and prolonged half-life precipitating encephalopathy through accumulating CNS suppression effect and/or associated constipation. Additionally, there is a potential for addiction especially in alcoholic patients and can affect patients listing for transplant. Hypotension is another side effect of narcotics that can exacerbate systemic hypotension seen in cirrhosis. Fentanyl seems to have less hypotensive effect, likely because of the unchanged pharmacokinetics in cirrhosis (151) and the lack of the histamine release seen with other narcotics (152). Tramadol appears relatively safe as it works through other mechanisms beside opioid receptors and it should be the first line narcotic used (153). Other narcotics as oxycodone, morphine and hydromorphone can be cautiously used if pain is not controlled but dose reduction and less frequent administration are recommended (154).

Other ways to control pain should be addressed like paracentesis for tense ascites and switching diuretics for symptomatic gynecomastia. Neuropathic pain can be managed with other medications. Theoretically, the safe tricyclic antidepressants (TCA) are nortriptyline and desipramine because they are less potent with less sedative effects, less hypotension and less intestinal slowing effect (155). Carbamazepine should be avoided due to high incidence of hepatotoxicity but other antiepileptic drugs as gabapentin can be used with careful dose reduction with abnormal kidney functions or with development of side effects as nausea or sedation. Pregabalin is a more expensive option with fewer side effects (154).

As a general rule unnecessary use of medication should be avoided in cirrhosis because of potential hepatotoxic or nephrotoxic effects and because of possible drug interaction. Examples are unnecessary antibiotics for likely viral respiratory infection, over the counter herbal "liver stimulants" and chronic oral vitamin K (9).

Nutrition

Muscle wasting is a common problem in cirrhosis due to appetite suppression that is either central or due to ascites and intestinal wall edema (156). It is estimated that up to 50% of patients have energy and protein malnutrition according to one Japanese study (157). Generally recommended calorie intake for cirrhotic patients is 40 kcal/kg/day in energy and 1.2-1.5 kcal/kg/day in proteins (158) with spreading the daily intake into 4-6 meals including a late evening snack of less than 200 kcal rich in branched chain amino acids (159). Further adjustment according to the patient's co morbidities and current nutritional status is required. For example, in case of impaired glucose tolerance, recommended daily calorie intake is 25-30 kcal/kg ideal body weight, with focusing on dietary fibers and complex rather than simple carbohydrates (160,161) and oral branched chain amino acid supplement as it was shown to improve insulin sensitivity (162).

Unnecessary diet restrictions should be avoided. This includes sodium restriction in compensated patients without evidence of fluid retention as this can worsen malnutrition by making food less palatable. Similarly free water restriction is not recommended unless serum sodium is markedly low. Unnecessary protein restriction should be avoided, as mentioned in the encephalopathy section (71).

Certain life style modifications are shown to improve cirrhosis progression. In addition to alcohol cessation, quitting smoking (163) and avoiding cannabis use (164) were also associated with less fibrosis progression in patients with chronic viral hepatitis. On the other hand, coffee was shown to have anti-oxidant helping with reducing fibrosis risk (165) increasing chance of sustained virological response (SVR) to antiviral treatment (166), and dark chocolate probably affects endothelial function helping portal hypertension (167).

Conclusions

The management of cirrhosis is an important element in treating patients with HCC given the associated morbidity and mortality. Despite advances in the management of patients with cirrhosis and availability of high-quality evidence as well as comprehensive clinical guidelines, there remains poor implementation of recommended care for patient with cirrhosis in clinical practice. Recognizing the subtle signs of cirrhosis and the decompensation events are essential to the successful management of cirrhosis. General measures (*Table 1*) should be applied to all patients

Table 1 General measures in patients with liver cirrhosis. Identification and treatment of underlying etiology

Avoid "second hit": alcohol cessation, avoid hepatotoxic medications/herbal preparations, immunization against HBV and HAV
Periodic estimation of severity of disease (using CP or MELD score) and development of complications
Improve nutritional status and avoid unnecessary dietary restrictions
Transplant evaluation
Life style modification that showed proven/probable benefit: avoid smoking, cannabis use, encourage weight loss, coffee, dark chocolate
Randomized controlled trials on liberal use of other medications as non selective beta blockers, statins, antibiotics and anticoagulation and their role in delaying progression of cirrhosis or side effects
HBV, hepatitis B virus; HAV, hepatitis A; CP score, Child-Pugh score; MELD, Model of end-stage liver disease.

Table 2 Current and future recommendation for common complications of liver cirrhosis

	Current interventions (beside liver transplant)	Future interventions
Ascites	Dietary sodium restriction; Combination oral diuretics; Paracentesis for tense or refractory ascites; TIPS for refractory ascites	Improve diuretic sensitivity using one or more of the following: midodrine, clonidine, vasopressin antagonists
Variceal bleeding	Screening endoscopy; Primary prophylaxis using NSBB and/or EVL; Secondary prophylaxis using NSBB and EVL. TIPS in selected cases; Acute bleeding: vasoconstrictors, antibiotic prophylaxis, urgent endoscopy, +/- emergency TIPS	More definite role for HVPG and variceal pressure measurement; Use of other beta blockers as carvedilol; Endoscopic therapy using laser or Argon plasma photocoagulation for GAVE and portal hypertensive enteropathy; Thrombin injection or retrograde transvenous obliteration for fundal varices
Hepatic encephalopathy	Rule out other diagnoses and specific precipitating factors; Treatment with Non-absorbable disaccharides and antibiotics; Avoid unnecessary protein restriction	Further studies on role of flumazenil, acarbose and Zinc supplement
Hyponatremia	Free water restriction; Adjusting/holding diuretics; Rare use of hypertonic saline; Tolavaptan is no longer recommended	Evaluation of other vasopressin receptor antagonists
Hepatorenal syndrome	Confirm diagnosis, exclude other reversible causes; Rule out infections; Treatment using combination albumin and vasoconstrictor (terlipressin or noradrenaline or both midodrine and octreotide)	Further evaluation of role of TIPS; Evaluation of new alternatives to dialysis as MARS and Prometheus extractor-poreal liver support system; New diagnostic tools that offer definite diagnosis as Urinary neutrophil gelatinase-associated lipocalin.
Spontaneous bacterial peritonitis	Confirm diagnosis with ascitic neutrophil count; Start treatment with third generation cephalosporin and albumin; Do not miss secondary peritonitis; Prophylaxis in all survivors and in other selected patients	Evaluating diagnosis using leukocyte esterase dipsticks or ascitic fluid lactoferrin; Evaluate benefits of selective intestinal decontamination on hemodynamics
NSBB, non-selective beta blocker; EVL, endoscopic variceal ligation; LVP, large volume paracentesis; TIPS, transjugular intrahepatic portosystemic shunt; MARS, molecular adsorbent recirculating system; HVPG, hepatic venous pressure gradient; GAVE, gastric antral vascular ectasia.		

with cirrhosis to prevent further damage and loss of the residual liver function, which in addition to worsening survival, also limits the available treatment options for HCC and affects response and safety of therapeutic interventions. Hepatotoxic medications should be avoided and whenever possible, underlying etiology of the liver disease should be treated. Early detection of manifestations of decompensation events including ascites, encephalopathy,

varices, SBP and hepatorenal syndrome and their management together with other important complications of cirrhosis (pruritis, cramps, malnutrition) can substantially minimize morbidity and improve outcomes (*Table 2*).

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Footnote

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Quality of life and hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a common and rapidly fatal cancer ranking third among the leading causes of cancer-related deaths. Potentially curative therapies like surgery, transplant and ablation are not an option for most patients as they are often diagnosed when the disease is advanced. Liver directed therapy and oral targeted therapies are used in these patients to prolong life and palliate symptoms of the cancer and associated liver failure. Overall survival remains poor and hence health-related quality of life (HRQoL) is of paramount importance in these patients. As novel therapies are developed to improve outcomes, a comprehensive knowledge of available tools to assess impact on QoL is needed. Hence we reviewed all the studies in HCC patients published within the last 13 years from 2001-2013 which assessed HRQoL as a primary or secondary endpoint. A total of 45 studies and 4 meta-analysis were identified. Commonly used tools were European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (15 studies) and the Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep) (14 studies). Of the 45 publications which incorporated HRQoL as end-point only 24 were clinical trials, 17/24 (71%) assessed systemic therapies while 7/24 (29%) assessed liver-directed therapies. Majority of the publications (trials + retrospective reviews) that had HRQoL as an endpoint in HCC patients were studies evaluating liver-directed therapies (23/45 or >50%). We discuss the measures included in the tools, their interpretation, and summarize existing QoL data that will help design future HCC trials.

Keywords: Hepatocellular carcinoma (HCC); health-related quality of life (HRQoL); endpoint; trial

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It is the 5th most common cancer worldwide and the 3rd leading cause of cancer-related deaths (1,2). This tumor is relatively uncommon in the United States although its incidence has been increasing due to the increased burden of hepatitis C infection. Risk factors associated with HCC include cirrhosis, hepatitis B and C infections and alcohol intake. Cirrhosis is present in 80-90% of HCC patients and is thereby the single largest risk factor (3). Non-alcoholic steatohepatitis has also emerged as an important cause of HCC (4).

The optimal therapeutic option for HCC is liver transplantation as it treats both the neoplasm and any

underlying cirrhosis; however, only 20% of patients diagnosed with HCC are candidates for transplantation (5). Other treatment options include surgical resection for patients with resectable HCC for those with preserved liver function, locoablative treatments for small, solitary HCC, liver-directed therapies for multifocal HCC without contraindications and systemic therapy for metastatic or multifocal HCC that is associated with limited hepatic reserve or portal vein involvement (2). Quality of life (QoL) after major surgical resection in patients with cancer is well known, and especially important, given the morbidities of liver resection and since recurrence is the natural course of the disease for many due to their underlying liver disease. Chemoembolization can also cause considerable pain/discomfort immediately after the procedure and also cause

decompensation of liver function and impact patient's QoL. Unfortunately 80% of the patients are unable to undergo surgical resection or transplantation (6). And non-surgical treatments, like transcatheter chemo-embolization or chemotherapy have a limited impact on patient survival that remains between 6 months to a year in majority of cases (2,7-10). The only approved therapy currently for HCC is sorafenib, an oral targeted agent with considerable off target side effects in ~80% of patients. Despite advances in treatment over the past decade, overall prognosis remains poor. Population-based studies in the United States indicate that 1- and 3-year survival rates for patients with HCC are approximately 20% and 5%, respectively, with a median survival of 8 months. There is therefore an urgent need for novel therapies that are being developed to palliate symptoms and prolong life.

QoL is considered important for patient outcome and is considered as important as disease-free survival and overall survival and should be an endpoint like response rate and time to progression (11-13). Health-related quality of life (HRQoL) subjectively perceived by the patient, is becoming a major outcome in the evaluation of any therapeutic intervention, mainly in patients with chronic or poorly curable diseases, where the aim of the interventions is to maintain patients either symptom-free and community-living for a long time, or to reduce the distress of the disease. Patients with HCC report several symptoms which are severe enough to affect the QoL like, sleep disorders, sexual dysfunction, ascites, gynecomastia, pruritis, fatigue, muscle cramps. The HRQoL indicators that have been used in trials thus far are based on these symptoms (14).

Goal of therapy in patients who present with symptoms is palliation but limited data exist on whether this goal is achieved with chosen therapies. Having this information could influence provider and patient decision-making given the short survival and many side-effects of therapy. Hence, HRQoL is of paramount importance in patients diagnosed with HCC enrolled on trials as this sparse trial eligible patient population data forms the basis for therapeutic decision-making for many others who are more symptomatic and hence in greater need for interventions that improve their QoL. HRQoL results may be more relevant than length of life, as patients are often more concerned about life-quality than longevity (15). HRQoL is an important aspect of palliative care and has been acknowledged as an important end point in several randomized clinical trials and clinical practice (16,17).

In HCC, both cancer and its treatment are severely debilitating and the need to consider their impact upon HRQoL when making patient management or treatment decision is well-accepted (18). Hence, we conducted a review of literature on all the studies published in the last 13 years assessing QoL in patients with HCC as a primary or secondary end point to help guide clinicians across many disciplines who are designing trials for these patients.

Patients and methods

We searched PUBMED for all English-language publications that dealt with HRQoL in HCC using the following terms: health utility, health status, health status indicators, activities of daily living (ADLs), QoL and HCC. Studies were included if they had been published in the last 13 years, and if patients were treated with surgery, hepatic arterial infusion, chemotherapy, radionuclide therapy, or observation. All trials included some QoL or functional measure as an outcome: either primary or secondary or as an independent variable.

The primary aim of this study was to describe the tools being used to assess HRQoL in patients with HCC and to summarize how to use and interpret data gathered using these tools.

Results

In our search, we found 25 relevant articles published in the last 13 years [2001-2013] that identified HRQoL as a primary end point (*Table 1*). We also found 20 other articles that had HRQoL as one of their secondary end points (*Table 2*). There were an additional four meta-analysis that met inclusion criteria for our search. In 12 of these studies, the numbers of patients with HCC were less than 50. In the cross-sectional studies, we can compare QoL in HCC patients who received different treatment modalities, such as, surgery, transarterial embolization, local liver-directed treatment, chemotherapy, or just supportive care. In the longitudinal study, we can compare the QoL in patients before and after the treatment. In our tables, the various HRQoL indicators included assessed general symptoms of well-being or liver-specific symptoms like fatigue, diarrhea, back pain, jaundice, and impairment in sexual functions. These QoL indicators are significantly impaired in HCC patients, and this can help in better addressing the management of these patients with HCC by the physicians in a patient-centered model of care.

Table 1 Studies with HRQoL as primary endpoint

Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Poon et al. 2001 (19)	Descriptive	1	76	76	66: surgical resection; 10: TACE (if unresectable)	Partial hepatectomy vs. TACE (if unresectable)	Yes	FACT-G	Preoperative and postoperative QoL using FACT-G for upto 2 years after surgery (at 3, 6, 9, 12, 18, 24 months). Hepatic resection results in a significant enhancement of GoL in patients with HCC. Development of recurrence is the main factor leading to deterioration in GoL over time after resection of HCC	
Tanabe et al. 2001 (20)	Descriptive	1	123	123	NS: repeat hepatic resection; NS: hepatic arterial infusion chemotherapy	Recurrence of HCC after hepatic resection: comparison of repeat hepatic resection vs. hepatic arterial infusion chemotherapy	Yes	4 item questionnaire		

Table 1 (continued)

Table 1 (continued)										
Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Brans <i>et al.</i> 2002 (21)	Descriptive		1	20	20	20: ¹³¹ I-lipoidal therapy; 10/20: cisplatin	¹³¹ I-lipoidal therapy (± 2 doses of HAI cisplatin)	Yes	EORTC QLQ-C30	Intra-arterial ¹³¹ I-lipoidal therapy with or without cisplatin: Questionnaires were completed 1 week before, 1 and 3 months subsequent to the therapy
Ueno <i>et al.</i> 2002 (22)	Descriptive		1	96	96	96: partial hepatectomy	Partial hepatectomy	Yes	14 item questionnaire	
Zhao <i>et al.</i> 2002 (23)	Descriptive		1	175	175	NS	TACE	Yes	QoL-LC	
Bianchi <i>et al.</i> 2003 (24)	Case-control		1	303	101	NS	Any treatment	No	SF-36, Nottingham Health Profile Questionnaires	Data stresses the relevance of pain in poor perceived health status of HCC patients, and the importance of minor symptoms, such as, sleep disorders
Steel <i>et al.</i> 2004 (25)	Validation	Phase II, non-randomized study	1	28	28	14: HAI of cisplatin; 14: infusional radiotherapy	HAI cisplatin vs. yttrium microspheres	Yes	FACT-Hep	Patients assessed at baseline, then every 3 months for first 6 months and then followed up at 1 year
Chen <i>et al.</i> 2004 (26)	Descriptive		1	36	30	30: major and minor hepatectomy	Surgical resection	Yes	GQLI	
Steel <i>et al.</i> 2005 (27)	Descriptive		1	82	82	82: HCC; 82: proxies	Any treatment	No	FACT-Hep	

Table 1 (continued)

Table 1 (continued)										
Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Wang et al. 2005 (28)	Descriptive		1	160	160	80: RFA; 40: TACE; 40: RFA + TACE	RFA, TACE-RFA, TACE	Yes	QoL-LC V2.0	
Eid et al. 2006 (29)	Descriptive		1	40	7	3/24: major hepatectomy; 1/8: minor hepatectomy; 3/8: radiofrequency ablation	Hepatic resection or ablation	Yes	FACT-Hep, FHSI-8, POMS; EORTC-QLQ-PAN; EORTC QLQ-C30	Patients were assessed at 5 time points: initial visit, initial postoperative visit, visit at 6 weeks, 3 and 6 months
Steel et al. 2006 (5)	Meta-analysis		3	158	135	93:TACE; 42: Yttrium	TACE or yttrium microspheres	Yes	FACT-Hep version 4.0	
Yeo et al. 2006 (16)	Meta-analysis		2	233	233	156 patients out of a total of 188 patients from chemo study and 77 patients out of a total of 324 patients from the hormonal study—both studies were phase 3 randomized controlled trials	Doxo alone, Doxo combination cisplatin/IFN/ Doxo/5-FU	No	EORTC QLQ-C30	
Lee et al. 2007 (30)	Descriptive		1	161	161	121: surgery; 31: TACE; 8: percutaneous ethanol injection; 1: supportive	Per treating physician	Yes	WHOQOL-BREF Taiwan version, EORTC QLQ-C30, VAS, Standard Gamble	

Table 1 (continued)

Table 1 (continued)										
Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Wang et al. 2007 (31)	Validation	Phase II	1	83	83	40: TACE; 43: TACE + RFA	TACE followed by RFA vs. TACE alone	Yes	FACT-G version 4	Questionnaires completed at baseline and 3 months after treatment, TACE-RFA group resulted in a significantly higher total QoL score, social-family well-being score, and functional well-being scores than TACE group, 3 months after respective treatment
Kondo et al. 2007 (32)	Case-control		1	194	97	97: percutaneous ablation-RFA or alcohol	Prior percutaneous ethanol or RFA in case group	Yes	SF-36	Raw scores were transformed using norm-based scoring
Steel et al. 2007 (33)	Descriptive		1	272	83	83: untreated; 51: chronic liver disease; 138: general population	Untreated	No	FACT-Hep	
Martin et al. 2007 (34)	Descriptive		1	32	4	3/24: major hepatectomy (>2 segments); 1/8: minor hepatectomy	Hepatic resection	Yes	FACT-Hep, FACT-FHSI-8, EORTC QLQ-C30, POMS, EORTC-QLQ-Pan2 Ca, Global Rating Scale	QoL assessed at the time of consent, discharge, first postoperative visit, 6 weeks, 3, 6 and 12 months

Table 1 (continued)

Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Sun <i>et al.</i> 2008 (35)	Descriptive		1	45	22	22: any treatment	Yttrium microspheres, TACE, chemotherapy, surgery	Yes	FACT-Hep, FACIT-Sp-12	Patients were assessed monthly for 3 months
Mendez <i>et al.</i> 2008 (36)	Validation	Phase I/II	1	28	9	9: external radiotherapy	Liver stereotactic body radiation therapy	Yes	EuroQoL-5D, EuroQoL-VAS, EORTC QLQ-C30	Quality of life was assessed before, 1, 3 and 6 months after treatment, first study to report quality of life associated with liver stereotactic body radiation therapy
Nowak <i>et al.</i> 2008 (37)	Validation	Phase II	1	46	46	NS	Octreotide LAR	No	FACT-Hep, patient DATA form, patient benefit form	Not found in original PUBMED search, recapitulates Cebon <i>et al.</i> 2006 (38)
Bonnetain <i>et al.</i> 2008 (39)	Meta-analysis		2	538	538	Doffoël 2008 (40): 122; Barbare 2005 (41): 416	Tamoxifen vs. supportive care or transarterial lipoidal chemoembolization	Yes	Spitzer QoL index	Articles included are Doffoël 2008 (40) and Barbare 2005 (41)

Table 1 (continued)

Table 1 (continued)										
Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Wible <i>et al.</i> 2010 (42)	Descriptive		1	73	73	73: TACE; 23/73 patients underwent 3 or more chemoembolisation procedures	TACE	Yes	SF-36	Baseline HRQoL scores were evaluated and again measured during 4, 8, 12 months of treatment, and separately within a subset of 23 patients who underwent 3 or more chemoembolisation procedures
Shun <i>et al.</i> 2012 (43)	Descriptive		1	89	89	89: TACE	TACE	Yes	SDS; HADS; SF-12	Pre and post discharge factors related to changes in physical and mental domains of QoL over a period of 2 months. Data were collected 3 times—within 3 days prior to discharge, at 4th and 8th weeks after discharge
Qiao <i>et al.</i> 2012 (15)	Descriptive		1	140	140	Any treatment	Any treatment	No	FACT-Hep	HRQoL of patients with hepatocellular carcinoma worsens gradually with progression of TNM stage

Table 1 (continued)

Table 1 (continued)

Author	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Eltawil <i>et al.</i> 2012 (44)	Validation	Phase II	1	48	46	46: TACE	TACE	Yes	WHO-QoL-BREF	QOL was compared to the pre-intervention state
Diouf <i>et al.</i> 2013 (45)	Validation	Phase III	1	271	271	134: Long acting octreotide; 137: placebo	Long acting octreotide	No	EORTC QLQ-C30	
Fan <i>et al.</i> 2013 (46)	Descriptive		1	286	286	117: surgery; 96: TACE; 73: chemotherapy	Surgery, TAE/TACE, chemotherapy	Yes	EORTC QLQ-C30, EORTC-QLQ-HCC18	

RFA, radiofrequency ablation; TACE, transarterial chemoembolisation; NS, not specified; GQLI, gastrointestinal quality of life index; POMS, profile of mood states; EORTC-QLQ-PAN, European Organization for Research and Treatment of Cancer QoL Questionnaire for patients with pancreatic cancer; SDS, symptom distress scale; HADS, hospital anxiety and depression scale; SF-12, short form -12 health survey; HRQoL, health-related quality of life; HCC, hepatocellular carcinoma.

Table 2 Studies with HRQoL as secondary endpoint

Study	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Samonakis <i>et al.</i> 2002 (47)	Validation	Phase I/II non-randomized trial	1	59	59	32: octreotide lar; 27: no treatment/supportive	Octreotide LAR	No	KPS	Superior quality of life was found in the treated group
Dimitroulopoulos <i>et al.</i> 2002 (48)	Validation	Phase I/II non-randomized trial	1	28	28	15: Octreotide LAR; 13: Control	Octreotide and octreotide LAR	No	EORTC QLQ-C30	
Chow <i>et al.</i> 2002 (49)	Validation	Phase III	1	324	324	194: Tamoxifen-low dose [74], high dose [120], 130: placebo	Tamoxifen (high and low dose)	No	EORTC QLQ-C30	QoL evaluated monthly. Comparisons between groups were made "graphically", multicenter phase III study; do not recommend the use of tamoxifen in patients with HCC because it does not offer any benefit in terms of QoL and is likely to be detrimental
Yuen <i>et al.</i> 2003 (50)	Validation	Phase I/II	1	70	70	35: octreotide LAR; 35: placebo	Octreotide	No	KPS	
Poon <i>et al.</i> 2004 (51)	Validation	Phase II	1	84	84	84: TACE; 41/84: oral branched chain amino acids; 43/84: control	TACE+/- branched chain amino acids	Yes	FACT-G	

Table 2 (continued)

Table 2 (continued)										
Study	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Steel et al. 2005 (52)	Descriptive		1	44	21	21: any treatment	Any treatment	No	FACT-Hep, Sexual History Questionnaire	When the entire sample was analyzed, patients reporting a sexual problem reported a clinically significant decrease in physical and emotional well-being compared with those who did not. People who reported a sexual problem also had a lower emotional well-being score on FACT-Hep. People diagnosed with HCC who reported increased rates of sexual problems also reported poorer HRQoL
Barbare et al. 2005 (41)	Validation	Phase III	1	420	420	210: tamoxifen; 210: control	Tamoxifen vs. no treatment	No	Spitzer QoL index	Among surviving patients (in each treatment group), mean change in QoL scores for these patients from their baseline were compared at 3, 6, and 9 months
Cebon et al. 2006 (38)	Validation	Phase II	1	63	63	NS	Octreotide LAR	No	FACT-Hep, patient DATA form, patient benefit form	HRQL data resummized in Nowak et al. 2008 (37). N.B. compliance with QoL only 73% at baseline, patients reported improvement in some symptoms but no major changes in QoL were detected

Table 2 (continued)

Table 2 (continued)

Study	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Kirchhoff <i>et al.</i> 2006 (53)	Validation	Phase II randomized	1	70	70	35: transarterial chemoocclusion with degradable starch microspheres; 35: transarterial chemoperfusion	TACO vs. HAI	Yes	EORTC QLQ-C30 Version 2	Quality of life was assessed in 40/70 patients due to incomplete questionnaires
Verset <i>et al.</i> 2007 (54)	Validation	Phase III randomized	1	109	109	53: Tamoxifen alone, 56: Tamoxifen and octreotide	Tamoxifen +/- octreotide	No	KPS	
Becker <i>et al.</i> 2007 (55)	Validation	Phase III randomized	1	119	119	60: octreotide LAR; 59: placebo	Octreotide LAR	No	EORTC QLQ-C30	All 15 subdomains of EORTC QLQ-C30 compared at baseline, 1, 3, 6 months and q3 months thereafter
Dimitroulopoulos <i>et al.</i> 2007 (56)	Validation	Phase III randomized	1	126	126	66: no treatment/control; 30: octreotide; 30: placebo	Octreotide LAR	No	EORTC QLQ-C30	Single center study and QoL was assessed monthly
Steel <i>et al.</i> 2008 (57)	Descriptive	Phase II	1	120	85	NS: TACE; NS: HAI of 90-yttrium	TACE vs. infusional radiotherapy vs. surgery	Yes	FACT-Hep	
Llovet <i>et al.</i> 2008 (58)	Validation	Phase III randomized placebo-controlled trial	1	602	602	299: sorafenib; 303: placebo	Sorafenib	No	FHSI-8	

Table 2 (continued)

Table 2 (continued)

Study	Study type	Phase of trial	No. of studies	Sample size	Sample size (HCC)	No. of patients who received treatment	Intervention	Post-surgery or post-liver directed therapy	HRQoL tools used	Notes
Doffoèl et al. 2008 (40)	Validation	Phase III	1	123	123	61: tamoxifen; 62: TACE	Tamoxifen vs. TACE	Yes	Spitzer QoL index	Spitzer QoL index evaluated every 2 months during 3 years until stopping treatment or until 10 cures of TACE done and then every 3 months until death
Cheng et al. 2009 (59)	Validation	Phase III	1	226	226	150: sorafenib; 76: placebo	Sorafenib	No	FACT-Hep, FHSI-8	
Barbare et al. 2009 (60)	Validation	Phase III randomised	1	272	272	135: octreotide; 137: placebo	Octreotide LAR	No	EORTC QLQ-C30	
Jia et al. 2010 (61)	Meta-analysis		4	373	373	153: octreotide, 154: control	Octreotide	No	QLQ-C30, KPS	4 studies included: Kouroumalis et al. (62) (28: octreotide, 30: control); Yuen et al. (50) (35: octreotide, 35: control); Becker et al. (55) (60: octreotide, 59: control); Dimitroulopoulos et al. (56) (30: octreotide, 30: control, 66: SSTR negative group)
Dollinger et al. 2010 (63)	Validation	Phase III	1	135	135	67: thymostimulin; 68: placebo	Thymostimulin vs. placebo	No	FACT-Hep	QoL was assessed at baseline and every 6 weeks thereafter
Chow et al. 2011 (64)	Validation	Phase III	1	204	204	69: placebo; 135: megestrol acetate	Megestrol acetate	No	EORTC QLQ-C30	
Soliman et al. 2013 (65)	Validation	Phase II	1	41	21	21: palliative liver radiotherapy	Liver radiotherapy	Yes	FACT-Hep, EORTC QLQ-C30	

RFA, radiofrequency ablation; TACE, transarterial chemoembolisation; NS, not specified; HRQoL, health-related quality of life; HCC, hepatocellular carcinoma.

Commonly used tools

The commonly used HRQoL tools included European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire (FACT-Hep), Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index (FHSI-8), Functional Assessment of Cancer Therapy-General (FACT-G), Spitzer QoL index, World Health Organization Quality of Life-BREF (WHO-BREF), Short Form 36 (SF-36) and European Organization for Research and treatment of Cancer Quality of Life Questionnaire - Pancreatic Cancer (EORTC QLQ-PAN).

EORTC QLQ-C30 was the most widely utilized tool, with 15 publications and 4 phase I/II and 6 phase III clinical trials identified.

FACT-Hep has also been widely published, with 14 publications identified in our literature review. The use in clinical trials, however, is not as extensive, with only five phase I/II trials and two phase III trials identified.

FHSI-8 was used in four publications with two phase III clinical trials.

FACT-G was used in three publications (two phase I/II clinical trials), SF-36 was used in three publications, WHO-BREF was used in two publications, Spitzer QoL index was used in two publications (two phase III trials), EORTC QLQ-PAN was used in two publications (*Table 3*).

HRQoL as primary or secondary endpoint

In our analysis, there were 25 publications (six trials) with HRQoL as a primary endpoint. Most commonly used tool as a primary endpoint was FACT-Hep (eight publications with two trials) followed by EORTC QLQ-C30 (seven publications with two trials). A total of 20 publications (18 trials) used HRQoL as a secondary endpoint. Most commonly used tool as a secondary endpoint was EORTC QLQ-C30 (eight publications, all of which were trials) followed by FACT-Hep (six publications including four trials). Most of the trials (18 out of 24) assessed HRQoL as a secondary endpoint with EORTC QLQ-C30 being the most commonly used tool (ten trials) followed by FACT-Hep (six trials). Several publications using these tools were data from case series rather than prospective trials.

Tools used to measure clinical outcome post-surgical intervention

In our analysis, there were ten publications with surgical

intervention (hepatic resection). The most widely used tools were FACT-Hep (four publications) and EORTC QLQ-C30 (four publications). However, none of the trials during this period assessed HRQoL as an outcome to measure the impact of surgical intervention.

Tools used to measure clinical outcome post liver-directed therapies

There were 23 publications (seven trials) where liver-directed therapies were used [liver-directed therapies include: transarterial chemoembolization (TACE)/infusional radiotherapy/hepatic resection/percutaneous ethanol ablation/radiofrequency ablation (RFA)/liver stereotactic body radiation]. The most widely used tools were EORTC QLQ-C30 (eight publications including three phase I/II trials), FACT-Hep (six publications including two phase II trials).

Hence, for surgical interventions and locoregional therapies, the tools most frequently used were EORTC QLQ-C30 and FACT-Hep. The additional questions they addressed were liver-specific questions like ascites, weight loss, loss of bowel control, back pain, fatigue, jaundice and pruritis.

Tools used to measure clinical outcome post-systemic/medical intervention

There were about 19 publications (17 trials) where HRQoL was used to monitor the impact of systemic intervention (octreotide, tamoxifen, sorafenib, thymostimulin, megestrol, chemotherapy). Majority of the trials assessed octreotide as a medical intervention (ten publications, that is, five phase I/II and five phase III trials) followed by tamoxifen (four publications, that is, one phase I/II and three phase III trials) and sorafenib (two publications, that is, two phase III trials). The most commonly used tool was EORTC QLQ-C30 (eight publications including seven trials) followed by FACT-Hep (five publications including four trials) and KPS (three publications, all of which were trials).

Studies which used generic HRQoL indices

Generic HRQoL indices (EORTC QLQ-C30, KPS, FACT-G, SF-36, Profile Of Mood States, EuroQoL-Visual Analogue Scale, WHO-QoL BREF, Patient DATA form, Patient BENEFIT form, Spitzer QoL index, Symptom Distress Scale, Hospital Anxiety Depression Scale, FACIT-Sp-12, sexual history questionnaire, Euro-QoL-5D, Standard gamble, SF-12, Nottingham Health Profile,

Table 3 Frequency of usage of different HRQoL tools in different publications

HRQoL tool	All publications	Phase I/II trials			Phase III trials			HRQoL indicator as primary end point			HRQoL indicator as secondary end point			Publications with liver directed therapies	Trials with liver-directed therapies	Studies with surgical interventions	Publications with systemic therapy	Trials with systemic therapy	Publications/trials		
		trials	trials	trials	trials	trials	trials	trials	trials	trials	trials	trials	Trials with systemic therapy						Octreotide	Tamoxifen	Sorafenib
EORTC QLQ-C30	15	4	6	7	2	2	8	8	8	3	3	4	8	7	5	1	0	0	0		
FACT-Hep	14	5	2	8	2	2	6	4	6	2	2	4	5	4	2	0	1	0	0		
FHSI-8	4	0	2	2	0	2	2	2	2	0	0	2	2	2	0	0	0	2	0		
KPS	3	2	1	0	0	0	3	3	0	0	0	0	3	3	3	1	0	0	0		
FACT-G	3	2	0	2	1	1	1	1	3	2	2	1	0	0	0	0	0	0	0		
SF-36	3	0	0	3	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0		
POMS	2	0	0	2	0	0	0	0	2	0	2	2	0	0	0	0	0	0	0		
EORTC-QLQ-PAN	2	0	0	2	0	0	0	0	2	0	2	2	0	0	0	0	0	0	0		
QLQ-LC	2	0	0	2	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0		
Euro QoL-VAS	2	1	0	2	1	0	0	0	2	1	1	1	0	0	0	0	0	0	0		
WHO-QoL-BREF	2	1	0	2	1	0	0	0	1	0	1	1	0	0	0	0	0	0	0		
Patient data form	2	2	0	1	1	1	1	1	0	0	0	0	2	2	2	2	0	0	0		
Patient benefit form	2	2	0	1	1	1	1	1	0	0	0	0	2	2	2	2	0	0	0		
Spitzer QoL	2	0	2	0	0	2	2	2	2	1	0	0	2	2	0	2	0	0	0		
EORTC-QLQ-HCC18	1	0	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0		
GQLI	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0		
SDS	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0		
HADS	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0		
FACIT-Sp-12	1	0	0	1	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0		
Sexual history questionnaire	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0		
EuroQoL5D	1	1	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0		
Standard gamble	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0		
Global rating scale	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0		
SF-12	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0		
Nottingham health profile	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
14 item questionnaire	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0		
4 item questionnaire	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0		

GQLI, gastrointestinal quality of life index; SDS, symptom distress scale; HADS, hospital anxiety depression scale; HRQoL, health-related quality of life.

14 and 4 item questionnaire) were used in 33 publications, which included 12 phase I/II trials and 8 phase III trials.

Studies which used liver-specific indices

Liver-specific HRQoL indices which included specific questions like ascites, weight loss, diarrhea, constipation, jaundice, pruritis (that is, FACT-Hep, FHSI-8, EORTC QLQ-PAN, QLQ-LC, EORTC QLQ-HCC18, Gastrointestinal Quality of Life Index, Global Rating Scale) were used in 19 publications which included 4 phase I/II trials and 3 phase III trials.

Discussion

There is a wide variety of symptom presentation in advanced HCC; compensated patients may be asymptomatic for months or decades. In patients who are symptomatic from HCC, the most common presenting clinical features are right upper quadrant pain, weight loss, anemia or erythrocytosis. These are often superimposed on signs of cirrhosis (e.g., jaundice, palmar erythema, gynecomastia) and portal hypertension (e.g., ascites, varices), and may also be associated with increase in liver transaminases (2). It has a significant impact on the patient's functioning and well-being. Emotional concerns associated with the disease and treatment give rise to anxiety in patients. The QoL, including physical, emotional, and functional well-being are significantly affected because of the complications and extra-hepatic manifestations of advanced disease (66). Trial eligible HCC patients are few, as most patients have liver dysfunction to some degree and aren't candidates for many available treatments. In addition, toxicities of therapies employed are significant.

QoL is defined as people's perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns (67). Patients often ask providers what to expect in terms of their QoL when choosing a therapy, especially when the survival is short even with treatment. Unfortunately, very few trials have used validated HRQoL tools, hence, patterns of clinical decision-making are more often guided by available data on toxicity of treatment which is not a true surrogate of QoL because it does not assess the impact of treatment on existing symptoms or the patient's perception of their health/ well-being. HRQoL questionnaires potentially play a significant role in bringing the patient's voice to evidence-

based health care. However, to fully realize this potential, HRQoL outcomes need to be interpreted to make decisions about treatment. Such decisions are made at both the individual level, when a patient (along with the patient's clinician and care team) chooses among treatment options, and the group level, when clinical research is conducted to test the effectiveness of new treatments relative to current routine treatment (68,69). New treatments that improve the HRQoL relative to the current best treatment may be able to change policies and practices regarding treatment of those conditions.

HRQoL is multifaceted and subjective, and there are a large number and wide range of measurement scales, each of which has a different scale. The two most commonly used cancer-specific instruments are the EORTC QLQ-C30 (70) and the FACT-G (71).

The development of valid and reliable HRQoL instruments is an essential part of quantifying the physical, social and psychological distress associated with cancer diagnosis and its treatment. Useful tools must satisfy the basic psychometric principles of validity and reliability in the patient population being studied (*Table 4*). Additional desirable features of HRQoL instruments include patient self-administration, multiple dimensions, low respondent burden, and the ability to obtain subscale scores and an overall score (38). With the recent expansion of interest in measuring QoL, there has been a proliferation of validated tools for the measurement of various aspects of HRQoL. A recent review of an online repository of HRQoL tools (proquolid.org) identified 70 neoplasia-specific questionnaires. Selection of an appropriate tool requires considering the specific population being studied, prior precedence for a given tool in the given population, and means by which both clinical significance and statistical significance can be inferred for the given tool.

Details of the development, measures, interpretation of the various tools is in appendix A. Here we briefly discuss the two most commonly used tools and the tool used in the landmark SHARP trial as a primary endpoint in advanced HCC.

The EORTC QLQ-C30 was originally devised by Aaronson *et al.* in the Netherlands (70) and the FACT G was developed by Cella *et al.* in the United States (71). Both of these instruments have undergone vigorous validation and have been translated and tested in more than 40 different languages. They are therefore suitable to be used in cancer clinical trials and allow for cross-cultural comparisons. Functional Hepatobiliary symptom index (FHSI-8) is an

Table 4 Reliability and validity in different studies

Reliability	
Inter-rater reliability	Degree to which scores obtained for the metric are unrelated to the individual who administered the test or the means by which the test was administered
Internal-consistency reliability	Degree to which individual items that are components of the metric (or same subscale of the metric) have similar scores. Most often assessed with Cronbach's alpha statistic
Test-retest reliability	Degree to which scores obtained on the metric can be reproduced by retesting the same population after an insignificant time interval has passed
Alternate forms reliability	Degree to which the given metric is correlated to a similar metric (often the same metric but with a different order of items or with subtle changes in wording) in the same population
Validity	
Face validity	Degree to which reviewers, usually experts such as patients, clinicians, and researchers, agree that the metric intuitively measures what it is purported to measure
Content validity	Degree to which experts agree that all components of a given concept are addressed by the selected metric
Concurrent validity	Degree to which the given metric agrees with another, usually well-established, metric when assessing the same concept in an identical population
Predictive validity	Degree to which the given metric can predict future events that are theoretically related to the concept being measured
Convergent validity	Degree to which the given metric is correlated to a separate metric that measures a concept for which there should be a theoretical correlation
Discriminant validity	Degree to which the given metric is uncorrelated to a separate metric that measures a concept for which there should not be a theoretical correlation

eight item questionnaire to assess symptoms that measure lack of energy, fatigue, stomach pain/discomfort, pain, back pain, weight loss, nausea, jaundice also developed by Dr. Cella's group in addition to the FACT tools.

The EORTC QLQ-C30 questionnaire is a cancer-specific self-administered structured questionnaire designed for use in clinical trials. It is an integrated system that assesses the HRQoL of cancer patients. It includes five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea or vomiting, and pain), global health status, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). High scores on the functional scales indicate a high level of functioning and high scores on the global health status indicate a high QoL; however, high scores on the symptom scales/items indicate high levels of health problems. Brans *et al.* evaluated the feasibility of using this questionnaire following radionuclide liver-directed therapy using palliative ¹³¹I-lipiodol therapy for HCC. In 20 patients treated with locoregional, intra-arterial ¹³¹I-lipiodol therapy with or without cisplatin, they found

(I) a number of important scales, i.e., overall QoL, physical functioning and pain, worsened between 0 and 3 months after ¹³¹I-lipiodol therapy, irrespective of tumor response; and (II) the occurrence of clinical side-effects was associated with a negative impact on QoL and physical functioning 1 and 3 months after ¹³¹I-lipiodol, demonstrating that the value of this tool is assessing clinical impact following what is considered by most to be a well-tolerated/non-toxic treatment.

The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) is a cancer-specific version of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system (72). The FACT-Hep contains the original FACT-General (FACT-G) scales that include a 27-item compilation of general questions divided into four primary QoL domains: physical, social/family, emotional, and functional well-being. An additional 18 questions that assess symptom and QoL concerns pertinent to patients with hepatobiliary cancer were included. In a clinical trial assessing benefit from octreotide in HCC given that 56% of patients have receptor expression detectable

by scintigraphy, Cebon *et al.* used this tool to assess impact on QoL. One patient of 63 had a partial response and overall survival was 8 months, few grade 3/4 side effects were reported, but no major changes in QoL were detected using the FACT-Hep tool that allowed better interpretation of the results.

In the SHARP trial by Llovet *et al.* 2008, a new drug sorafenib was assessed in advanced HCC (58). In this study, 602 patients were randomly assigned to either drug or placebo group. The HRQoL indicator FHSI-8 questionnaire was used to assess the primary outcome, that is, median time to symptomatic progression, which was defined as either a decrease of four or more points from the baseline score on the FHSI-8 questionnaire or an ECOG status of four or death. No significant differences were observed between the sorafenib and the placebo groups. Symptoms related to the toxic effects of the drug or effect of response to tumor-related symptoms might have influenced the outcomes of the FHSI-8 questionnaire. The lack of a significant difference in responses to the FHSI-8 questionnaire might reflect the effect of the reporting of sorafenib's toxic effects by the patients, insensitive measurement tool, lack of power for the TTSP endpoint, or absence of any benefit from sorafenib or lack of the study design to be powered for this endpoint (58).

Thus, in each of the three trials discussed above, although the sample sizes are different (20, 63 and 602 respectively), interventions tested were different and the tools used were different, clinically meaningful data was added that would guide treatment decision-making. Radiolabeled liver-directed therapies, even when successful can have a significant negative impact due to side effects, a relatively benign therapy such as octreotide may not positively impact QoL even though side effects are few, and an oral drug like sorafenib that adds meaningful survival benefit may not improve existing symptoms and patient's perception of well-being.

Conclusions

Historically, outcome measurements in oncology have been limited to survival and treatment toxicity. However, nowadays it has been widely accepted by clinicians that QoL is an important prognostic indicator, as important as length of survival. The available literature on HRQoL is limited in hepatobiliary cancers and no gold standard exists for measuring HRQoL. However, in the last two decades there has been development of several HRQoL

instruments. The QoL components measured in the various HRQoL questionnaires and their analysis is presented in the discussion to help clinicians understand and interpret the results from published studies. Here we summarize the take home points- how available data can help guide future trial design and highlight areas of need where additional validation or QoL data are badly needed.

In our literature review, the HRQoL indicators that have been most frequently used are EORTC QLQ-C30 which has been used in 15 publications with 4 phase I/II trials and 6 phase III trials, followed by FACT-Hep which has been used in 14 publications which include 5 phase I/II trials and 2 phase III trials. More studies need to incorporate these tools as they have been extensively used making it easier to compare QoL outcomes between similar interventions, and the broad range of QoL elements studied make them suitable for studies where therapies are toxic and survival is poor.

In addition to being validated as a primary outcome measure, the same tools (EORTC QLQ-C30 and FACT-Hep) have also been most commonly used as secondary endpoint assessment tools to measure the impact of different interventions.

Liver specific QoL is an important variable especially when studying liver-directed therapy outcomes. Most of the studies that met our inclusion criteria, used generic HRQoL indices (33/45 studies-both trial and case series), however, liver-specific indices were not used that frequently (19/45 studies). More studies in the future need to incorporate liver-specific indices as endpoints in HCC patients.

Analyzing the trend over the past 13 years, there has been no bias towards a particular HRQoL tool to assess the impact of a particular therapeutic intervention. Although surgical or liver-directed interventions are most likely to have a negative short-term impact on QoL with a higher potential for long-term favorable outcomes, and systemic therapies are offered to individuals who are more symptomatic, have a shorter survival, the tools used have been the same. Although the populations getting potentially curative *vs.* palliative therapies vary in their expectations and their outlook towards their cancer, having the same tool provides a uniformity of QoL assessment. HRQoL indicators were chosen as an endpoint for over 50% of studies evaluating liver-directed therapies (23 out of 45 publications). This may be reflection of the time period included in the study inclusion 2001-2013. As more than 80% of patients have multifocal/advanced disease and no therapy had been shown to improve survival in this setting until 2007, hence rationalizing selection of liver-

directed therapies that favorably impacted QoL was a focus. Sorafenib is the only systemic therapy that showed improved survival and received FDA approval for treatment of advanced hepatocellular cancer in Nov 2007, although the trial did not meet its primary QoL endpoint. Survival even with sorafenib remains under one year and has led to a surge of new systemic therapy trials that began following the approval of sorafenib. As these studies get completed and published, future reviews of QoL endpoint trials maybe biased towards systemic therapy or combination therapy trials.

Very few publications (10/45, that is, 22%) addressed HRQoL indicators as endpoints for post-surgical interventions maybe a reflection of the lower frequency of patients being surgical candidates and highlight the need for greater awareness of the value of these tools in the surgical community and closer collaborations between surgical and other supportive care providers with greater familiarity with such endpoints. Of the 45 publications utilizing HRQoL endpoints, only 24 were clinical trials. More trials (17/24, 71%) using systemic therapies (medications) incorporated HRQoL as endpoints, compared to trials of liver-directed therapies (7/24, 29%). This may represent a publication bias, i.e., novel therapy evaluations are more readily publishable, while trials of routinely used interventions are published only when compared to another intervention (chemoembolization versus radioembolization) and are able to be conducted only in high volume centers as there is a lot of variability in technique and patient selection between centers. Unfortunately, funding for QoL studies as a primary endpoint is sparse as well.

We have provided a summary of HRQoL instruments that are available and being used in patients with HCC to guide future HCC trial design and interpretation of existing QoL data.

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Footnote

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Prediction of postoperative liver failure in patients diagnosed with hepatocellular carcinoma using ^{99m}Tc -GSA SPECT/CT

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Although relatively rare in the Western countries, hepatocellular carcinoma (HCC) is the third cause of death due to cancer in the world and its incidence increases each year (1,2). Complete excision remains the treatment of choice, whether by liver resection or liver transplantation. In patients considered for liver resection, assessment of the future remnant liver (FRL) is of utmost importance in order to prevent postoperative liver failure. Computed tomography (CT) volumetry is the most widely used method in the preoperative assessment of the FRL, but, although it is the gold standard, does not provide any information on the function of FRL and its role in the preoperative work-up for liver surgery is therefore questionable (3). The same accounts for the laboratory liver function tests as they merely offer an approximation of the liver's metabolic processes as an entire organ (i.e., uptake, synthesis, biotransformation and excretion) (4). Furthermore, it has been shown that there is only moderate correlation between FRL volume and FRL function in patients with hepatic comorbidity (3). Consequently, interest in imaging based quantitative liver function tests has increased. There are two main challenges in the preoperative assessment of function of the FRL: selective segmental measurement of FRL function independently of the quality of liver parenchyma and validation of a threshold value for safe resection.

^{99m}Tc -labeled diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) scintigraphy is a frequently reported method of preoperative assessment of liver function, unfortunately until now, limited to the Asian market. The asialoglycoprotein receptor is specific for asialoglycoproteins and its decrease is associated with chronic liver disease (5). ^{99m}Tc -labeled GSA is used for

clinical imaging of the receptor (6,7). ^{99m}Tc -GSA allows not only for measurement of total liver function but also enables segmental assessment of liver function (8-10), rendering ^{99m}Tc -GSA along with the hepatic ^{99m}Tc -mebrofenin uptake-rate scintigraphy used in the Western world, one of the most advanced techniques in the assessment of FRL to date (3,11,12). Many models using ^{99m}Tc -GSA have been proposed since the introduction of the test, all of them showing promising results. Unfortunately, most of the models have proven rather complex. The uptake index (UI) of ^{99m}Tc -GSA, i.e., a kinetic model of ^{99m}Tc -GSA to show the speed of asialoglycoprotein receptor-mediated endocytosis, is one of the last introduced parameters awaiting validation in clinical practice (13), which was recently published (14).

In their paper, Mao *et al.* evaluate the validity of the Zhong System for the assessment of hepatic function in patients before and after hepatectomy (14). This imaging system combines the assessment of liver function with ^{99m}Tc -GSA and the UI with 3-dimensional CT imaging, providing 3D functional imaging of the liver. Moreover, in this prospective study among patients with HCC Child-Pugh A/B and healthy volunteers, the authors establish the functional liver volume index (FLVI). FLVI is the ratio between the UI value measured in a patient and the median UI measured in the healthy population.

The authors describe a significant difference in UI values between patients with Child-Pugh A (score 5 and 6) and patients with Child-Pugh B (score 7, 8 and 9), suggesting that UI could be used as a universal parameter for accurate differentiation between the different grades of chronic liver disease. Furthermore, preoperative UI correlated well with preoperative clinical and biochemical parameters, as well as the ICG test, a widely used clearance test of plasma

indocyanine green; i.e., patients with and without ascites, elevated bilirubin levels and/or prolonged ICG15 can be distinguished based on the UI value. However, one should mind the small sample size this analysis was based on (n=69).

Another key finding of Mao and colleagues was the excellent correlation of the preoperatively predicted UI value with the actual postoperative UI value in 33 patients who underwent preoperative and postoperative ^{99m}Tc -GSA measurements. The authors also described good correlation of the predicted UI values with the occurrence of postoperative ascites and elevated bilirubin levels.

In the same study, the authors propose a critical value that is able to accurately indicate patients at risk for developing liver insufficiency. However, the authors had to overcome the main limitation in their study of examining liver function in this particular, small patient population. The UI values measured in patients with Child-Pugh C liver disease ideally, should have been used to discriminate the critical value. However, as the authors describe in their article, it was difficult to recruit patients of this category. Consequently, Moa and colleagues considered the probability of having liver disease beyond Child-Pugh A or B as surrogate for suffering from liver failure. A critical UI of 0.73 and FLVI of 26% were defined as the lower threshold of the test indicating patients at high risk for liver failure.

Due to its lethal character, postoperative liver failure is one of the most feared complications after liver resection, especially in patients with cirrhosis. In order to validate the ability of ^{99m}Tc -GSA to predict postoperative liver failure, the authors performed a ROC analysis. The objective of this analysis was to define a cut-off value at which patients would be at risk for postoperative liver failure. Preoperative measurements of the patients who underwent surgery but no postoperative ^{99m}Tc -GSA (n=36) and postoperative measurements of the patients who did (n=33), were used for the analysis. For this purpose, the authors decided to define patients with Child-Pugh score 9 as patients at high risk for developing postoperative liver failure, because none of the included patients was diagnosed with Child-Pugh C (score ≥ 10) and because of ethical concerns regarding surgery in patients in whom postoperative Child-Pugh C was expected. Using ROC analysis the authors found a cut-off value for UI of 0.9 (FLVI =32%) with a corresponding sensitivity of 100% and specificity of 92%.

However, there are several concerns regarding the methodological design of the prediction model used in this study. Firstly, major liver surgery (≥ 3 segments)

was performed in only 7 out of the 33 patients who had undergone both preoperative and postoperative ^{99m}Tc -GSA. Among the remaining patients, more than one segment was resected in 25 patients while 1 patient had undergone minor liver surgery only. Secondly, the validity of a model designed to predict liver failure should be evaluated by means of liver failure as the primary endpoint of the study. In this context, other primary hepatic or metastatic tumor types and patients with and without preoperative neoadjuvant chemotherapy should be taken into account. Ideally, consecutive patients should undergo preoperative ^{99m}Tc -GSA while the decision to resect or not, must be based on the regular gold standard applied at the same centre. Analysis of patients who develop postoperative liver failure or not will reveal the true cut-off values of the functional test.

The abovementioned study design was applied by de Graaf and colleagues in their paper on the estimation of the cut-off value for hepatic ^{99m}Tc -mebrofenin uptake-rate scintigraphy [^{99m}Tc -mebrofenin hepatobiliary scintigraphy (HBS)] (3). The authors describe a heterogeneous cohort of 55 patients with compromised and non-compromised liver parenchyma and diagnosed with different hepatic lesions, all of whom underwent resection of at least 3 segments. Preoperative HBS was performed in all patients, although the results were not taken into account during the preoperative work-up. Nine of the 55 patients developed postoperative liver failure. From the analysis, a universal cut-off value was calculated whereupon the test was implemented in standard patient care for all patients scheduled to undergo major liver surgery, independently of the quality of the liver parenchyma and of the suspected diagnosis.

In conclusion, quantitative liver function tests as opposed to CT volumetric studies, provide the only means to accurately determine the functional capacity of the FRL. UI and FLVI threshold values measured using ^{99m}Tc -GSA, as the Zhong System, are interesting and promising but clinical application awaits further evaluation in controlled studies.

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Footnote

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Post-hepatectomy liver failure

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Abstract: Hepatectomies are among some of the most complex operative interventions performed. Mortality rates after major hepatectomy are as high as 30%, with post-hepatic liver failure (PHLF) representing the major source of morbidity and mortality. We present a review of PHLF, including the current definition, predictive factors, pre-operative risk assessment, techniques to prevent PHLF, identification and management. Despite great improvements in morbidity and mortality, liver surgery continues to demand excellent clinical judgement in selecting patients for surgery. Appropriate choice of pre-operative techniques to improve the functional liver remnant (FLR), fastidious surgical technique, and excellent post-operative management are essential to optimize patient outcomes.

Keywords: Post-hepatectomy liver failure (PHLF); prevention of liver failure; predictive factors for liver failure

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Introduction

Hepatic resections are among some of the most complex operative interventions performed, and are fraught with risk and the potential for complications. Mortality rates after major hepatic resection have been reported to be as high as 30% (1,2) with post-hepatectomy liver failure (PHLF) representing the major source of morbidity and mortality after liver resection. Despite great improvements in outcomes after major liver resection due to refinements in operative technique and advances in critical care, PHLF remains one of the most serious complications of major liver resection, and occurs in up to 10% of cases (3,4). Several studies report a lower rate of PHLF in East Asian countries (1-2%), but when present, PHLF represents a significant source of morbidity and mortality (5).

Definition

The definition of PHLF has varied widely among groups, making comparison of rates between studies challenging. Numerous definitions of PHLF exist in the literature, with variations by country and between hospitals within the same country. Many definitions include complicated formulas or

obscure laboratory tests, such as hepaplastin or hyaluronic acid levels, limiting their utility (6). The Model for End-Stage Liver Disease (MELD) score is one such definition that is widely used. The MELD score is calculated using serum creatinine, INR, and bilirubin, but requires a complex mathematical formula computation (7). The '50-50 criterion' (PT <50% and bilirubin >50 µmL/L) have also been proposed as a simple definition for PHLF (8). However, this definition does not account for any clinical parameters, and relies only on two laboratory values. In 2011, the International Study Group of Liver Surgery (ISGLS) proposed a standardized definition and severity of grading of PHLF. After evaluating more than 50 studies on PHLF after hepatic resection, the consensus conference committee defined PHLF as "a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5" (2). While other definitions of PHLF utilizing biochemical or clinical parameters are used by some centers, the ease with which the ISGLS definition can be calculated and used for comparison renders it the definition that ought to be standardized and used.

While PHLF is the most feared complication, the

Table 1 ISGLS definition and grading of PHLF (2)

Grade	Clinical description	Treatment	Diagnosis	Clinical symptoms	Location for care
A	Deterioration in liver function	None	<ul style="list-style-type: none"> • UOP >0.5 mL/kg/h • BUN <150 mg/dL • >90% O₂ saturation • INR <1.5 	None	Surgical ward
B	Deviation from expected post-operative course without requirement for invasive procedures	Non-invasive: fresh frozen plasma; albumin; diuretics; non-invasive ventilatory support; abdominal ultrasound; CT scan	<ul style="list-style-type: none"> • UOP ≤0.5 mL/kg/h • BUN <150 mg/dL • <90% O₂ saturation despite oxygen supplementation • INR ≥1.5, <2.0 	<ul style="list-style-type: none"> • Ascites • Weight gain • Mild respiratory insufficiency • Confusion • Encephalopathy 	Intermediate unit or ICU
C	Multi-system failure requiring invasive treatment	Invasive: hemodialysis; intubation; extracorporeal liver support; salvage hepatectomy; vasopressors; intravenous glucose for hypoglycemia; ICP monitor	<ul style="list-style-type: none"> • UOP ≤0.5 mL/kg/h • BUN ≥150 mg/dL • ≤85% O₂ saturation despite high fraction of inspired oxygen support • INR ≥2.0 	<ul style="list-style-type: none"> • Renal failure • Hemodynamic Instability • Respiratory failure • Large-volume ascites • Encephalopathy 	ICU

ISGLS, International Study Group of Liver Surgery; PHLF, post-hepatectomy liver failure.

Table 2 Predictive factors associated with increased risk of PHLF

Patient related
Diabetes mellitus
Obesity
Chemotherapy-associated steatohepatitis
Hepatitis B, C
Malnutrition
Renal insufficiency
Hyperbilirubinemia
Thrombocytopenia
Lung disease
Cirrhosis
Age >65 years
Surgery related
EBL >1,200 mL
Intra-operative transfusions
Need for vascular resection
>50% liver volume resected
Major hepatectomy including right lobectomy
Skeletonization of hepatoduodenal ligament
<25% of liver volume remaining
Post-operative management
Post-operative hemorrhage
Intra-abdominal infection
PHLF, post-hepatectomy liver failure.

severity of its clinical manifestation ranges from temporary hepatic insufficiency to fulminant hepatic failure. The ISGLS group advocated a simple grading system of PHLF, in which laboratory values, clinical symptoms, and need for increasingly invasive treatments define severity of PHLF. The mildest grade of PHLF, grade A, represents a minor, temporary deterioration in liver function that does not require invasive treatment or transfer to the intensive care unit. The most severe, grade C, is characterized by severe liver failure with multisystem failure and the requirement for management of multi-system failure in the intensive care unit (2) (*Table 1*). The peri-operative mortality of patients with grades A, B, and C PHLF as determined by this grading schema is 0%, 12% and 54%, respectively (9).

Predictive factors

Patient factors

Various patient-related factors are associated with increased risk of PHLF (*Table 2*). Operative mortality in patients with diabetes undergoing curative-intent hepatic resection for treatment of colorectal metastases has been shown to be higher than comparable patients without diabetes mellitus (6). In that series, operative mortality was 8% in diabetics compared to 2% in non-diabetics ($P < 0.02$). Furthermore, 80% of peri-operative deaths in diabetic patients were



Figure 1 CT scan image of steatohepatitis, with liver attenuation lower than that of the spleen.

secondary to PHLF. Excess mortality seen in diabetic patients undergoing major hepatic resection is likely multifactorial, with alterations in liver metabolism, decreased immune function, and hepatic steatosis contributing to post-operative liver dysfunction (10).

Chemotherapy-associated steatohepatitis (CASH) is an increasing challenge in the era of novel chemotherapeutic and biologic agents. Many commonly-used chemotherapy agents cause damage to hepatocytes, including 5-fluorouracil, irinotecan, oxaliplatin, cituximab, and bevacizumab (11-14). Additionally, pre-operative malnutrition or renal insufficiency, hyperbilirubinemia, thrombocytopenia, presence of co-morbidities (lung disease), and advanced age are associated with increased risk of PHLF (15-18).

Surgical factors

In addition to patient-specific factors, the performance of the surgical procedure itself influences risk of PHLF. Factors associated with increased risk are shown in *Table 2* and include operative estimated blood loss >1,200 mL (19,20), intra-operative transfusion requirement, need for vena caval or other vascular resection (21), operative time >240 minutes (13), resection of >50% of liver volume, major hepatectomy including right lobe (22), and skeletonization of the hepatoduodenal ligament in cases of biliary malignancy (23). In patients for whom <25% of the pre-operative liver volume is left post-resection, the risk of PHLF is 3 times that of patients with $\geq 25\%$ of liver volume remaining (24).

Post-operative factors

Issues of post-operative management influence the risk of

PHLF, with post-operative hemorrhage (15) and occurrence of intra-abdominal infection (16) conferring increased risk (*Table 2*).

Pre-operative risk assessment

Given the high mortality rate associated with PHLF, there has been great interest in techniques to pre-operatively identify patients at high risk for hepatic dysfunction or failure. CT-based volumetric analysis is an effective tool that utilizes helical CT scans to assess the volume of resection by semi-automated contouring of the liver. A study by Shoup *et al.* utilized this technique to show that the percentage of remaining liver was closely correlated with increasing prothrombin time (>18 seconds) and bilirubin level (>3 mg/dL) (24). In their analysis, 90% of patients undergoing trisegmentectomy with $\leq 25\%$ of liver remaining developed hepatic dysfunction, compared to none of the patients who had >25% of liver remaining after the same operation (24). Furthermore, the percentage of remaining liver, as determined by volumetric analysis, was more specific in predicting PHLF than the anatomic extent of resection (24).

Careful evaluation of pre-operative CT scan imaging should focus on liver attenuation. Liver attenuation that is lower than that observed in the spleen indicates fatty infiltration indicative of steatohepatitis (11,24,25) (*Figure 1*). Similarly, splenomegaly, varices, ascites, or consumptive thrombocytopenia should prompt the clinician to suspect underlying cirrhosis (11) (*Figure 2A,B*).

Although ultrasound and 3-dimensional ultrasound has been advocated by some as a means by which to assess the pre-operative volume of the liver, CT or MRI provide more objective data that is less subject to operator-error. Both CT and MRI show excellent accuracy and precise quantification of hepatic volume (26-28), and are particularly useful in estimating the future liver remnant (FLR) (29).

Numerous methods have been developed for calculating liver volume, using either CT or MRI images. The first technique involved manual tracing of the outline of the liver (30), but has been criticized its time-intensity. Most recently, automatic or semi-automatic techniques have been developed that utilize mathematical formulas to measure liver volumes obtained from CT scan images, utilizing commercially-available software programming. These software-based programs have been shown to correlate well with manual volume estimation, but are performed in a fraction of the time (31).

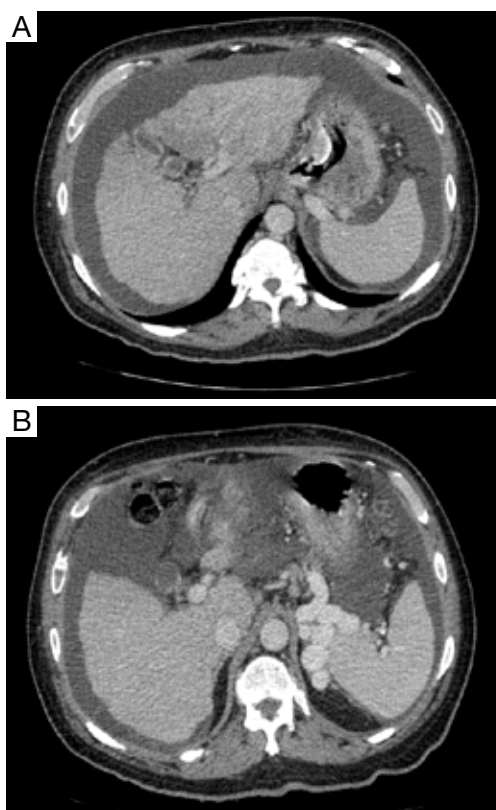


Figure 2 (A) CT scan demonstrating evidence of cirrhosis, with ascites, small liver, and splenomegaly; (B) CT scan demonstrating evidence of cirrhosis, with ascites, small liver, splenic varices, and splenomegaly.

Although pre-operative estimation of functional liver volume after resection remains the most advanced method for estimating hepatic functional reserve, newer techniques, such as indocyanine green (ICG) clearance and ICG retention rate (ICG R15) have been reported. Under normal conditions, nearly all ICG administered is cleared by the liver. Because the ICG reflects intra-hepatic blood flow, it has long been used to assess liver functional reserve in patients with cirrhosis (32). Only recently, however, have investigations begun into the application of ICG and ICG R15 to estimating functional hepatic reserve after resection of normal livers in the setting of malignancy. In this method, ICG elimination is measured by pulse spectrophotometry (32), and the indocyanine green plasma disappearance rate (ICG PDR) is determined. The study by de Liguori Carino and colleagues reported that when the pre-operative ICG PDR was less than 17.6%/min and the pre-operative serum bilirubin was $>17 \mu\text{mol/L}$, the positive

predictive value for post-operative liver dysfunction was 75%, and the negative predictive value was 90% (32). While additional study is needed, this method appears to be a non-invasive tool for prediction of PHLF.

There is increasing interest in the use of $^{99\text{m}}\text{Tc}$ -diethylenetriamine-pentaacetic acid-galactosyl human serum albumin (GSA) scintigraphy for the pre-operative evaluation of cirrhotic patients. In this technique, the molecule is taken up by the liver, reflecting the volume of functional liver (33). Uptake corresponds to bilirubin level, INR, and ICG clearance (33). In 9-20% of patients, the severity of liver disease is underestimated by ICG clearance testing, and better represented by GSA scintigraphy. This may be due to the fact that GSA scintigraphy is unaffected by hyperbilirubinemia (33). Use of GSA scintigraphy pre-operatively allows for highly accurate estimation of FLR (33).

Beyond imaging, a number of laboratory parameters have been shown to correlate with risk of PHLF, including prothrombin activity $<70\%$ and hyaluronic acid level $\geq 200 \text{ ng/mL}$. When elevated pre-operatively, these values portend greater risk of PHLF (34), and can be used as indications for or against major hepatectomy (*Table 3*).

Prevention

Treatment of PHLF hinges first on its prevention. In patients identified as high-risk by preoperative evaluation of underlying patient factors, presence of cirrhosis, pre-operative laboratory values, volume of liver to be resected, or estimated functional liver volume after resection, consideration should be given to techniques to minimize the risk of PHLF. One such technique is portal vein embolization (PVE), which manipulates portal blood flow, by embolizing portal branches in the liver to be resected, directing blood flow to the intended remnant liver, and thereby inducing hypertrophy of the remnant liver before major hepatectomy (35). By increasing the volume of the intended remnant liver, the risk for PHLF is decreased, even after extended liver resection. Furthermore, pre-operative PVE minimizes intra-operative hepatocyte injury that would otherwise be caused by the abrupt increase in portal venous pressure at the time of resection (35). Current guidelines recommend PVE for patients with underlying cirrhosis and an anticipated FLR of $\leq 40\%$, or patients with normal liver function and intended FLR of $<20\%$ (35). This procedure can be performed with minimal morbidity and mortality, and allows for improved safety of extended hepatectomies (36,37). Even when concurrent

Table 3 Determinants of low vs. high risk for PHLF

Risk category	Imaging	Laboratory data	Patient factors	Number of safe segments for resection
Low	<ul style="list-style-type: none"> • Predicted FLR >25% • Normal splenic size, no vascular collaterals • Indocyanine green plasma disappearance rate $\geq 17.6\%/min$ 	<ul style="list-style-type: none"> • Prothrombin activity $\geq 70\%$ • Hyaluronic acid <200 ng/mL • Platelets >300,000/μL • Normal serum bilirubin level 	<ul style="list-style-type: none"> • No history of cirrhosis • No previous hepato-toxic chemotherapy 	Up to 6 (80% of functional liver volume)
High	<ul style="list-style-type: none"> • Predicted FLR $\leq 25\%$ • Splenomegaly, presence of vascular collaterals • Steatohepatitis • Indocyanine green plasma disappearance rate <17.6%/min 	<ul style="list-style-type: none"> • Prothrombin activity <70% • Hyaluronic acid ≥ 200 ng/mL • Platelets <100,000/μL • Hyperbilirubinemia 	<ul style="list-style-type: none"> • History of cirrhosis • Previous administration of hepato-toxic chemotherapy 	No more than 3 (60% of functional liver volume)

PHLF, post-hepatectomy liver failure.

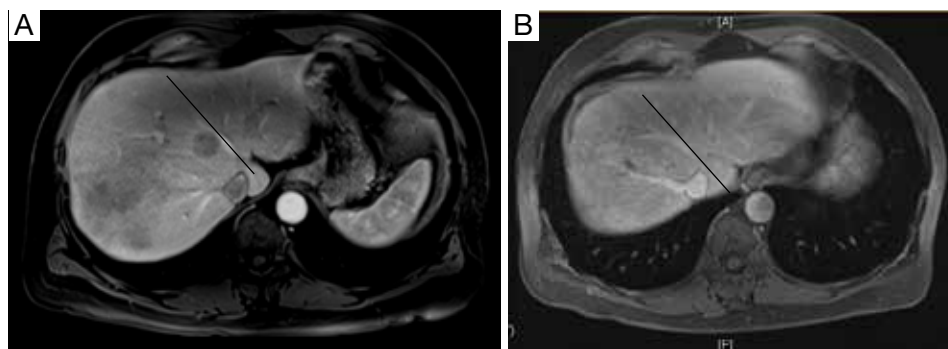


Figure 3 (A) Pre-portal vein embolization of right lobe of liver to induce hypertrophy of left lobe of liver; (B) six weeks post-portal vein embolization of right lobe of liver to induce hypertrophy of left lobe of liver. Line marks middle hepatic vein, dividing right and left hemilivers.

neoadjuvant chemotherapy is administered, sufficient hepatic hypertrophy occurs after PVE to allow for major liver resection (38). CT volumetry should be performed 3–4 weeks after PVE to assess the degree of hypertrophy (35). A degree of hypertrophy >5% is associated with improved patient outcomes (39) (Figure 3A,B).

Access to the portal system for PVE can be performed via transhepatic contralateral or transhepatic ipsilateral approach. The transhepatic contralateral approach accesses the portal system through the intended FLR, and is technically easier than an ipsilateral approach, but risks injury to the FLR. Additionally, access to segment 4 for embolization is technically difficult when performed from a contralateral approach (35). While the transhepatic

ipsilateral approach spares the FLR from potential injury, acute angulations of the portal branches may render this approach too technically difficult to be feasible (35). If an extended right hepatectomy is planned, segment 4 could be embolized first to minimize risk of dislodgement of embolic substances to the left liver during manipulation of the catheter (35).

Because PVE is not always technically feasible and some patients may experience disease progression during the waiting time between PVE and surgery, the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure has been advocated by some, particularly for patients requiring trisectionectomy for bilateral liver metastases, or intrahepatic cholangiocarcinoma. In this

Table 4 Techniques for preventing and minimizing the risk of PHLF

Period	Techniques
Pre-operative	Weight loss in obese patients Nutritional supplementation Aggressive management of co-morbid conditions Portal vein embolization to enlarge FLR
Intra-operative	Avoidance of skeletonization of hepatoduodenal ligament unless required for R0 resection Minimize EBL (resection under low CVP conditions) Avoidance of blood transfusions if able Close attention to hemostasis to avoid post-operative hemorrhage
Post-operative	Early recognition and treatment of post-op hemorrhage Early recognition and treatment of biliary obstruction or leak Early recognition and treatment of intra-abdominal infection

PHLF, post-hepatectomy liver failure; FLR, functional liver remnant.

procedure, blood supply to segments 4-8 is diminished by right portal vein branch ligation, combined with parenchymal transaction along the falciform ligament (40). This technique has shown a 74% increase in the volume of the FLR, but with high postoperative morbidity (68%) and mortality (12%) (41). Although there have been promising results in small series, with rapid liver hypertrophy and enlargement of the FLR, this technique requires additional study to refine its indications and place in the repertoire of techniques for minimizing the risk of PHLF (42).

Beyond pre-operative techniques to enlarge the FLR, fastidious intra-operative technique and excellent post-operative management contribute greatly to minimizing the risk of PHLF (*Table 4*). In cases of very heavy disease burden in the liver, when resection of all lesions would result in an FLR too small to avoid PHLF, a combination of resection and ablation may be used to minimize the amount of liver resected. Additionally, wedge resections with minimal tumor-free margins may be used to treat multi-focal disease, leaving sufficient liver intact to avoid PHLF.

Identification and management

When present, PHLF is manifest by progressive multi-system organ failure, including renal insufficiency, encephalopathy, need for ventilator support, and need for pressor support. As hepatic function worsens, patients develop persistent hyperbilirubinemia and coagulopathy (43). The development of coagulopathy is a particularly poor prognostic indicator (20). Daily measurement of serum C-reactive protein (CRP) may help with the early

identification of patients who are developing hepatic insufficiency after hepatectomy. A study by Rahman and colleagues showed that patients who developed PHLF had a lower CRP level on post-operative day 1 than patients who did not develop PHLF. A serum CRP <32 g/dL was an independent predictor of PHLF in multivariate regression analysis (44). Other tools for predicting PHLF include the '50-50 criteria', MELD system, and Acute Physiology and Chronic Health Evaluation (APACHE) III. While the MELD system has a sensitivity of 55% for morbidity and 71% for mortality, the ISGLS criteria for PHLF perform particularly well in assessing the risk of increased mortality after hepatectomy (45). The 50-50 criterion allows for early detection of PHLF, but is not a marker for increased morbidity after liver resection (45). The APACHE III score predicts mortality after hepatectomy, but has only been validated in patients with cholangiocellular carcinoma (46).

The most effective treatment for PHLF is liver transplantation, but this is typically reserved for patients who have failed all other supportive therapies (47). Initial treatment of PHLF includes supportive care of failing systems, including intubation, pressors, or dialysis. Treatment includes infusion of albumin, fibrinogen, fresh frozen plasma, blood transfusion, and initiation of nutritional supplementation (20).

Intra-hepatic cholestasis is a type of PHLF that warrants particular mention. It is characterized by a continued increase in serum bilirubin, in the absence of biliary obstruction, with preservation of the synthetic function of the liver (48). Biopsy confirming this entity should be

obtained at 2 weeks post-operatively, if the diagnosis remains uncertain. Although the course is protracted, PHLF nearly always occurs, with mortality rates approaching 90% despite best supportive care.

Conclusions

PHLF remains a severe complication of hepatic resection, occurring in approximately 8% of patients undergoing major hepatectomy (49). It ranges from mild hepatic insufficiency, characterized by transient hyperbilirubinemia that does not alter the expected post-operative course, to liver failure resulting in multi-system failure requiring invasive treatment in an intensive care unit. Multiple factors increase the risk of PHLF, including obesity, diabetes, neoadjuvant treatment with chemotherapy, underlying cirrhosis, increased age, male gender, need for extended liver resection, and long operation with high intra-operative EBL. Risk of PHLF can be minimized by accurate pre-operative assessment of the FLR to be left after resection, and the induction of hypertrophy of the liver remnant via PVE if the expected FLR is <20% in a person with a normal liver, <30% in a patient with steatosis, or <40% in a cirrhotic patient (50). Early recognition and initiation of supportive care is crucial to improving patient survival in the setting of PHLF. Despite great improvements in morbidity and mortality, liver surgery continues to demand excellent clinical judgement in selecting patients for surgery. Appropriate choice of pre-operative techniques to improve the functional liver remnant (FLR), fastidious surgical technique, and excellent post-operative management are essential to optimize patient outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Importance of tumor/stroma interactions in prognosis of hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the third largest cause of cancer deaths worldwide. It seems to be needed to find new ways to address the mechanisms involved in the progression of HCC, which can provide a prognostic evaluation and new therapeutic targets. Several studies have established that crosstalk between tumor cells and the microenvironment plays a key role in tumor progression and metastasis. In this context, the work of Zhu *et al.* contributes to assess interactions between tumor and microenvironment associated-macrophages promoting tumor progression and metastasis. Indeed, they concluded that the interplay of osteopontin (OPN) and peritumoral macrophages (PTMs) represents a new insight into tumor progression and therapeutic targets for HCC. Historically, tumor-infiltrating leukocytes have been considered to be manifestations of an intrinsic defensive mechanism against developing tumors, however, now, it is known that leukocyte infiltration can promote tumor phenotypes, such as angiogenesis, growth, and invasion. Characterization of functional heterogeneity of stromal cell components, and specifically the analysis of stromal fibroblasts can provide a new focus on mechanisms involved in the progression of HCC. All of this opens the possibility to provide prognostic information for HCC based on biological parameters derived from peritumoral status from tumors.

Keywords: Hepatocellular carcinoma (HCC); tumor microenvironment; macrophages; fibroblasts

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Hepatocellular carcinoma (HCC) is the third largest cause of cancer deaths worldwide. The 5-year risk of HCC recurrence after resection is as high as 70% because the underlying chronic liver disease continues to put the patient at risk for the development of a new one (1). Even in those patients with early-stage disease, tumor relapse after treatment remains the major obstacle for outcomes improvement. Recent advances in whole-genome technologies have revealed an overwhelming amount of molecular data on human carcinomas, including HCC. However, spite of all of these data, HCC prognostic evaluation is based on clinicopathological parameters such as tumor stage. This reflects the complexity and heterogeneity of HCC biology, and it leads us to consider the need to find new ways to address the mechanisms involved in the progression of HCC, which can provide a

prognostic evaluation and new therapeutic targets.

There are several evidences indicating that progression of solid tumors towards a malignant phenotype does not depend exclusively on cell-autonomous properties of cancer cells, but is also deeply influenced by tumor stroma reactivity (2). Crosstalk between tumor cells and the microenvironment plays a key role in tumor progression and metastasis. The two well-studied and populous cellular component of the tumor stroma are mononuclear inflammatory cells (MICs) and cancer associated fibroblasts (CAFs). On the basis of this concept, recently Zhu *et al.* (3) have attempted to elucidate the prognostic significance of combining tumor-secreted osteopontin (OPN) with microenvironment-associated peritumoral macrophages (PTMs) in HCC, especially for those with early-stage disease. Using tissue microarray-based

immunohistochemistry, they have investigated OPN and PTMs expression in two independent cohorts consisting of 374 patients with HCC who underwent radical resection. The prognostic value of these two factors, alone or in combination, was investigated in these patients. They found that OPN combined with PTMs was a significant and independent prognostic factor for both overall survival and time to recurrence from the learning cohort (n=96). Their combined value for prognosis was validated in early-stage HCCs using another independent cohort. This combination remained significant in HCCs with low α -fetoprotein levels in both cohorts, and was predictive for early recurrence and death risk (<2 years) compared with a single marker. Therefore, Zhu *et al.* (3) have concluded that tumor OPN combined with PTMs is a promising predictor of tumor recurrence and survival in patients with HCC, especially for those with early-stage disease, and that the interplay of OPN and PTMs represents a new insight into tumor progression and therapeutic targets for HCC.

These results support previous studies reporting a key role of the stroma in tumor progression. Tumors are composed not only of cancer cells but also of other cell types constituting the stroma. These stromal cells include CAFs, endothelial cells, pericytes, and a variable representation of leukocytes. Leukocytes can represent up to 50% of the total tumor mass in many human tumors. Initially, tumor cells and tumor microenvironment, respond to tumor hypoxia and necrosis secondary to excessive tumor cell proliferation, by releasing a number of growth factors and cytokines that are chemoattractive for monocytes and macrophages [colony stimulating factor (CSF)-1, granulocyte-monocyte (GM)-CSF, transforming growth factor (TGF)- β and chemokines] (4). In this context, the work of Zhu *et al.* contributes to assess interactions between tumor and microenvironment associated-macrophages facilitating tumor progression and metastasis. This is due to that OPN has alternatively been suggested as a possible stimulator of immune function, a chemoattractant for macrophages and endothelial cells, and a tumor defense against cytotoxic macrophages (5). The authors hypothesized that high OPN expression in tumor tissues could recruit more macrophages in the peritumoral liver tissue and facilitates HCC growth and metastasis, resulting in a dismal survival rate. In addition, it is relevant to note that the peritumoral invasive front is the area where some of the most important interactions between cancer cells and tumor supporting stroma take place.

Historically, tumor-infiltrating leukocytes have been considered to be manifestations of an intrinsic defensive

mechanism against developing tumors. The presence of leukocytes in tumors was subsequently interpreted as an aborted attempt of the immune system to reject the tumor. However, increasing evidence indicates that leukocytes infiltration can promote tumor phenotypes, such as angiogenesis, growth, and invasion. This may be due inflammatory cells probably influence cancer promotion by secreting cytokines, growth factors, chemokines and proteases, which stimulate proliferation and invasiveness of cancer cells (6). Indeed, accumulating clinical data for solid tumors show a correlation between high-density leukocytic infiltration into tumors and poor outcome of patients with several malignances of very different origins (such as of breast, bladder, rectum, endometrium, melanomas, gliomas or leiomyosarcomas). Nevertheless, the presence of inflammatory cells can be an indicators of favorable prognosis in some tumor types, as for example the presence of macrophages in colorectal cancer, gastric or ovarian carcinomas (6). The controversy over the prognostic significance of lymphoid infiltrate in the tumor site, may be due to the fact that the criteria for evaluation of tumor infiltrates are not sufficiently standardized to produce reliable and reproducible results in different institutions. Leukocyte infiltrate includes a variable representation of leukocytes, including macrophages, neutrophils, mast cells, and T and B lymphocytes. In addition, inflammatory cells and immunomodulatory mediators present in the tumor microenvironment polarize host immune response toward specific phenotypes impacting tumor progression.

Such as mentioned Zhu *et al.* in their work, the macrophage is a pivotal member in tumor stroma, strongly correlated with poor prognosis in different types of solid tumors, including HCC (7,8). Macrophages are often the most abundant immune cells population in the tumor microenvironment. It has been reported that, once recruited to tumors, macrophages can assume two different phenotypes: M1 or M2, based on environmental stimuli and each expressing specialized functional properties (9). The M1 phenotype is associated with inflammation and microbial killing activity, whereas M2 phenotype is associated with activities which are predominant and key events in cancer, including inhibition of Th1 adaptive immunity by immunosuppressive mediators (TGF β , IL-10 or PGE2), production of growth and survival factors (EGF, IL-6 and CXCL8), secretion of angiogenic factors (VEGF, TGF α or PGE2), production of matrix metalloproteases (MMPs) which degrade extracellular matrix (ECM), and chemokines capable of recruiting more inflammatory cells

(CCL17, CCL18 or CCL22) (9).

Results obtained by Zhu *et al.* suggest other further and interesting lines of investigation in HCC. One of these may be to investigate the clinical relevance of the relative amount of macrophages (CD68⁺), T-cells (CD3⁺) and B-cells (CD20⁺). It is known that macrophages have several pro-tumor functions and their infiltration into the tumor has been associated with worse prognosis (10-12). By contrary, it has been reported that both T- and B-lymphocytes perform an important immunological response by inhibiting cancer development and progression (13,14). In this line, for example recently we found that an increased CD68 count and CD68/(CD3⁺CD20) ratio in the invasive front were directly associated with a higher probability of shortened relapse-free survival in breast cancer (15).

An important aspect in studies of the mechanisms involved in the progression of HCC, is the characterization of functional heterogeneity of stromal cell components, and specifically the analysis of stromal fibroblasts. Normal fibroblasts are the most abundant cell type in the connective tissue and are responsible for the synthesis and turnover of the ECM. However, characteristics of CAFs are distinct from that of normal fibroblasts, including a higher proliferation rate, as well as capacity to promote tumor phenotypes such as survival, proliferation, metabolism reprogramming, angiogenic shift, ECM remodeling, EMT activation, stem cell trait achievement, metabolic reprogramming toward a reverse Warburg phenotype, or inflammatory cells recruitment (16). All of characteristics of CAFs may be due to the production of a repertoire of growth factors and cytokines that influence the behavior of the epithelium, such as HGF, EGF, IGFs, IGFFBPs, b-FGF or TGFβ (2). It is also known that CAFs are capable of evoking a proinflammatory response. After activation, CAFs initiate a pro-inflammatory response including the secretion of IL-1β, IL-6, IL-8, SDF-1, and nuclear factor kappa B (NF-κB), which may induce inflammation by recruiting components of the immune system (16). Thus, CAFs may orchestrate a distorted architecture of the host tissue and a functional “corrupted” stroma which in turn helps metastatic spread. In accordance with this, it was of note our findings indicating that the expression of several metalloproteases and their inhibitors, which are implicated in invasion and metastasis, by fibroblasts or MICs was associated with a poor prognostic in HCC (17). Likewise, TLR9 expression by fibroblast-like cells was significantly associated with a shortened overall survival in patients with HCC (18). Although strong pro-inflammatory and antiviral responses after TLR stimulation may be beneficial in the short term to eradicate pathogens, a prolonged or

exaggerated activation of TLR signaling may have deleterious effects. As molecular sensors, TLRs detect pathogen-derived products and couple to different adapter proteins that trigger specific signaling pathways such as the interleukin 1 (IL1) receptor-associated kinase (IRAK) family and TANK-binding kinase 1 (TBK-1). These adapters initiate pathways leading to the activation of their respective transcription factors, NF-κB and interferon regulatory factor 3 (IRF3), which induce the release of various immune and inflammatory cytokines [such as tumor necrosis factor (TNF) and IL6] and carcinogenesis (19).

The liver is probably a good example for the link between chronic inflammation and cancer that was postulated by Rudolf Virchow more than 100 years ago (20). It is estimated that almost 80% of HCC in the western world develop as a consequence of chronic inflammation and arise in fibrotic or cirrhotic livers. Due to its anatomical links to the gut, the liver is constantly exposed, via the portal vein, to gut-derived bacterial products, viral infection, alcohol or other products, which may be cause of chronic liver damage, therefore increasing risk for HCC. Now, the paper of Zhu *et al.*, open the possibility to provide prognostic information for HCC based on biological parameters derived from inflammatory peritumoral status from tumors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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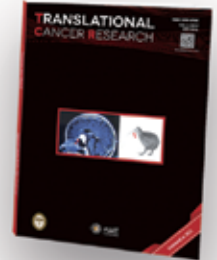


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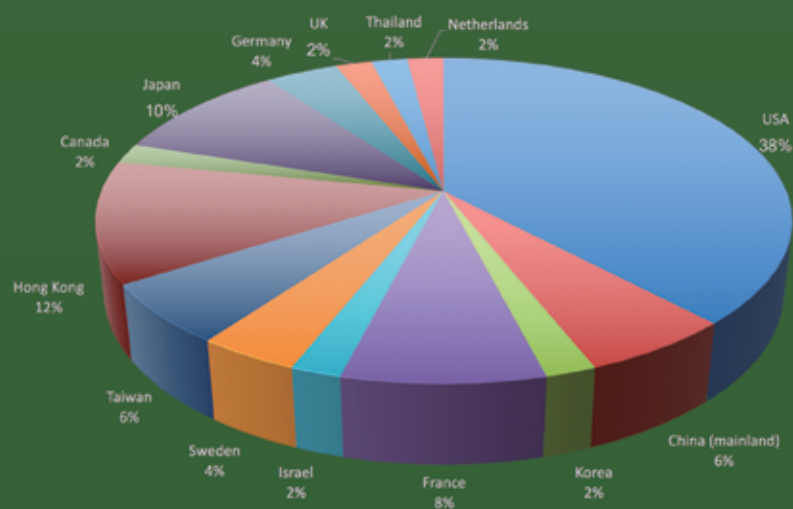
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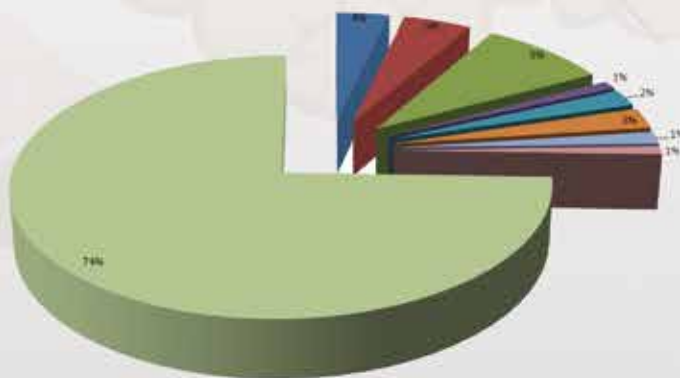
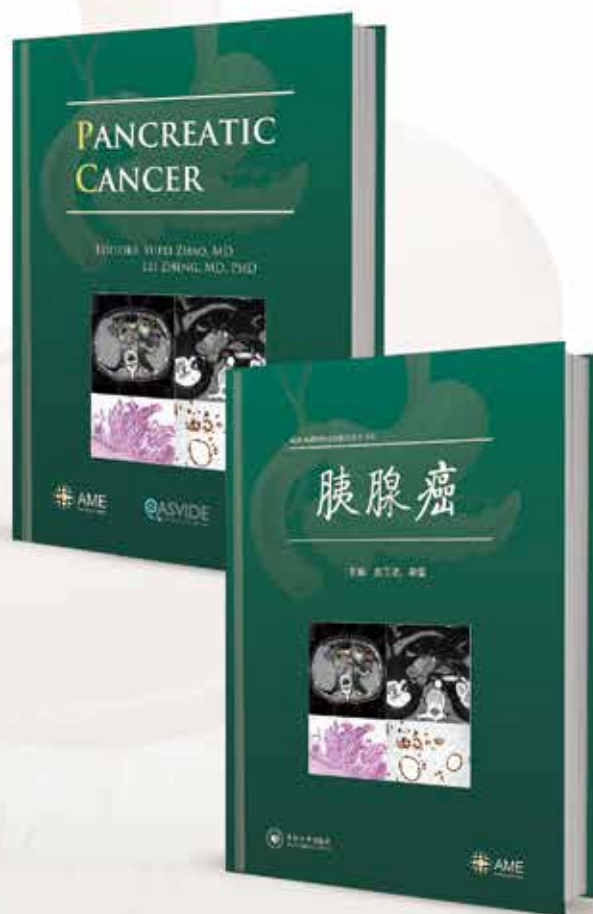
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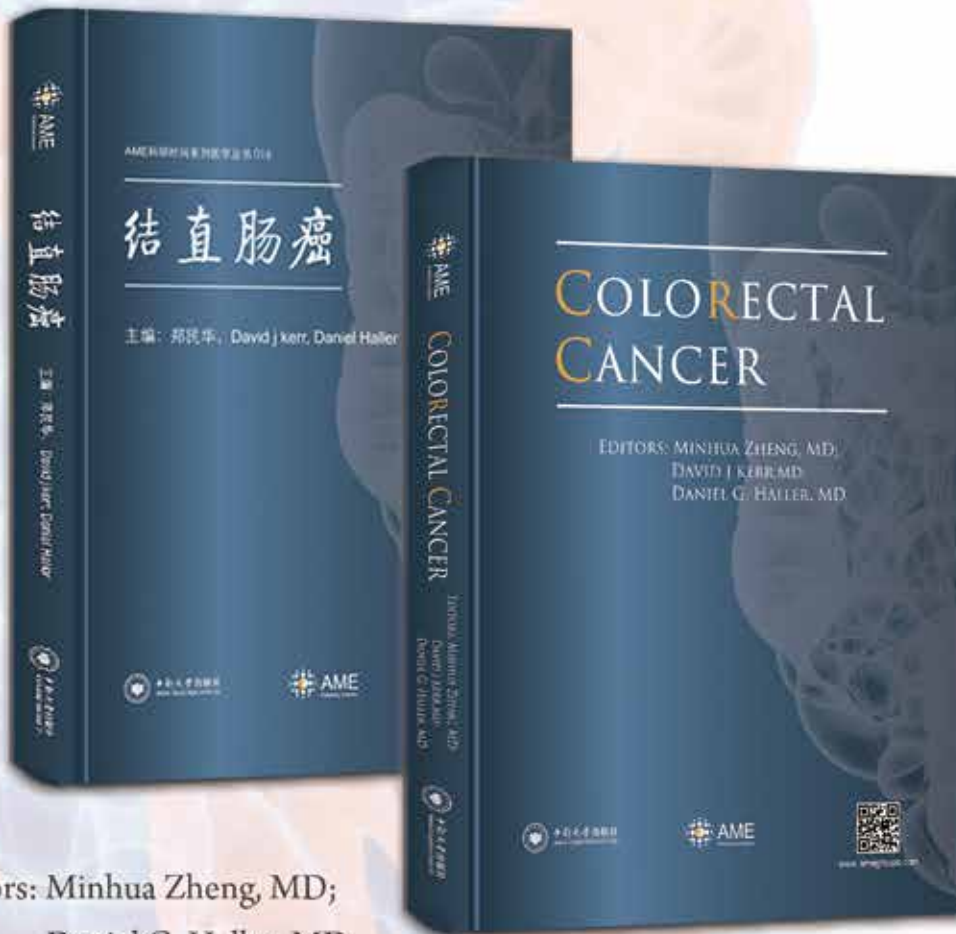
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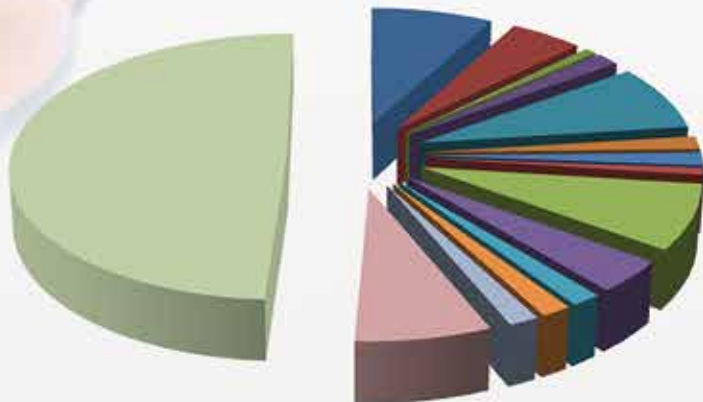


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