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Important insight into liver surgery improves patient outcomes

Liver surgeries are challenging procedures that carry risks of morbidity and mortality. Surgeons have tried their very best to keep operations as safe as possible. Meanwhile, we are trying to extend the indications for surgery as wide as possible to save more patients. The concept of treating liver disease is improving and the techniques of liver operations have been evolving.

The use of the multidisciplinary approach has streamlined the best treatment options for patients with different conditions at different stages. However, surgery remains a mainstay of treatment strategy and surgeons and clinicians are becoming experts in liver disease.

This book is an accumulation of the wisdom of many experts in the field. It provides us with a most updated view on the philosophy of disease management and, most importantly, it shares tips and tricks for more effective surgical treatment for liver diseases and cancers.

We hope that by providing a focused issue of book chapters by various experts around the globe, this book will provide practitioners with the best updates on and insights into holistic liver disease management.

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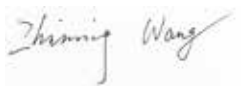
Unceasingly has the concept of hepatic surgery been renewed in terms of not only the deepened knowledge of liver anatomy, but also the development of advanced surgical instruments and the perfection of surgical techniques. Throughout history, we witnessed how hepatic surgery has marched into the no-go areas one after another, and how the operative mortality is gradually diminishing. More and more patients have been benefited by the flexible use of robotic and laparoscopic precise hepatectomy guided by minimally invasive surgery and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), the maturity of living donor liver transplantation (LDLT) techniques, and the popularization of multi-disciplinary team (MDT).

Today's hepatic surgery meets with both challenges and opportunities. This is especially true for the management of hepatocellular carcinoma (HCC), which is a complex genetic disease with high tumor heterogeneity, high recurrence and metastasis, and poor prognosis. Surgeons are constantly faced with the following questions: "Should all resectable HCCs receive hepatectomy?", "Which type of pathology has better hepatectomy outcome?", "Should tumor-associated immune factors be taken into account when evaluating the clinical stage of HCC?" and so on. It is believed that in the future, with the reveal of novel HCC-related gene sequence, the maturity of three-dimensional reconstruction of molecular images and intelligent medical module, the growing understanding of the recurrence and metastasis mechanisms, the improvement of pathological research methods to expand the coverage of HCC tissue sample, and preclinical studies in personalized medicine with gene editing, future clinical and basic research are anticipated to set a new milestone in the surgical treatment of liver cancer.

This book, *Hepatic Surgery*, is an amalgamation of reviews from distinguished hepatic experts all around the world. It is without a doubt that the book will provide practitioners with more cutting-edge information and promote the art of liver surgery.



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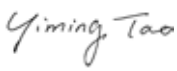

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This book on his first edition hepatic surgery assemble the most worldwide up-to-date on hepatic surgery. The liver as well as the pancreas are the two last organs approached with a minimally invasive technique. However, as well represented in this book laparoscopic and robotic liver surgery are in an exponential growth. This book is an amalgamation of chapters from experts around the world covering topics that range from the latest advances technique for all liver disease. All hot topics on liver surgery have been insert in this book. The minimally invasive surgery for liver cancer and metastatic liver cancer are still debated in every congress each years. The very hot topic of hepatocellular carcinoma even in patients with cirrhosis is an important contribution in this book for every hepatobiliary surgeons and students. We hope that this very comprehensive compilation of highly focused chapters will provide the practitioner with fresh new ideas and insights into the minimally invasive approach to liver surgery.

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From benign conditions to primary and secondary malignant disease, hepatic surgery encompasses the entire gamut of multidisciplinary care. Advances in diagnostic imaging, surgical technology and technique as well as an improved understanding of liver physiology have allowed liver surgeons to expand and refine their ability to manage complex hepatobiliary disease. This book is a comprehensive collection of chapters and articles from experts around the world and encompasses everything from preoperative preparation and imaging and surgical technique, to specific chapters on primary liver cancers, metastatic disease as well as liver trauma. The first part of the book concentrates on topics ranging from specific techniques to facilitate hepatic resection especially when faced with unique challenges, as well as several chapters dedicated to minimally invasive (laparoscopic and robotic) liver surgery. The second part is organized by disease processes with a section dedicated to primary liver cancers followed by a section on metastatic disease that includes discussions of multimodality therapy. It is our hope that this collection of highly focused chapters authored by international experts will provide medical providers with a tool to use in their daily practice as well as a stimulus for ongoing research and innovation.

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In this first edition of Hepatic Surgery, over 30 selected articles from *Hepatobiliary Surgery and Nutrition* are presented in an easily accessible format. *Hepatobiliary Surgery and Nutrition* was established to provide current and practical information to prevent, diagnose and treat hepatobiliary and associated nutritional disease. Unlike other journals that have proliferated over the last decade, HBSN has prominent editorial leadership, a true peer review process, and is not fee-for-service. As such, the high quality scholarly contributions have been recognized by growing readership, increased citations, and indexing in PubMed and Science Citation Index Expanded.

Manuscripts in *Hepatic Surgery* cover topics from genetics and biomarkers, to physiology and anatomy, to diagnostic and functional imaging, to peri-operative planning and post-resection recovery and treatment. Strengths include the balance between current science and practical application, and exposure to Eastern and Western expertise. Written by authoritative hepatobiliary surgeons from around the world, these manuscripts are a guide to the forefront of our field. This edition is sure to educate the trainee and professor alike, and provide substance for further innovation.

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The main goal of "Hepatic Surgery" is to introduce the reader to the modern era of liver surgery and to discuss its current features. The basics of liver anatomy are reviewed, along with the current surgical techniques for primary liver cancer and hepatic metastasis, as well as interventional radiology techniques for liver preparation before elective hepatic resections. This textbook provides a pleasant reading experience through a concise but comprehensive overwiew of surgical techniques thanks to an impressive list of contributors including experts from famous centers devoted to hepatic surgery around the world. The book puts together the multidisciplinary treatment for liver cancer from perspective of surgeons, oncologists, and interventional radiologists. Anyone has interests to treat with liver cancer should consider buying this book as a reference text.

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Table of Contents

Hepatic Surgical Technique

Minimally Invasive Liver Surgery

Liver Cancer

Metastatic Liver Cancer

Liver Injury

Hepatic Surgical Technique

How could we image the future in hepatic surgery

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On June 1952, 11 years before the first liver transplantation by Thomas Starzl and 40 years before the first use of a partial graft from a living donor, Jean Louis Lortat Jacob, in his publication reporting the first anatomic right hepatectomy, anticipated that "*once the problems of tolerance to tissue grafts and their rejection have been solved, this procedure might be indicated for some hepatic diseases…*". The idea to use a partial graft in patients with "hepatic diseases" will then open the concept of the minimal liver function required to survive using its unique potential of regeneration, even under immunosuppression. Anatomic resection with primary control of both inflow and outflow pedicles leaving an autonomous remnant parenchyma allowed the standardization of major hepatectomies. This approach of liver surgery ushered the modern era of hepatic resectional surgery, which aims at defining the optimal plan of resection with minimal blood loss (1).

Once the feasibility of major liver resection was established, the following years mainly focused on improving the safety of liver resections. In this setting, three main advances, played a critical part, including: (I) preoperative portal vein embolization in order to enhance the hypertrophy of the future liver remnant; (II) maintenance of a low central venous pressure to decrease backflow bleeding; and (III) intraoperative ultrasonography to achieve a better location of intraparenchymal tumors and a clear delimitation of the vascular plans. Other technical improvements, such as the hanging maneuver in order to facilitate the anterior approach; the ultrasonic dissector to achieve a rapid and precise parenchymal transection and the peritoneal patch to easily provide an immediate and safe vascular graft, should only be considered as incremental innovations. In the same line, the next logical step allowing significant improvement of the postoperative course will be to develop an efficient coating to suppress the risk of biliary leakage (2).

Obviously, overcoming the risk of small for size syndrome would represent a dramatic advance. Yet, we should avoid being blinded by misleading and spectacular volumetric figures. Basic functional principles should always be kept in mind and recall us that, like a man without a social structure is not a human, a hepatocyte without any support is useless. Hence, rather than focusing on a purely quantitative hypertrophy, future strategies should probably aim at achieving a more qualitative regeneration.

A large approach with wide exposure was one of the turning points that ensured the safety of major resections. Since then, ongoing efforts to minimize abdominal wall trauma have led to popularize the use of the laparoscopic approach (3). This allowed to decrease postoperative pain and several complications resulting in lower hospital stays and accelerated recovery. It is therefore not surprising that laparoscopy has been accepted as the approach of choice for left lateral sectionectomy and we can expect that major hepatectomies will meet a similar fate within years from now. Rather than attempting to define indications for laparoscopy, we should therefore now accept its principles and focus on defining its contraindications. Of course, the expansion of laparoscopic hepatectomies to more complex resections, such as extended right hepatectomies or anatomical resections involving segments VII and VIII will require a certain degree of training and we can expect a stable rate of conversion for several years. In this context, we believe that the classical notion of learning curve should be abandoned until a true expertise has been achieved.

Likewise, while surgeons focus on the feasibility of these laparoscopic resections, they should also keep on following basic oncological principles and never sacrifice surgical margin width or lymphadenectomy in the name of a mini-invasive technical achievement. In the same line, while the use of high-tech devices will always be appealing, we should avoid their inherent pitfalls and retain only those aiming at ensuring patient's safety rather than improving surgeons' comfort. In this setting, current hepatic robotic surgery still lacks demonstrated benefits in terms of surgical quality and postoperative complications. Altogether, while there is no doubt that the future of liver surgery will be played on a screen, it is currently difficult to precisely predict if this will be a laparoscopic or a robotic screen (4).

Finally, it is likely that the refinement of surgical indications will represent the only true future less invasive innovation. Increasing non-surgical policies for benign lesions should be expected and adaptive strategies based on the natural history of malignant diseases will avoid futile surgeries such as some multiple CRLM controlled by chemotherapy (5). In the end, surgeons should never forget that a justified non-operative approach will always be less invasive than the least invasive surgical approach.

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Footnote

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References

1. Belghiti J. The first anatomical right resection announcing liver donation. J Hepatol 2003;39:475-9.
2. Agrawal S, Belghiti J. Oncologic resection for malignant tumors of the liver. Ann Surg 2011;253:656-65.
3. Pessaux P, Diana M, Soler L, et al. Towards cybernetic surgery: robotic and augmented reality-assisted liver segmentectomy. Langenbecks Arch Surg 2015;400:381-5.
4. Tsung A, Geller DA, Sukato DC, et al. Robotic versus laparoscopic hepatectomy: a matched comparison. Ann Surg 2014;259:549-55.
5. Cauchy F, Fuks D, Nomi T, et al. Risk factors and consequences of conversion in laparoscopic major liver resection. Br J Surg 2015;102:785-95.

Hepatic Surgical Technique

Patient specific anatomy: the new area of anatomy based on computer science illustrated on liver

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Background: Over the past century, medical imaging has brought a new revolution: internal anatomy of a patient could be seen without any invasive technique. This revolution has highlighted the two main limits of current anatomy: the anatomical description is physician dependent, and the average anatomy is more and more frequently insufficient to describe anatomical variations. These drawbacks can sometimes be so important that they create mistakes but they can be overcome through the use of 3D patient-specific surgical anatomy.

Methods: In this article, we propose to illustrate such improvement of standard anatomy on liver. We first propose a general scheme allowing to easily compare the four main liver anatomical descriptions by Takasaki, Goldsmith and Woodburne, Bismuth and Couinaud. From this general scheme we propose four rules to apply in order to correct these initial anatomical definitions. Application of these rules allows to correct usual vascular topological mistakes of standard anatomy. We finally validate such correction on a database of 20 clinical cases compared to the 111 clinical cases of a Couinaud article.

Results: Out of the 20 images of the database, we note a revealing difference in 14 cases (70%) on at least one important branch of the portal network. Only six cases (30%) do not present a revealing difference between both labellings. We also show that the right portal fissure location on our 20 cases defined between segment V and VI of our anatomical definition is well correlated with the real position described by Couinaud on 111 cases, knowing that the theoretical position was only found in 46 cases out of 111, i.e., 41.44% of cases with the non-corrected Couinaud definition.

Conclusions: We have proposed a new anatomical segmentation of the liver based on four main rules to apply in order to correct topological errors of the four main standard segmentations. Our validation clearly illustrates that this new definition corrects the large amount of mistakes created by the current standard definitions, increased by physician interpretation that can vary from one case to another.

Keywords: Liver anatomy; patient-specific; liver segmentation; surgical planning; computer-assisted planning

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Introduction

Patient anatomy is the most important component of any surgical procedure definition. Modern anatomical description introduced by Andrée Vésale is based on a description of human anatomy from "human alive or having lived" represented by an average and standardized anatomy. All patients being different, the average anatomy has been defined by variation or exception. Since Andrée Vésale and his "*De Humani Corporis Fabrica*", anatomy has been progressively improved thanks to new techniques and technologies, increasing variations but making the average anatomy more precise. This anatomy has a major benefit: it allows physicians to use standardized names and labels.

Surgical procedures have then been more easily explained and described for improved knowledge sharing.

Over the past century, medical imaging has brought a new revolution: internal anatomy of a patient could be seen without any invasive technique. Current 3D and 4D medical imaging can thus provide today patient-specific anatomical data including geometry, topology and also function of organs. But this revolution has highlighted both main limits of the current anatomy. The first one is that interpretation of image information and of visible anatomical variations is totally dependent on the physician's knowledge and can vary from one case to another. The second one is that variation description is ever more important, all patients being different. These drawbacks can sometimes be so great that they create mistakes in the anatomical description of patients and their associated surgical eligibility.

The liver is here a perfect illustration of such limits. Systemic chemotherapy of advanced colorectal cancer (CRC) produces a 9% 5-year survival rate with modern chemotherapy (1). On the opposite, surgery offers the foremost success rates against liver tumour (more than 50% 5-year survival rate). The 5-year survival rate exceeds 80% in case of liver transplant. Regretfully, less than 20% of patients are eligible to surgery due to anatomical limitation. Indeed, the eligibility is based on various criteria and rules such as the Milan criteria for liver transplants, or the 2006 San Francisco consensus rules for partial liver resection. This conference established that two adjacent liver segments can be separated with an adequate vascular inflow and outflow as well as biliary drainage and that the standardized Future Liver Remnant (FLR) (standardized FLR = remnant liver volume/liver volume) must be over 20% for patients with an otherwise normal liver, 30% for patients who have received extensive preoperative systemic chemotherapy, and 40% for patients with existing chronic liver diseases such as hepatitis, fibrosis or cirrhosis. Precise knowledge of the liver anatomy is thus a key point for any surgical procedure, including resection of liver tumours or living donor transplant, the surgical eligibility being linked to the definition of liver segments.

There are today four main anatomical definitions used in routine worldwide (*Figure 1*): the Takasaki segments definition (2) essentially used in Asia, the Goldsmith and Woodburne sectors (3) definition essentially in North America, the corrected Bismuth sectors (4) definition essentially used in Europe and the Couinaud segment (5) definition used worldwide.

These definitions are based on a labelling of the portal tree distribution in the liver following essentially geometrical criteria on relative location in the liver: right, middle, left, anterior, posterior, lateral, median and caudal. We can also notice that the hepatic veins define separating limits between main sectors in Goldsmith and Woodburne and Bismuth definitions. This general overview also clearly illustrates that Couinaud segmentation is the most precise one, all other segmentations can be obtained by a grouping of Couinaud segments in different sets. But Couinaud segmentation contains major errors. Platzer and Maurer (6) surely were the first ones to show in 1966 that the variability of segment contours was too important for any general scheme to be viable. Many research works (7-13) have subsequently completed that first study by providing quantifiable results thanks to 3D medical imaging. Couinaud himself (14) described in 2002 topographic anomalies. In 34 cases out of 111 (i.e., 30.63% of cases), he demonstrated that the real anatomical anterior sector of the liver (segment V + segment VIII) was different from his own definition. This may have surgical consequences. Thus, by clamping the right paramedian vein, portal branches which are topologically considered as being in segment VI took in fact their origin on the right paramedian branch, and were topologically in the anterior sector of the liver. Couinaud concluded that there was incoherence between vascular topology and the topography of the segments that could be corrected by using our 3D modelling and segmentation software (15) that we have clinically validated (16-19).

Indeed, the progress in imaging and computer sciences progressively allowed to visualize the portal and hepatic vascularization of the liver without pathology dissection. These works all showed that indirect landmarks, such as hepatic veins, are not suitable for a proper delineation of portal segments of the liver. Inappropriate delineation of the segments as defined by Couinaud classification can then lead to tumour localisation in an erroneous segment in about 16% of cases (study on 126 patients). Such an error should lead to reducing surgical eligibility. These various works illustrate and demonstrate the problem of modern anatomy based on an average patient and the necessity to develop a new personalized anatomy based on labelling and naming rules applied on 3D modelled medical images of the patient. We will present here such a new definition for liver surgery. In opposition with the Fasel definition (9) or other existing ones, this definition will be based on existing labelling (Takasaki, Goldsmith & Woodburne, Bismuth and Couinaud) that will be corrected by an easy labelling rule. It is thus easier to use in surgical routine.

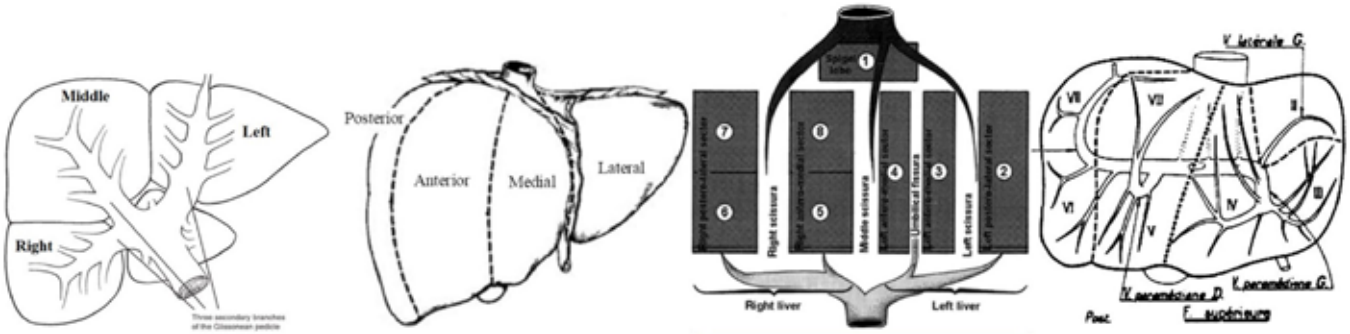

Figure 1 The four main anatomical segmentations of the liver. From left to right: Takasaki, Goldsmith and Woodburne, Bismuth and Couinaud.

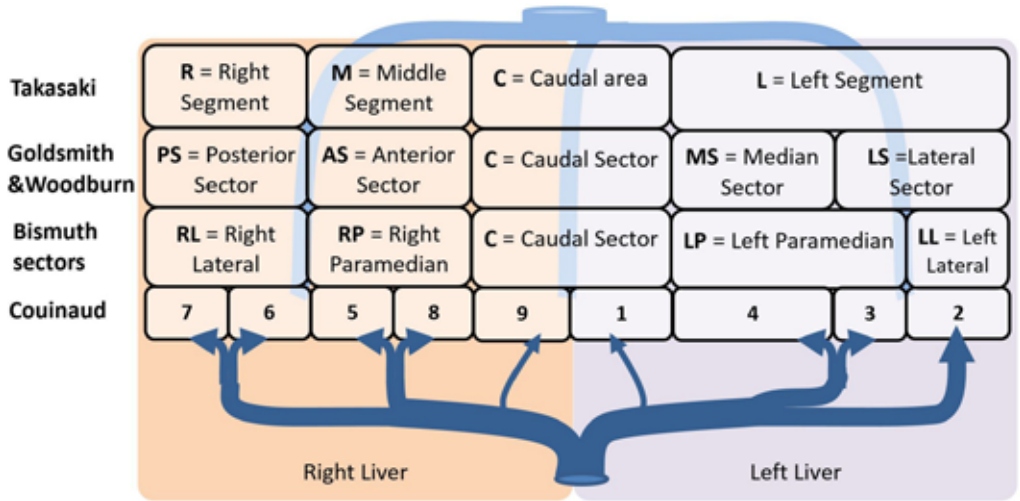

Figure 2 Link between the four main anatomical segmentations of the liver.

Material and methods

For the following part of this article, we propose to extend the Bismuth comparison realized in 1982, in order to add Takasaki and Goldsmith and Woodburne descriptions of the liver segmentation. This general description clearly illustrates links and differences between the four main definitions (*Figure 2*). We will also replace the full name of segments or sectors by capital letters simplifying segment labelling.

In the current anatomical segmentations, when two branches (green and yellow arrows in *Figure 3*) of the portal network are pooled in a same segment or sector, and are thus labelled with a same label, four cases can arise:

(I) Both branches come from the same common portal branch and are drained by a same hepatic branch;

(II) Both branches come from the same common portal branch but are drained by two separate hepatic branches;

(III) Both branches come from two separate portal branches but are drained by a same hepatic branch;

(IV) Both branches come from two separate portal branches and are drained by two separate hepatic branches.

Among these cases, only cases 1 and 2 allow to guarantee a correct topology in terms of labelling of portal branches. Indeed, a single ligature of the common portal branch is sufficient to stop the blood flow in this segment. This shows that applying a simple labelling rule would be enough to ensure correct topology for the labelling of portal branches. A new and unique "surgical" rule arises from this and can be defined as follow: two portal venous sub-networks can

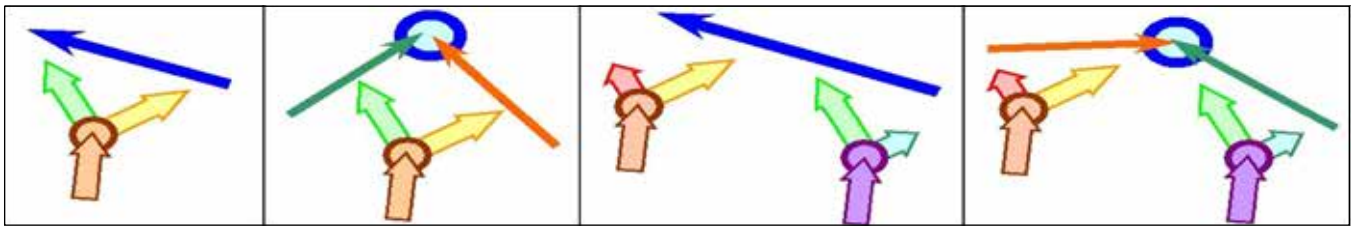

Figure 3 Illustration of the four possible cases of the pooling of two portal branches (green and orange) in a same anatomical segment or sector.

only be in a same segment, if and only if they come from the same crossing of a same portal branch. This purely topologic definition does not add any artificial topographic limitation so as to avoid the limitation or errors of existing segmentation. It allows to define segments of highly variable sizes according to the requested accuracy level. But this rule does not include any labelling mandatory to clinic description of tumour location. For the sake of rigour and in order to facilitate the use of that definition in clinical routine, we proposed to define a labelling from the four main label definitions described previously (see *Figure 2*). Correction of the label is done following the two new correcting rules:

- If a right (respectively a left) sector or segment is vascularized with a portal subtree coming from the left (respectively the right) portal vein, we add the letter ^{L} (respectively ^{R}) to indicate this unusual topological origin, which corrects standard surgical errors of the current segmentation. The same way, if a right or left sector or segment is vascularized with a portal subtree coming from the portal trunk, we add the letter ^{T} to indicate this unusual topological origin.
- When several subtrees with two different portal crossing origins vascularize a same area, we add a letter (a, b, c…) to differentiate their topological origin. Resulting segments have therefore different names in respect with our topological rule.

To these two labelling correcting rules, we have added two other rules, which are not mandatory to assume the topological rule but useful in practice to provide more detailed anatomical segmentation and thus more accurate surgical eligibility:

- When several subtrees with a same portal crossing origins vascularize a same area, we can add a number (1, 2, 3…) to differentiate these different subtrees in a same segment. The labelling order, from 1 to N, is defined by following the clockwise direction from the portal crossing origin in an anterior view.
- When a segment is drained by only one left, median, right or accessory hepatic vein (case 1 of *Figure 3*), we can add a drainage letter L, M, R or A at the end of the new label.

The two correcting rules can be summarized by following letter addition:

+ ^{L}, ^{R}, ^{T} or ^{M} = left, right, tronc or middle portal branch origin;

+ a, b, c…if different venous origins for a same segment area.

The optional correcting rules can be summarized by following label addition:

+ 1, 2, 3…if a same venous origin for a same segment area;

+ R, M, L, A = right, median, left, accessory hepatic drainage

Applications of these correcting rules are illustrated on two different portal system distributions in *Figure 4* from the four usual anatomical segmentation definitions. However, it is also possible to combine these different definitions. Indeed, the best way to proceed is to start from the most general one (Takasaki) to the most detailed one (Couinaud) according to the surgical need of precision. This need will be defined from the tumour location and from the vessels (portal and hepatic veins) that will define or complicate the surgical procedure. For instance, if no tumour is localized in the left liver, and if the median hepatic branch will not have to be resected by surgery, then it is not necessary to go over the Takasaki level of precision, a unique left segment is sufficient (*Figure 5*). If for the same clinical case a tumour is localized only in a part of segment 6 without any risk of sacrifice of the right hepatic branch, it will be possible to separate the right liver in a median segment, the right segment being separated by using the Couinaud level of precision and so associated labelling. In case of a tumour in segment 7 with a sacrifice of the right branch, the right liver will then be labelled following the Couinaud level of precision.

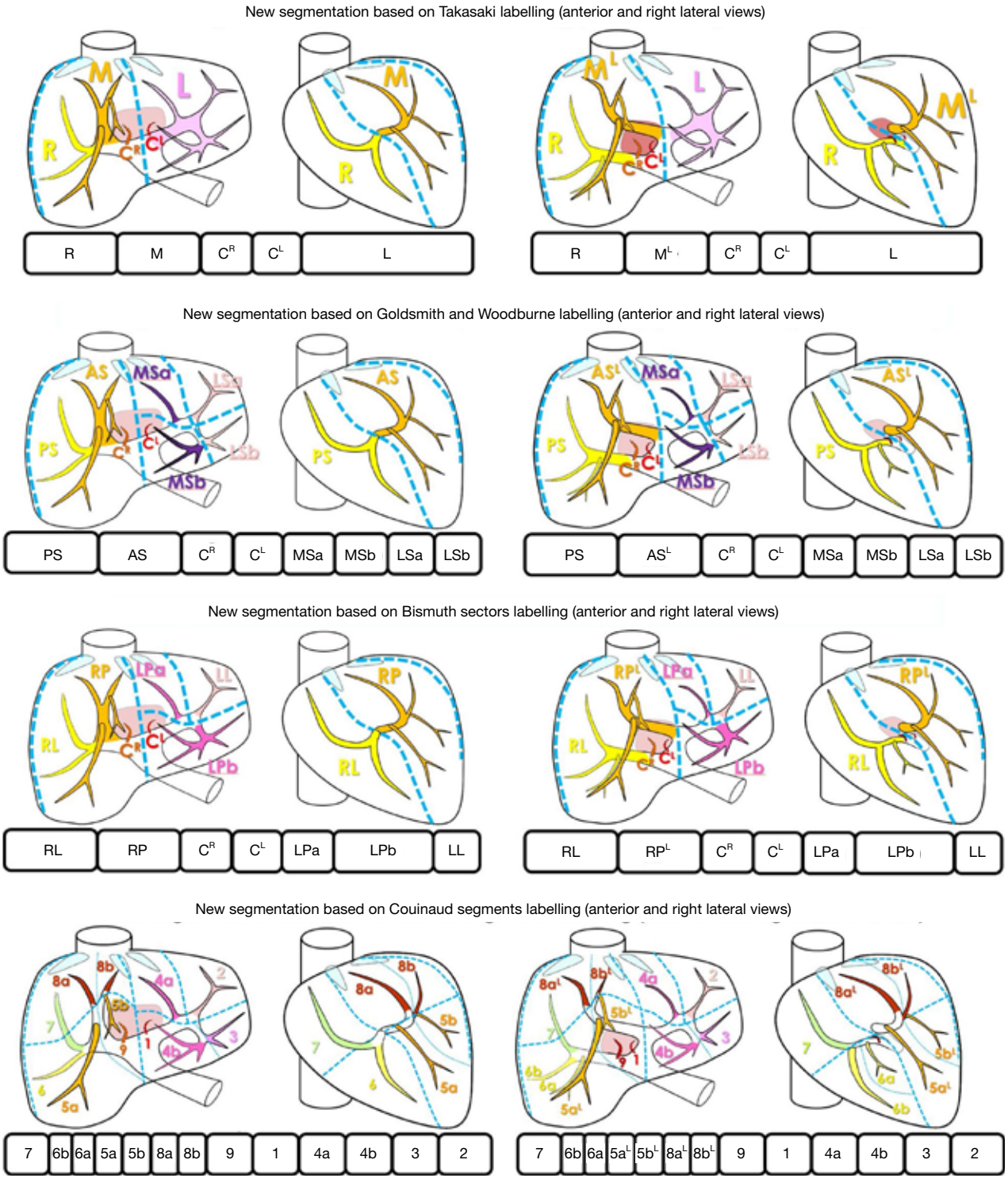

Figure 4 The new anatomical definition obtained with the application of the two correcting rules.

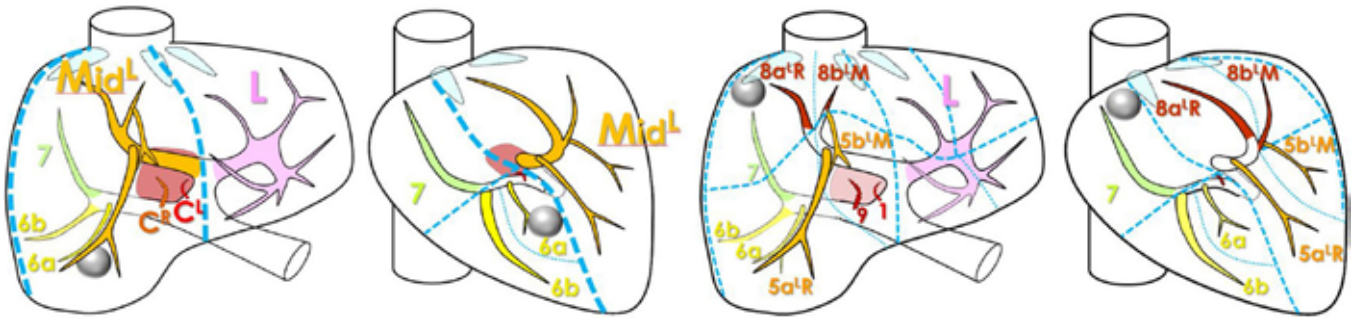

Figure 5 Two samples with tumour (in grey) of our definition combining different levels of precision.

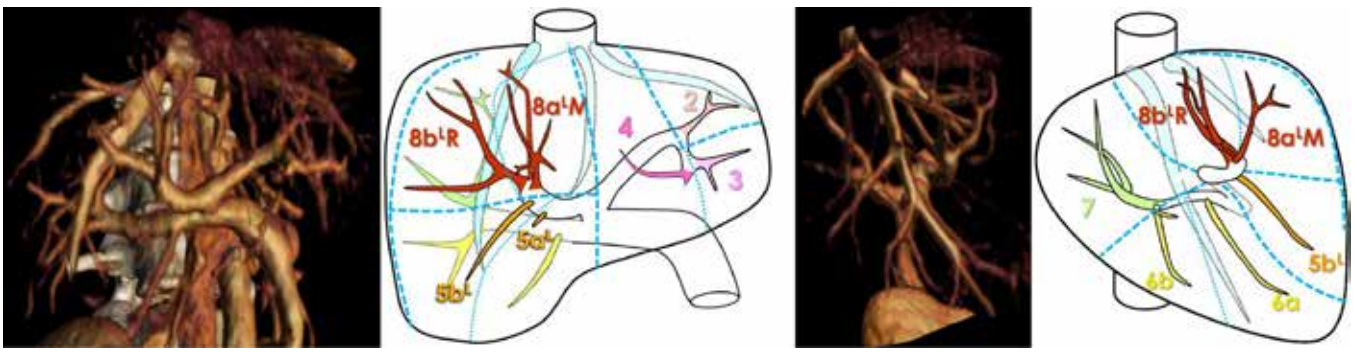

Figure 6 Direct volume rendering in anterior (left) and right lateral view (right) allows to define precisely the anatomical segment following our new anatomical segmentation.

When applied, these rules provide a different anatomical segmentation even if close to the existing ones. What seems to be a small difference in the labelling provided by the addition of new letters is indeed significant as we will see in the result chapter. It is the main benefit of this new proposal, easy to apply because based on existing labelling used every day by all experts worldwide, but anatomically correct thanks to the corrective rules.

To be applied in clinical routine, this new definition requires the 3D visualisation of venous networks. A contrasted CT image at venous time (70 seconds after injection) or a MRI will have to be done so as to visualize these vessels thanks to direct volume rendering which is available on all current workstations. That volume rendering can also be obtained on a personal computer thanks to certified software such as OsirixMD (http://pixmeo.pixmeo.com/products.html#OsiriXMD) on Mac-OS, or free of charge VP-Planning (https://www.visiblepatient.com/en/products/software/) on Mac-OS and Windows. VP-Planning© visible patient integrates an automatic transfer function dedicated to vessel visualization. As illustrated in *Figure 6*, such volume rendering should be sufficient to define precisely the anatomical segment using our new definition.

However, it is considers by physicians as complex to use. Another solution consists in using an image segmentation algorithm allowing to extract vessels from the medical image. To do it, several software tools are available on the market (Myrian© from Intrasense, Ziostation© from Ziosoft, Synapse© Vincent from Fujinon, Iqqa® Liver from Edda Technology, Scout™ Liver from Pathfinder). Another solution consist in using distant 3D Modelling services (Mevis Distant Service, Visible Patient Service from Visible Patient) that do not request the purchase and use of expensive modelling workstations, the modelling being realized at distance by experts in image processing. *Figure* 7 illustrates the use of VP-Planning software after the Visible Patient Service has modelled a liver. As illustrated, the software allows for a virtual clip applying that provides in real-time the vascular territory of the clipped portal subtree defining the anatomical segment.

In order to clinically validate this new definition, a database of 20 injected CT images was set up. Images were

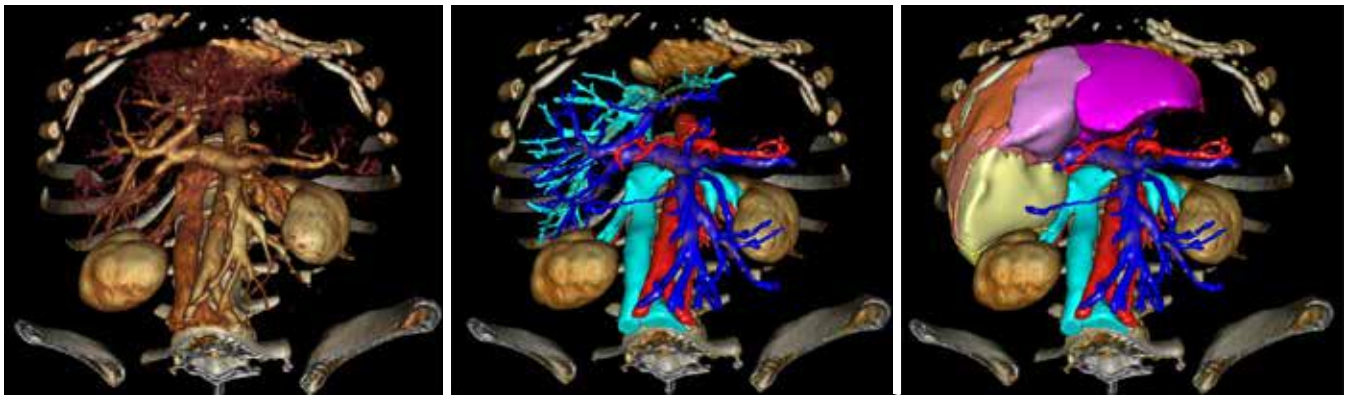

Figure 7 VP-Planning© visible patient Direct Volume rendering (left) compared with the Visible Patient Service 3D modelling of vessels (centre) and anatomical segment (right) rendering.

acquired at venous time, i.e., 70 seconds after injection of the contrast medium. These images have been collected and anonymized after patient consent by the Digestive and Endocrine Surgery Department, University Hospital of Strasbourg, France. Patients have not been selected to be included in the database but their images. The single criterion was the quality of the CT image injected at venous time. Images of 10 women and 10 men, among which 2 women and 2 men had no hepatic pathology (i.e., 20%) have been collected. Women were aged between 38 and 62 and men were aged between 33 and 66. Five patients had a single tumour (25%), five patients had two tumours (25%), four patients had between three and eight tumours (20%) and two patients had more than 20 tumours (10%). This database presents a good variability of hepatic pathologies and features as many women as men.

A 3D modelling of the liver, its potential tumours and its hepatic and portal venous networks were provided by the Visible Patient Service. For each acquisition, an image in anterior and right lateral view has been edited. A hepatic surgeon was asked to delineate the standard Couinaud segmentation on each view. The same way, in parallel and blindly, computer scientists have indicated the computer-based segmentation on each view. In both cases segmentations have been realized with the 3D rendering software, allowing for a better vision of vessel localization. Finally, the results obtained by highlighting the most revealing differences were compared (*Figure 8*).

Results

Out of the 20 images of the database, we note a revealing difference in 14 cases (70%) on at least one important branch of the portal network. Only six cases (30%) do not present a revealing difference between both labellings. The main differences summarized in *Table 1* and illustrated on *Figure 9* are as follows:

- In 11 cases (55%) a large branch, normally in segment V according to Couinaud's segmentation, was topologically assessed to be located in one of segments VI according to the new definition. This figure even rose to 60% (12 cases) if smaller branches with that same labelling modification were integrated.
- In four cases (20%) a large branch, normally in segment V according to Couinaud's segmentation, was topologically assessed to be located in one of segments VIII according to the new definition. This figure even rose to 30% (six cases) if smaller branches with that same labelling modification were integrated.
- In four cases (20%) a large branch, normally in segment VII according to Couinaud's segmentation, was topologically assessed to be located in one of segments VIII according to the new definition. This figure doubles (40%) if smaller branches with that same labelling modification were integrated.
- In two cases (10%) a large branch, normally in segment VIII according to Couinaud's segmentation, was topologically assessed to be located in segment IIa (called IVa in Couinaud's classification) according to the new definition. These two atypical anatomies included a branch going from the left portal vein up to the cranial part of the liver such as a branch of segment IVa according to Couinaud, but reaching beyond the limit of the median hepatic vein to end up

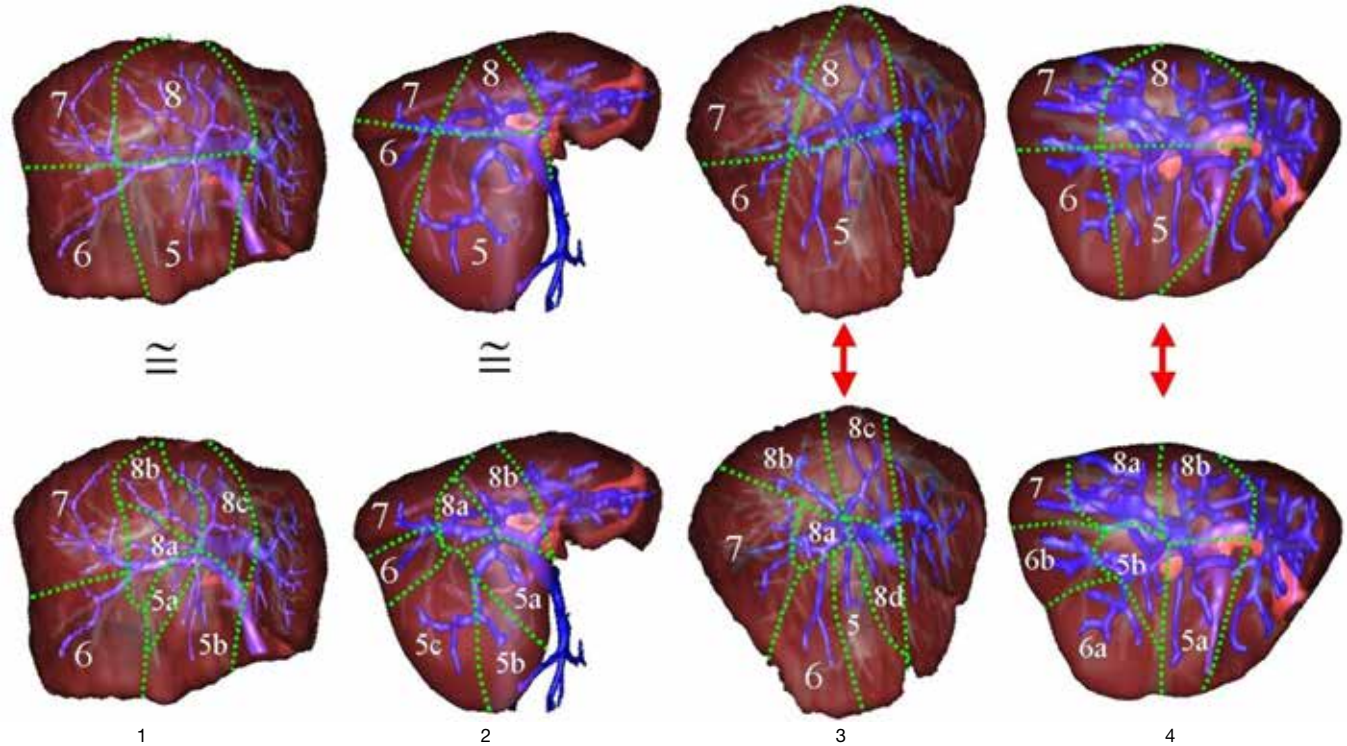

Figure 8 Comparison of Couinaud's segmentation delineated by a surgeon, and the newly demonstrated computer-based segmentation on images 1 to 4 from the test database composed of 20 patients.

Table 1 Percentage of labelling modification between Couinaud's and IRCAD's new segmentation on large branches and small branches of the portal network carried out from CT data of 20 livers

Modification	5→6x	5→8x	7→8x	8→2a	6→5 or 8
% large branches	55	20	20	10	10
% small branches	5	10	20	-	-

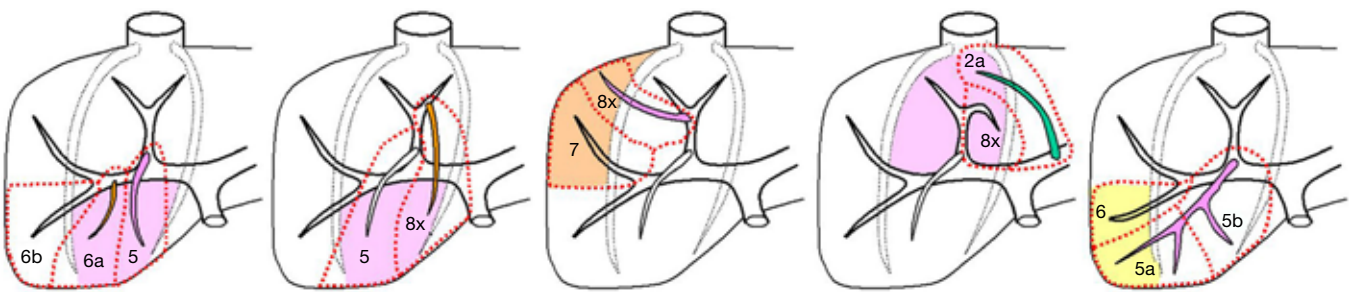

Figure 9 Illustration of the main differences noticed between Couinaud's segments (coloured zones) and IRCAD's new classification (red dotted segments) using each variation indicated in *Table 1*.

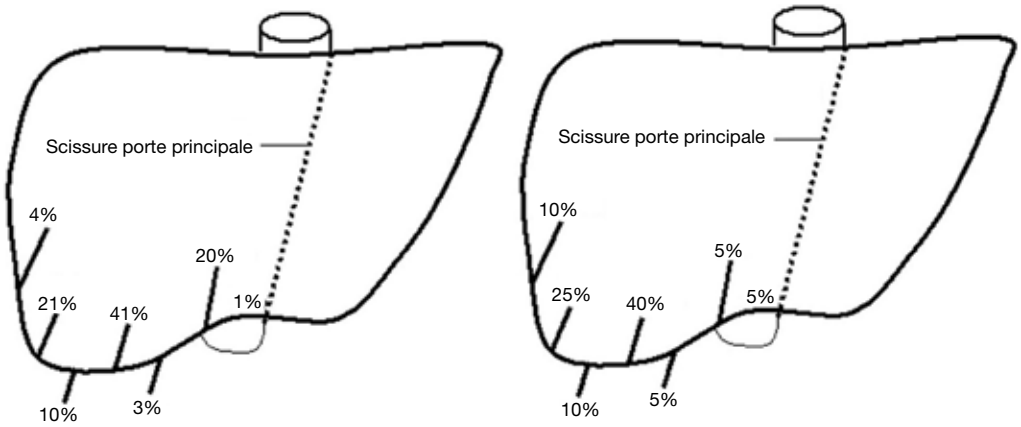

Figure 10 Comparison between the real position of the right portal fissure extracted from Couinaud's work on 111 cases (left) and the position issued from our anatomical segmentation on the 20 cases of our study (right). Results are well correlated.

in the topographic territory of segment VIII according to Couinaud.

- In two cases (10%) a large branch, normally in segment VI according to Couinaud's segmentation, was topologically assessed to be located in one of segments V or VIII according to the new definition.

Discussion

We propose herein a new anatomical segmentation of the liver aiming at correcting the topologic errors of Couinaud's segmentation. To be applied, it requires a 3D visualization of portal and hepatic venous networks of the liver. The application of a simple labelling rule allows to guarantee a proper and logical anatomical segmentation. This first study carried out on 20 clinical cases showed a good correlation between its results and those observed in the literature. It moreover highlights the limits of Couinaud's segmentation, which appears erroneous in more than 50% of cases when compared to our database for the definition of the segments of the right liver.

As expected, these results confirmed Couinaud's observations reported in his recent study. But rather surprisingly, we found a revealing modification in segment V. Indeed, for over half of patients from the present database, at least one branch of segment VI according to the new definition was considered as belonging to segment V according to Couinaud's classification. This particularity did not appear in the study published in 2002 and presenting a database of 111 cases. If such cases were present, they necessarily had to be part of the 77 cases (69.37%) sorted as being normal. In order to check the anatomic accuracy of our method regarding that difference of limit between segment V and VI, we proposed another method consisting in locating the right portal fissura (limit between segment V and VI) using the segment's delineation. In the case of Couinaud's anatomical segmentation, this fissure was theoretically located halfway between the right anterior angle and the main portal fissure. Couinaud indicated in his work (12) that this theoretical position was only found in 46 cases out of 111, i.e., 41.44% of cases. In fact, Couinaud indicated in that same work the real anatomical position of the fissure for the 111 cases, which is summarized on *Figure 10*. Thus, its position could be drawn in the same way in the new model of reconstruction, and it could be noted, as shown on *Figure 6*, that a good correlation between both results could be observed. This showed that the limit between segment V and VI provided by our new topologically corrected segmentation appears to correlate with the anatomic reality.

The present segmentation allows to achieve a segmentation similar to the sector segmentation described by Goldsmith & Woodburne, or a segmentation similar to that described by Bismuth using Couinaud's classification (*Figure 11*). It defines a "true anatomical segment" based on a topologically correct labelling and merging of territories supplied by the portal venous sub-tree(s).

In comparison with other existing work, Fasel is the single author who has proposed to really modify Couinaud's segmentation by proposing a new topologically correct definition called 1-2-20 in a recent work (14). The idea

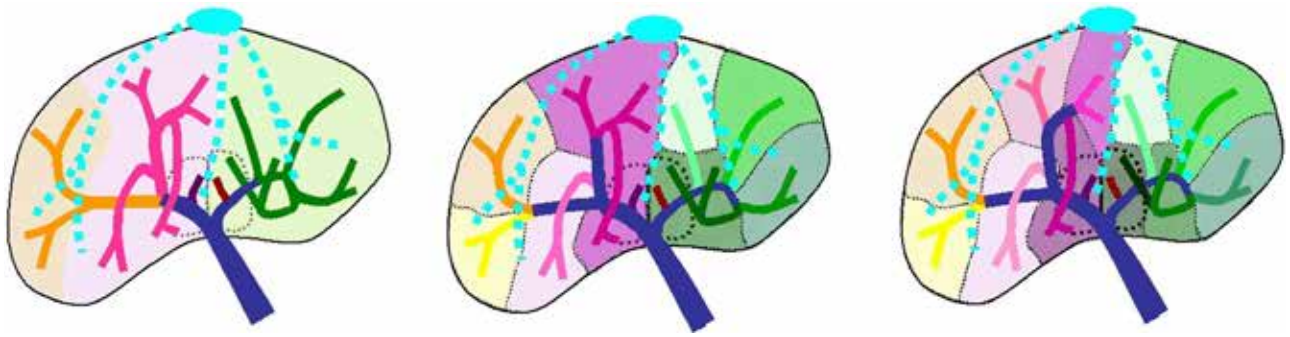

Figure 11 Illustration of the new segmentation using the topological rule. A same rule provides several detail levels, as shown on the three examples, close to the Goldsmith & Woodburne segmentation (left) or the Couinaud/Bismuth segmentation (centre).

was to create a segment around each secondary branch originating from the left and right portal vein of the liver. By definition, this concept provided a topologically correct anatomy. However, by default it provided a very large number of segments in the left liver and rather few segments in the right liver. This was mainly due to the fact that in this work the left portal vein ended at the Rex Recessus, including thus the left paramedian vein while in the right liver the right portal vein was limited to the first main bifurcation. Moreover, variability of segment number resulting from the Fasel segmentation implied that a number did not represent an area. It was thus impossible to describe the location of a tumour by its number (the segment 6 for instance can be in the right paramedian or lateral sector, or in the left paramedian or lateral sector from one patient to another). Such a variability made its clinical application complex; all clinicians would have to use the same software.

Our presented study is limited to the evaluation of the right liver. It has to be completed by a similar analysis of the left liver which, according to Couinaud, should present fewer variations. However, the labelling of the branches of segment IVa according to Couinaud will at least entail a difference that has already been noted in the study of the right liver. Indeed, in two cases, we observed that a vein issued from the left portal branch joined the territory of segment VIII according to Couinaud. Renaming such branches into branch of segment IIa would illustrate a first variation which was featured in 10% of our cases. Further evaluation would consist in checking the potential clinical benefit provided by that anatomically corrected segmentation. A clinical study would have to allow the comparison of postoperative results of patients operated respecting Couinaud's segmentation with patients operated following the new segmental definition of the anatomical segmentation. From a clinical point of view, this new segmentation process could allow to reduce tumour recurrence in patients operated for HepatoCellular Carcinoma (HCC), as it has been demonstrated that HCC has a portal segmental dissemination. It could further allow to reduce resected regions to smaller segments depending on tumour localisation.

Finally, it is furthermore interesting to note that this definition does not require any specific research or development on computer sciences level. In clinical routine, visualization through volume rendering will be sufficient to realize the presented labelling. Territories associated to each labelled branch can then be estimated on such 3D view knowing that direct volume rendering techniques are available on all current CT and MRI equipment as well as on certified software applications such as OSIRIXMD (on MacOS) or the free of charge Visible Patient Planning (on Windows and MacOs) (*Figure 12*).

Conclusions

We have proposed a new anatomical segmentation of the liver based on four main rules to apply in order to correct topological errors of the four main standard segmentations. Our validation clearly illustrates the large amount of mistakes created by the current standard definitions, increased by physician interpretation that can vary from one case to another. In the past, the only way to correct common anatomical mistakes was to clamp vessels during surgery, associated vascular territories appearing then clearly. By applying these rules, we can now obtain the same results preoperatively, these rules being based on the surgical logic of vascular territory clamping and using

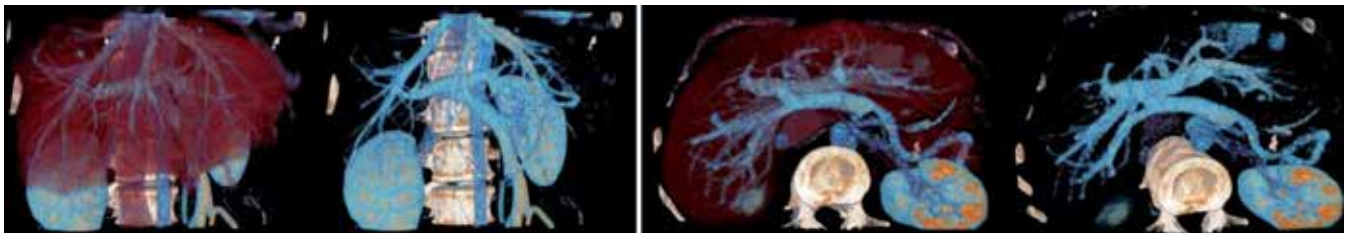

Figure 12 Volume rendering of liver and vessels realized with the VP-Planning software from the CT image of patient 1 of our database of clinical cases in anterior (left) and inferior view (right). It gives the opportunity to locate anatomical segments thanks to venous networks without any pre-processing or segmentation.

virtual reality technologies. Moreover, more recent software can simulate in the same way virtual clip applying on vessels and thus virtually provide the vascular territory in real-time. These rules should thus be applied in any organ to optimize and personalize their functional anatomical definition.

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Footnote

Conflicts of Interest: Luc Soler and Jacques Marescaux have stock ownership of the Visible Patient company. The other authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

1. Sanoff HK, Sargent DJ, Campbell ME, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol 2008;26:5721-7.
2. Takasaki K. Glissonean pedicle transection method for hepatic resection: a new concept of liver segmentation. J Hepatobiliary Pancreat Surg 1998;5:286-91.
3. Goldsmith NA, Woodburne RT. The surgical anatomy pertaining to liver resection. Surg Gynecol Obstet 1957;105:310-8.
4. Bismuth H. Surgical anatomy and anatomical surgery of the liver. World J Surg 1982;6:3-9.
5. Couinaud C. Liver anatomy: portal (and suprahepatic) or biliary segmentation. Dig Surg 1999;16:459-67.
6. Platzer W, Maurer H. On the segmental arrangement of the liver. Acta Anat (Basel) 1966;63:8-31.
7. Nelson RC, Chezmar JL, Sugarbaker PH, et al. Preoperative localization of focal liver lesions to specific liver segments: utility of CT during arterial portography. Radiology 1990;176:89-94.
8. Soyer P, Roche A, Gad M, et al. Preoperative segmental localization of hepatic metastases: utility of three-dimensional CT during arterial portography. Radiology 1991;180:653-8.
9. Fasel JH, Selle D, Evertsz CJ, et al. Segmental anatomy of the liver: poor correlation with CT. Radiology 1998;206:151-6.
10. Rieker O, Mildenberger P, Hintze C, et al. Segmental anatomy of the liver in computed tomography: do we localize the lesion accurately? Rofo 2000;172:147-52.
11. Fischer L, Cardenas C, Thorn M, et al. Limits of Couinaud's liver segment classification: a quantitative computer-based three-dimensional analysis. J Comput Assist Tomogr 2002;26:962-7.
12. Strunk H, Stuckmann G, Textor J, et al. Limitations and pitfalls of Couinaud's segmentation of the liver in transaxial Imaging. Eur Radiol 2003;13:2472-82.
13. Fasel JH. Portal venous territories within the human liver: an anatomical reappraisal. Anat Rec (Hoboken) 2008;291:636-42.
14. Couinaud C. Errors in the topographic diagnosis of liver diseases. Ann Chir 2002;127:418-30.
15. Soler L, Delingette H, Malandain G, et al. Fully automatic anatomical, pathological, and functional segmentation from CT scans for hepatic surgery. Comput Aided Surg

2001;6:131-42.
16. Bégin A, Martel G, Lapointe R, et al. Accuracy of preoperative automatic measurement of the liver volume by CT-scan combined to a 3D virtual surgical planning software (3DVSP). Surg Endosc 2014;28:3408-12.
17. Soler L, Nicolau S, Pessaux P, et al. Real-time 3D image reconstruction guidance in liver resection surgery. Hepatobiliary Surg Nutr 2014;3:73-81.
18. Mutter D, Soler L, Marescaux J. Recent advances in liver imaging. Expert Rev Gastroenterol Hepatol 2010;4:613-21.
19. Mutter D, Dallemagne B, Bailey Ch, et al. 3D virtual reality and selective vascular control for laparoscopic left hepatic lobectomy. Surg Endosc 2009;23:432-5.

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How much ischemia can the liver tolerate during resection?

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Abstract: The use of vascular inflow occlusion (VIO, also known as the Pringle maneuver) during liver surgery prevents severe blood loss and the need for blood transfusion. The most commonly used technique for VIO entails clamping of the portal triad, which simultaneously occludes the proper hepatic artery and portal vein. Although VIO is an effective technique to reduce intraoperative blood loss, it also inevitably inflicts hepatic ischemia/reperfusion (I/R) injury as a side effect. I/R injury induces formation of reactive oxygen species that cause oxidative stress and cell death, ultimately leading to a sterile inflammatory response that causes hepatocellular damage and liver dysfunction that can result in acute liver failure in most severe cases. Since the duration of ischemia correlates positively with the severity of liver injury, there is a need to find the balance between preventing severe blood loss and inducing liver damage through the use of VIO. Although research on the maximum duration of hepatic ischemia has intensified since the beginning of the 1980s, there still is no consensus on the tolerable upper limit. Based on the available literature, it is concluded that intermittent and continuous VIO can both be used safely when ischemia times do not exceed 120 min. However, intermittent VIO should be the preferred technique in cases that require >120 min duration of ischemia.

Keywords: Hepatectomy; ischemia; ischemic preconditioning (IP); oxidative stress; reperfusion injury

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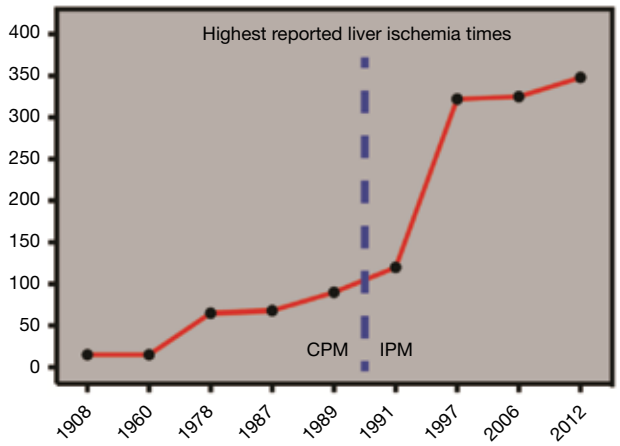
Introduction

The Pringle maneuver is eponymously attached to the Australian surgeon James Hogart Pringle, who, while working at the Royal Infirmary in Glasgow, in 1908 first reported occlusion of the portal vein and hepatic artery [i.e., vascular inflow occlusion (VIO)] by compressing the hepatoduodenal ligament to control blood loss in trauma patients with a liver laceration (1). The induction of total liver ischemia is inherent to this technique, and for several decades it was believed it could only be applied for 15-20 min. VIO was therefore not extensively used, until Huguet *et al.* claimed that ischemia time in non-diseased livers could be extended to 65 min (2,3). As a result, the use of continuous VIO during resection became more popular during the 1980s (4) and in 1987 the application of intermittent VIO was first described by Makuuchi *et al.* (5). In this procedure, VIO was applied in cycles of 30 min that were followed by 5 min of reperfusion, which could be repeated in cases that necessitated prolonged VIO.

The main aim of VIO is to reduce intraoperative blood loss and the consequent need for blood transfusion (6), which is a risk factor for postoperative mortality and morbidity (7-9). VIO, however, also results in hepatic ischemia/reperfusion (I/R) injury, which refers to the sterile inflammatory response and hepatocellular damage that are triggered when the hepatic blood (i.e., oxygen) supply is restored after a period of ischemia. Insofar as the duration of ischemia correlates positively with the hallmarks of I/R injury [e.g., ATP depletion and oxidative stress (10-12)],



Year	Ischemia time (min)	VIO technique	Reference
1908	15	CPM	(1)
1978	65	CPM	(2)
1987	68	CPM	(17)
1989	90	CPM	(4)
1991	150	IPM	(18)
1997	201	IPM	(19)
1999	322	IPM	(20)
2006	325	IPM	(21)
2012	348	IPM	(22)

Figure 1 The maximum duration of (cumulative) ischemia time in minutes (*y*-axis) plotted versus the year of publication (*x*-axis) (1,2,4,17-22). VIO, vascular inflow occlusion; CPM, continuous Pringle maneuver; IPM, intermittent Pringle maneuver.

animal studies indicate that prolonged ischemia leads to an increased mortality risk (13,14). In addition, livers affected by parenchymal disorders such as (non-)alcoholic fatty liver disease, cirrhosis, and chemotherapy-induced sinusoidal obstruction syndrome are more susceptible to I/R injury and therefore have a lower ischemic tolerance (15,16). As such, the routine use of VIO during liver surgery may be abandoned in the near future. For complex cases that require (on demand) VIO to safely complete parenchymal transection, however, the maximum acceptable duration of hepatic ischemia remains a relevant issue.

In an attempt to address this issue, Gurusamy *et al.* have reviewed the status quo of VIO during liver surgery (6). It was concluded that VIO effectively reduces intra-operative blood loss and decreases blood transfusion requirements, while no negative effects on post-operative mortality and morbidity rates were noted. The use of VIO during liver resections is therefore generally considered safe. However, since all the studies included used different clamping regimens, no conclusion could be drawn concerning the maximum tolerable ischemia time.

Over the past decades, several reports have challenged the maximum duration of ischemia the liver can tolerate (*Figure 1*). Man *et al.* reported a safe upper limit of 120 min of intermittent VIO in 1999 (23), while in 2012 Torzilli *et al.* claimed that ischemia times exceeding 120 min are well tolerated using this technique (24). In addition, two case reports mention the successful use of exceptionally long durations of liver ischemia: 322 min (20) and 348 min (22), respectively. These reports have reinvigorated the discussion about how much ischemia the liver can actually tolerate.

Nevertheless, the abovementioned reports exclusively cover cases in which the patient was not affected by any type of parenchymal liver disease. This is relevant since several studies indicate that compromised livers poorly tolerate prolonged VIO (25-29). Due to a steep increase in the global prevalence of conditions that underlie parenchymal liver disease such as the metabolic syndrome, VIO is nowadays frequently used in livers with a compromised parenchymal status. Very little data is however available on the effect of prolonged VIO (i.e., >90 min) in this patient category, with only one reported case that describes a cumulative VIO duration of 204 min in a cirrhotic liver (27).

Although several reviews on VIO techniques have been published (30,31), none have focused specifically on the duration of ischemia that the liver can tolerate. In this paper, the relation between parenchymal liver disease and the upper limit of VIO duration is therefore discussed, with specific focus on the use of prolonged (>60 min) ischemia times during liver resection.

VIO techniques

Several techniques to induce VIO during liver surgery have been introduced. Of these, the Pringle maneuver, or hepatic pedicle clamping, is the best known VIO method. A sling is placed around the hepatoduodenal ligament, which comprises both the hepatic artery and the portal vein, and tightened to halt the hepatic blood supply (1). The Pringle maneuver can be used continuously [continuous Pringle maneuver (CPM)] or intermittently [intermittent Pringle maneuver (IPM)]. During IPM, the portal triad is generally occluded for 15-20 min (ischemia) followed by a period of 5-10 min of declamping (reperfusion). Consequently, IPM is applied repeatedly during parenchymal transection.

Table 1 Overview of studies using continuous VIO

Author, year (reference)	Parenchymal status [N]	VIO technique [N]	Groups compared [N]	VIO time (min)	Longest VIO time (min)	Conclusion
Delva *et al.* 1989 (4)	Cirrhosis [15]	CPM [107]	Cirrhosis [15]	34.1±4.2‡	90	The human liver can tolerate continuous VIO ≤90 min
	Non-diseased [127]	THVE [35]	Non-diseased [127]	32.6±1.2‡		
Huguet *et al.* 1992 (37)	Non-diseased [53]	CPM [28]	VIO time <30 min [9]	21±4§	85	Non-diseased livers can at least tolerate 60 min of continuous VIO
			VIO time 30-60 min [29]	41±6§		
		THVE [25]	VIO time >60 min [15]	67.5±7.4§		
Hannoun *et al.* 1993 (25)	Non-diseased [34]	CPM [15]	CPM [15]	70±3‡	127	Continuous VIO may be applied ≤90 min in livers with a healthy parenchyma
		THVE [15]	THVE [15]	72±3‡		
		CPM + THVE [4]				
Huguet *et al.* 1994 (38)	Diseased [9]†	CPM [14]	Diseased [9]	64.7±6.8‡	85	Continuous VIO ≤85 min is not a risk factor in healthy livers. Diseased livers are more prone to complications after >60 min of VIO
	Non-diseased [17]	THVE [12]	Non-diseased [17]	68±7.5‡		
Kim *et al.* 1993 (39)	Cirrhosis [26]	CPM [26]	VIO time >50 min [14]	57.1±8.4§	75	Cirrhotic livers can tolerate VIO ≤50 min
			VIO time <50 min [12]	33.1±3.7§		

†, chemotherapy-induced liver disease, cirrhosis, or steatosis; ‡, mean ± SEM; §, mean ± SD. VIO, vascular inflow occlusion; CPM, continuous Pringle maneuver; THVE, total hepatic vascular exclusion.

Another technique for VIO is total hepatic vascular exclusion (THVE) (32). The infrahepatic and suprahepatic vena cava are clamped, as is the portal pedicle, resulting in complete isolation of the liver from the circulation. A similar technique is selective hepatic vascular exclusion (SHVE), also referred to as THVE with preservation of caval flow (33,34). SHVE requires that the liver is disconnected from the vena cava by ligation of the short perforator veins, after which the hepatic veins and the portal pedicle are clamped, thereby inducing hepatic in- and out-flow occlusion with a patent vena cava.

In order to counteract the risks of I/R injury, all techniques for VIO are occasionally combined with ischemic preconditioning (IP). IP is a technique that aims to reduce hepatic I/R injury by inflicting a short ischemic insult followed by a short period of reperfusion prior to a prolonged period of VIO (35,36).

Ischemia times reported using continuous VIO

Continuous VIO is one of the most widely used techniques that aim to reduce blood loss in liver surgery. Multiple studies have been published on continuous vascular occlusion, several of which will be discussed in the following section. The results of these studies are also summarized in *Table 1*. In 1989, the operative management of 142 cases using continuous VIO (THVE, N=35 or CPM, N=107) was reported (4). Liver failure occurred more in patients with cirrhosis (5/15) compared to patients with a non-diseased liver (4/127, P<0.001). The duration of ischemia (mean ± SEM) was similar in patients with non-diseased livers compared to those with cirrhotic livers [(32.6±1.2) *vs.* (34.1±4.2) min in N=127 and N=15, respectively]. No differences in mortality and morbidity were found between the VIO <45 min (range, 8-44 min, N=119) and the VIO >45 min (range, 45-90 min, N=23) groups. Intergroup

differences in postoperative mortality and morbidity were also not observed in 53 hepatectomies with three groups divided by the duration of VIO [THVE (N=25) or CPM (N=28)] (37). VIO was applied <30 min in group 1 (range, 15-29 min, N=9), 30-60 min in group 2 (N=29), and >60 min in group 3 (range, 60-85 min, N=15). Consequently, it was suggested that the liver could tolerate continuous VIO for >60 min, although no exact maximum duration was specified. When continuous VIO time in 34 patients with uncompromised liver parenchyma was >60 min [THVE (N=15), CPM (N=15) or THVE and CPM sequentially (N=4)] with a mean ± SEM VIO time of 73.6±2.5 min (range, 60-127 min), no correlation between the duration of ischemia and postoperative liver injury [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], liver function (bilirubin, prothrombin time), or postoperative complications was seen (25). Accordingly, it was concluded that CPM could be safely applied for up to 90 min in healthy livers. Another study addressing 26 patients who underwent continuous VIO [CPM (N=14) or THVE (N=12)] with ischemia times exceeding 1 h was published in 1994 (38). The mean ± SEM duration of VIO was 68±7.5 min in patients with non-diseased livers (N=17) and 64.7±6.8 min in patients with compromised livers (chemotherapy-induced liver disease, cirrhosis, or steatosis, N=9). Liver failure was seen in 4 patients with cirrhosis, which was reflected by the finding that postoperative morbidity was higher in diseased livers (77.8% *vs.* 11.8%, P<0.05). It was therefore concluded that continuous VIO of ≤85 min was not a risk factor in healthy livers, but that diseased livers are more prone to complications after continuous VIO of >60 min. In 26 cirrhotic patients exposed to 50-75 min (group 1, N=14) or 30-42 min (group 2, N=12) of VIO, less blood loss (mean ± SD) was seen compared with cirrhotic patients operated without VIO (group 3, N=21; 819±572, 523±457, and 1,652±1,240 mL blood loss in group 1, 2, and 3, respectively) (39). Although peak postoperative serum ALT levels were higher in group 1 than in groups 2 and 3 (P=0.02), no differences were found in postoperative mortality and morbidity. It was therefore concluded that continuous VIO could be tolerated for about 50 min in cirrhotic livers. However, considering that 12 patients underwent continuous VIO for >50 min, with a maximum of 75 min, cirrhotic livers can possibly withstand the use of CPM for ≤75 min.

Taken together, these studies show that continuous VIO can be used for a period up to 90 min in uncompromised livers and to at least 50 min in diseased livers without increasing mortality and morbidity rates.

Ischemia times reported using intermittent VIO

It was suggested that intermittent VIO reduces I/R injury and could therefore prolong the tolerable ischemia time (5). Several reports using intermittent VIO in either damaged (i.e., cirrhosis, steatosis, or chronic hepatitis) or uncompromised liver parenchyma are highlighted in the next section and are summarized in *Table 2*. Elias *et al.* started to use IPM routinely since 1987 (18). They retrospectively analyzed 20 patients exposed to intermittent VIO of >90 min in cycles of 20 min of ischemia and 5 min of reperfusion (20/5 min cycle). The mean VIO time was 109 min (range, 90-150 min), with a VIO duration of >140 min in two patients. Postoperative complications occurred in 7 patients (28.7%), which is in line with other reports (4,19,40). Total blood loss was the only parameter that positively correlated with prolonged ischemia times. Thus, it was concluded that intermittent VIO might even be safe for ≤150 min. In 100 patients with non-diseased and pre-damaged livers (i.e., due to cirrhosis or chronic hepatitis) randomized between IPM (N=50) or no VIO (N=50), mortality and morbidity rates were comparable (19). The median ischemia time was 88 min (range, 24-201 min). Total blood loss was lower in the VIO group (median, 1,280 mL; range, 90-8,500 mL) compared with the control group (median, 1,990 mL; range, 260-13,900 mL; P<0.001). It was therefore concluded by the authors that IPM is safe and effective in both compromised and uncompromised livers, but that it should not be applied for >120 min. Subsequently, a group of 12 patients who were operated with cumulative ischemia times of >120 min was compared with this cohort (23). The median ischemia time in this additional group was 134.5 min (range, 123-201 min) and 83 min (range, 24-114 min) in the patients that were randomized to IPM (N=50). A tendency towards lower blood loss was observed for <120 min IPM compared to >120 min IPM [(median, 1,010 mL; range, 230-9,020 mL) *vs.* (median, 2,030 mL; range, 560-9,420 mL), P=0.06)]. No differences were found in terms of mortality and morbidity. Based on these results, it was concluded that IPM can be used safely for 120 min without increasing postoperative mortality and morbidity rates in both non-diseased and diseased livers. IPM of >90 min (15/5 min cycles) was retrospectively evaluated in 34 cases by Ishizaki *et al.* (21). In group 1 (N=25), cumulative VIO duration was 90-120 min and in group 2 (N=9), cumulative VIO duration was >120 min

Table 2 Overview of studies using intermittent VIO

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean ± SD (min)	Longest VIO time (min)	Conclusion
Elias *et al.* 1991 (18)	Diseased [13]†	IPM [20]	109±18	150	Intermittent VIO can be used safely ≤120 min, and might even be safe up to 150 min
	Non-diseased [7]				
Man *et al.* 1997 (19)	Diseased [59]†	IPM [50]	88 (unknown)	201	IPM can be used safely and effectively in both compromised and uncompromised livers, but should not be applied for >120 min
	Non-diseased [41]	No VIO [50]			
Man *et al.* 1999 (23)	Diseased [69]†	IPM >120 min [12]	134.5 (unknown)	201	IPM can be used safely for 120 min without increasing postoperative mortality and morbidity in both non-diseased and diseased livers
		IPM <120 min [50]	83 (unknown)		
	Non-diseased [43]	No VIO [50]			
Ishizaki *et al.* 2006 (21)	Diseased [13]†	IPM >120 min [9]	176.1±68	325	IPM can be used safely for >120 min in difficult cases
	Non-diseased [21]	IPM 90-120 min [25]	99.4±8.4		
Torzilli *et al.* 2012 (24)	Diseased [148]†	IPM >120 min [72]	161±48	348	IPM can be safely used >120 min
	Non-diseased [41]	IPM 60-120 min [117]	86±17		
Wu *et al.* 1996 (27)	Cirrhosis [83]	IPM >80 min [16]	110.5±34.7	204	Carefully selected patients with cirrhotic livers can safely withstand prolonged IPM of >120 min
		IPM 40-80 min [28]	58.3±10.2		
		IPM <40 min [39]	25.5±6.7		

†, chemotherapy-induced liver disease, cirrhosis, or steatosis. VIO, vascular inflow occlusion; IPM, intermittent Pringle maneuver.

(range, 120-325 min). There was less blood loss (mean ± SD) in group 1 (883±461 mL) compared with group 2 (1,409±1,039 mL) (P=0.047). Moreover, lower peak transaminase levels (mean ± SD) were noted for group 1 compared with group 2 [AST: (410±324) *vs.* (966±590) U/L, P=0.001; ALT: (383±350) *vs.* (913±690) U/L, P=0.006], although peak total bilirubin levels were comparable. Additionally, there were no intergroup differences in postoperative mortality or complications. This was confirmed in 189 patients operated with a cumulative IPM time of >60 min (15/5 min cycles), in which underlying cirrhosis or steatosis was seen in 65 and 83 patients, respectively (24). Patients with ischemia times (mean ± SD) of 60-120 min (group 1, 86±17 min, N=117) were compared to patients with ischemia times of >120 min (group 2, 161±48 min, N=72), ranging from 120 to 348 min. Peak levels of AST, ALT, and total bilirubin were all higher in group 2 (P=0.002, P<0.001, P=0.004, respectively), but mortality and morbidity rates were similar. Consequently, it was proposed that IPM can be used for >120 min when absolutely necessary, with a reported maximum VIO duration of 325 to 348 min (21,24).

As stated earlier, cirrhotic livers are more susceptible to I/R injury, which limits the maximum VIO duration in these patients (26). Eighty-three patients with cirrhotic livers who did not have ascites, had a serum bilirubin concentration <3.5 mg/dL, and had an indocyanine green clearance rate of less than 40% were divided into three groups: group 1 with <40 min ischemia (N=39), group 2 with 40-80 min of ischemia (N=28), and group 3 with >80 min of ischemia (range, 84-204 min) (N=16) (27). The mean ± SD cumulative ischemia time was 25.5±6.7, 58.3±10.2, and 110.5±34.7 min in group 1, 2, and 3, respectively. In one patient, a VIO time of 204 min was necessary. Operative blood loss and blood transfusion requirements were higher in group 3 compared to group 1 (P<0.001). Peak AST and ALT levels were also higher in group 3 compared with the other study arms (both P<0.001). Nevertheless, mortality and morbidity rates were comparable between all groups. Accordingly, it was concluded that carefully selected patients with cirrhotic livers can safely withstand prolonged IPM of >120 min, possibly up to a maximum of 204 min.

Based on the abovementioned results, prolonged IPM can be safely used beyond 120 min in uncompromised

Table 3 Overview of studies comparing intermittent VIO with continuous VIO

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean ± SD (min)	Longest VIO time (min)	Conclusion
Belghiti *et al.* 1999 (28)	Diseased [36]†	IPM [44]	46±18	118	IPM is superior to CPM, especially when underlying liver disease is present
	Non-diseased [50]	CPM [42]	41±13	67	
Capussotti *et al.* 2003 (29)	Cirrhosis [35]	IPM [17]	40.4±11.7	65	Both IPM and CPM are effective in reducing blood loss. There is no difference in the severity of hepatic I/R injury between the two techniques
		CPM [18]	35.5±13.9	84	

†, chemotherapy-induced liver disease, cirrhosis, or steatosis. VIO, vascular inflow occlusion; IPM, intermittent Pringle maneuver; CPM, continuous Pringle maneuver; I/R injury, ischemia/reperfusion injury.

livers with a potential maximum duration of 348 min and in thoroughly selected cirrhotic livers with an apparent upper limit of 204 min.

Ischemia times in continuous versus intermittent VIO

Continuous and intermittent VIO have been extensively studied, but few studies have compared the two techniques directly (summarized in *Table 3*). In 1999, IPM (20/5 min cycles, group 1, N=44) was compared with CPM (group 2, N=42) in a randomized clinical trial with a mean duration of VIO of 46 min (range, 20-118 min) and 41 min (range, 16-67 min) in group 1 and 2, respectively (28). Postoperative liver injury markers were similar in both groups, but the correlation between elevation of serum ALT levels and duration of VIO was stronger in group 2 (Pearson's r=0.68, P<0.001) than in group 1 (Pearson's r=0.38, P<0.01). This finding suggests that the liver tolerates IPM better than CPM. The overall incidence of postoperative complications was comparable between both groups (30% in group 1 *vs.* 26% in group 2) although a trend was noted towards a higher incidence of acute liver failure in group 2 (4 patients) *vs.* group 1 (0 patients, P=0.05). All patients who developed acute liver failure had pre-existent liver disease (cirrhosis or steatosis). Therefore, 3 subgroups were compared with respect to the use of IPM and CPM: patients with healthy livers (group 1, N=50), patients with steatotic livers (group 2, N=11, >20% steatosis), and patients with cirrhotic livers (group 3, N=25). In group 2, the lowest peak prothrombin time was seen following IPM. The use of CPM resulted in significantly higher serum ALT levels in groups 2 and 3 compared with IPM (both P<0.05). Higher bilirubin levels in group 3 were found for CPM compared to IPM (P<0.05). The authors therefore concluded that IPM is superior to CPM in terms of parenchymal tolerance to ischemia, especially when underlying liver disease was present. This was however not confirmed in a study with 35 cirrhotic patients comparing IPM (15/5 min cycles) (group 1, N=17) with CPM (group 2, N=18) (29). Only patients aged <75 years with hepatocellular carcinoma and Child Pugh Score A were included. The mean ± SD VIO time was 40.4±1.7 min (range, 20-65 min) and 35.5±13.9 min (range, 16-84 min) in group 1 and 2, respectively. Postoperative complications and mortality were similar (P=0.2 and P=0.1, respectively). When VIO duration was compared (<30 *vs.* >30 min) instead of VIO technique, patients with >30 min developed more complications (N=8 *vs.* N=0, P=0.02). No differences were found in postoperative AST, ALT, prothrombin time, or bilirubin levels. Because approximately 75% of the patients did not receive blood transfusions, it was concluded that both techniques were effective in reducing blood loss and that there was no difference in the severity of hepatic I/R injury. This fueled the discussion that IPM might not be necessary in the cirrhotic liver for ischemia times of up to 60 min.

The effects of prolonged IPM and CPM on hepatic I/R injury were also investigated in two animal models (results are summarized in *Table 4*) (41,42). In swine, 120 min of IPM (12/3 min cycles) was better tolerated than 120 min of CPM (41). Sinusoidal endothelial cell function, reflected by the ability to clear hyaluronic acid from the circulation, was superior in the IPM group. Corroboratively, the extent of hepatocellular necrosis at 6 h of reperfusion was higher in the CPM group. Similar results were obtained in rat models of IPM and CPM (42). Three VIO regimens were compared: IPM in 15/5 min cycle (group 1), IPM in 30/5 min cycle (group 2), and CPM (group 3). Three

Table 4 Overview of preclinical studies comparing intermittent VIO with continuous VIO

Author, year (reference)	Animal	Groups compared [N]	VIO time (min)	Results	Conclusion
van Wagensveld *et al.* 1999 (41)	Pig	IPM [6]	120	More hepatocellular necrosis in CPM after 6 h of reperfusion	IPM is superior to CPM when prolonged VIO (120 min) is required
		CPM [6]	120	Better sinusoidal endothelial cell function in IPM group	
Chiappa *et al.* 2001 (42)	Rat	IPM, 15/5 min cycle	60, 90, 120	Higher survival in IPM groups after 120 min VIO	IPM allows longer VIO durations than CPM and therefore is the preferred technique for complex hepatectomies
		IPM, 30/5 min cycle	60, 90, 120	Lower AST and ALT serum levels on POD 1 in IPM groups after 90 or 120 min of VIO	
		CPM	60, 90, 120		

VIO, vascular inflow occlusion; IPM, intermittent Pringle maneuver; CPM, continuous Pringle maneuver; AST, aspartate aminotransferase; ALT, alanine aminotransferase; POD, post-operative day.

different cumulative ischemia times were compared: 60, 90, and 120 min. Survival rates were similar up to 90 min of ischemia. When VIO time was prolonged to 120 min, however, survival was better using IPM (70%, 70%, and 20% in group 1, 2, and 3 respectively, group 1 or group 2 *vs.* group 3, P<0.05). Serum AST and ALT levels were significantly lower on post-operative day 1 following IPM, irrespective of the employed IPM regimen, compared with CPM for both 90 and 120 min of ischemia (P<0.05 for group 1 or group 2 *vs.* group 3). There were no intergroup differences noted when VIO periods of 60 min were compared.

Although the differences are generally small and mostly seen in serum transaminase levels in contrast to mortality and morbidity rates, IPM seems to be better tolerated than CPM in both uncompromised and compromised livers, especially when prolonged ischemia times (>60 min) are necessary.

Ischemia times with IP followed by continuous VIO

IP was first clinically tested by Clavien *et al.* in 1999 in 24 patients undergoing major hepatectomy (35). After that, it became a topic of interest in liver surgery, of which several studies are discussed (also see *Table 5*). Using a standardized CPM regimen of 30 min, Clavien *et al.* found lower post-operative serum ALT and AST levels in the 12 patients who received IP with CPM (IP-CPM) compared with the 12 patients who received CPM alone (35). This effect was even more pronounced in a small subgroup of patients with steatosis. In a subsequent randomized trial, 100 patients were randomized between IP-CPM (group 1, N=50) or CPM alone (group 2, N=50) (43). Peak ALT and AST levels were lower in group 1 (406 *vs.* 519 U/L and 364 *vs.* 520 U/L, P=0.049 and P=0.028, respectively), although mortality and morbidity rates were comparable. Ischemia times of <60 min were associated with better outcomes in group 1. Based on a small subgroup analysis (N=13), it was additionally claimed that steatotic livers benefited more from IP than healthy livers. This was evidenced by the considerable reduction in peak transaminase levels seen in fatty livers treated with IP compared to those subjected to CPM alone (363 *vs.* 602 U/L, respectively, P=0.049). Guided by these results, IP could be mostly beneficial in ischemia times of ≤60 min. Another study found lower serum AST levels on postoperative day 1 in patients operated with IP-CPM (N=21) than in patients operated with CPM only (N=21), despite the fact that these patients were subjected to longer ischemia times [(54±19) *vs.* (36±14) min in IP-CPM and CPM, respectively, P=0.001] (44). It is unclear whether the 10 min of IP were added to the cumulative duration of ischemia, but despite this, IP imparted a protective effect given the lower serum AST levels found. One study comparing IP followed by SHVE (group 1, N=30) to

Table 5 Overview of studies comparing ischemic preconditioning followed by continuous VIO with continuous VIO only

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean ± SD (min)	Longest VIO time (min)	Conclusion
Clavien *et al.* 2000 (35)	Steatosis [7]	IP-CPM [12]	30	30	IP-CPM seems to have a beneficial effect over CPM only
	Non-diseased [13]	CPM [12]	30		
Clavien *et al.* 2003 (43)	Steatosis [13]	IP-CPM [50]	36±5.9	60	IP-CPM seems superior to CPM for VIO durations of <60 min in healthy livers
	Non-diseased [87]	CPM [50]	35±6.8		
Nuzzo *et al.* 2004 (44)	Non-diseased [42]	IP-CPM [21]	54±19	110	IP imparts a protective effect in non-diseased livers despite the longer cumulative VIO time
		IPM [21]	36±14*	70	
Azoulay *et al.* 2006 (45)	Diseased [13]†	IP-SHVE [30]	44.5±9.2	67	IP does not reduce I/R injury and has no effect on clinical outcomes when used prior to SHVE
	Non-diseased [47]	SHVE [30]	47.7±8.3		
Heizmann *et al.* 2008 (46)	Steatosis (unspecified)	IP-CPM [30]	34±14	82	IP-CPM shows benefits over CPM only in routine liver surgery
	Non-diseased (unspecified)	CPM [31]	33±12	67	
Arkadopoulos *et al.* 2009 (47)	Non-diseased [84]	IP-SHVE [41]	42±11	Unknown	IP prior to SHVE shows a protective effect in non-diseased livers
		SHVE [43]	42±10		

†, chemotherapy-induced liver disease, cirrhosis, or steatosis; *, lower duration of VIO, P<0.05. VIO, vascular inflow occlusion; IP-CPM, ischemic preconditioning followed by continuous Pringle maneuver; CPM, continuous Pringle maneuver; SHVE, selective hepatic vascular exclusion; IP-SHVE, ischemic preconditioning followed by selective hepatic vascular exclusion; I/R injury, ischemia/reperfusion injury.

SHVE only (group 2, N=30) during major hepatectomies with similar VIO durations [44.5±9.2 min (group 1) and 47.7±8.3 min (group 2), P=0.2], found comparable peak post-operative (mean ± SD, group 1 *vs.* group 2) serum AST [(851±1,733) *vs.* (427±166) U/L, P=0.2], ALT [(717±995) *vs.* (403±200) U/L, P=0.1], and bilirubin [(63.0±60.0) *vs.* (81.2±71.0) µmol/L, P=0.3] levels, as were the severity and number of complications (45). Better clinical outcomes were seen, however, in a randomized controlled trial comparing IP-CPM (group 1, N=30) with CPM alone (group 2, N=31) (46). Specifically, there was reduced (mean ± SD) blood loss [(1,280±910) *vs.* (1,940±760) mL, P=0.001], a lower transfusion incidence (17% *vs.* 48% of patients, P=0.006), and a lower complication rate (20% *vs.* 45% overall complications, P=0.04) in group 1. Serum ALT and bilirubin levels did not differ between the two groups during the first postoperative week. In a trial in which 84 patients were randomly assigned to IP (10 min ischemia, 15 min of reperfusion) followed by SHVE (group 1, N=41) or SHVE alone (group 2, N=43), post-operative (day 1; mean ± SD, group 1 *vs.* group 2) levels of AST [(288±140) *vs.* (498±255) U/L, P<0.05] as well as the cytokines IL-6 [(177±88) *vs.* (325±198) pg/dL, P<0.05] and IL-8 [(219±112) *vs.* (369±187) pg/dL, P<0.05] levels were lower in group 1 (47). Mean ± SD VIO duration was similar in group 1 (42±11 min) and group 2 (42±10 min), implying that IP prior to SHVE effectively attenuated I/R injury. In liver biopsies taken at 1 h of reperfusion, the number of apoptotic cells was lower in group 1, further highlighting the protective effect of IP.

All studies discussed above applied IP prior to a period of continuous VIO of <60 min. The protective effect of IP before prolonged (>60 min) ischemia has only been investigated in animal models (summarized in *Table 6*) (13,48,49). One study assigned 24 pigs to undergo partial liver resection (65%) with IP (10 min ischemia, 10 min reperfusion) followed by 90 (N=6, group 1) or 120 (N=6, group 2) min of CPM either 90 (N=6, group 3) or 120 (N=6, group 4) min IPM only (48). Plasma AST and oxidative stress metabolite (i.e., malondialdehyde) levels were lower when IP followed by CPM was compared to IPM only following 90 min of ischemia. However, there

Table 6 Overview of preclinical studies comparing ischemic preconditioning followed by continuous VIO with intermittent VIO or continuous VIO only

Author, year (reference)	Animal	Groups compared [N]	Results	Conclusion
Smyrniotis *et al.* 2005, (48)	Pig	IP-CPM 90 min [6]	90 min of VIO: lower levels serum AST in IP-CPM	IP-CPM is superior to IPM when VIO duration is ≤90 min
		IP-CPM 120 min [6]	120 min of VIO: lower levels serum AST in IPM	
		IPM 90 min [6]		
		IPM 120 min [6]		
Rüdiger *et al.* 2002, (13)	Mouse	IP-CPM 75 min [5]	IP-CPM after 75 min of VIO is superior to CPM (100% *vs.* 0% survival)	IP-CPM yields better results than CPM only following 75 min of VIO
		IP-CPM 120 min [5]		
		IPM 75 min [5]		
		IPM 120 min [5]	IPM is superior to IP-CPM after 120 min of VIO (71% *vs.* 14% survival)	IPM is superior to IP-CPM following prolonged (120 min) VIO
		CPM 75 min [5]		
		CPM 120 min [5]		
Seyama *et al.* 2013, (49)	Rat	IPM, 15/5 min cycle [8]	Lower level serum ALT in IPM groups and less necrosis at 3 h reperfusion	IPM is better tolerated than IP-CPM or CPM when VIO is 60 min
		IPM, 10/3.3 min cycle [8]		
		IPM, 5/1.7 min cycle [8]		
		IP-CPM [8]	No differences between IPM groups individually and between IP-CPM and CPM	
		CPM [8]		

VIO, vascular inflow occlusion; IP-CPM, ischemic preconditioning followed by continuous Pringle maneuver; IPM, intermittent Pringle maneuver; CPM, continuous Pringle maneuver; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

was no intergroup difference with respect to the extent of hepatocellular necrosis. When the ischemic insult was extended to 120 min, IPM proved superior to IP-CPM in terms of AST release, plasma malondialdehyde levels, and histological necrosis score. IP-CPM therefore appears more beneficial when the VIO duration does not exceed 90 min, whereas IPM seems preferred when VIO is extended to 120 min. The same conclusions were drawn based on a mouse model comparing IP followed by CPM (group 1), IPM only (group 2), and CPM only (group 3) for VIO times of 75 and 120 min (13). IP-CPM is protective up to 75 min, which was evidenced by the 100% survival 3 days after surgery in groups 1 and 2 *vs.* 0% survival in group 3. When ischemia times were extended to 120 min, a survival rate of only 14% was seen in group 1 *vs.* 71.4% in group 2, and 0% in group 3, indicating that IPM offers the best results when prolonged VIO is required. These results are supported by a study by Seyama *et al.* (49), in which the severity of hepatic I/R injury was evaluated as a function of five different VIO regimens in rats. Three groups underwent different cycles of IPM [4 15/5 min cycles (group 1), 6 10/3.3 min cycles (group 2), or 12 5/1.7 min cycles (group 3)]. In addition, group 4 received 10 min of IP followed by 60 min CPM and group 5 was subjected to 60 min CPM only. The IPM groups all showed lower ALT levels and less hepatocellular necrosis at 3 h of reperfusion compared with the CPM groups (groups 4 and 5). There were no differences in liver injury when individually comparing the 2 CPM groups (groups 4 and 5) or the 3 IPM groups (groups 1-3). IPM therefore seems better tolerated by the liver than IP-CPM or CPM alone when ischemia times exceed 60 min.

Table 7 Overview of studies comparing ischemic preconditioning followed by intermittent VIO with intermittent VIO only

Author, year (reference)	Parenchymal status [N]	Groups compared [N]	VIO time, mean ± SD (min)	Longest VIO time (min)	Conclusion
Scatton *et al.* 2011, (50)	Non-diseased	IP-IPM [41]	45.0±19.6	96	IP-IPM shows no clinical benefit and should not be preferred over IPM only
		IPM [43]	52.4±27.7	157	
Winbladh *et al.* 2012, (51)	Diseased [5]†	IP-IPM major [8]‡	35±11	Unknown	The therapeutic value of IP-IPM is questionable
		IPM major [8]‡	44±8		
	Non-diseased [27]	IP-IPM minor [8]§	44±10		
		IPM minor [8]§	44±13		

†, chemotherapy-induced liver disease, cirrhosis, or steatosis; ‡, major hepatectomy (≥3 segments according to Couinaud); §, minor hepatectomy (≤2 segments according to Couinaud). VIO, vascular inflow occlusion; IP-IPM, ischemic preconditioning followed by intermittent Pringle maneuver; IPM, intermittent Pringle maneuver.

Taken together, IP-CPM seems to aggravate I/R injury when ischemic intervals of more than 75 min are used. However, IP may improve post-operative outcomes when applied before a shorter (<75 min) period of continuous VIO.

Ischemia times in IP followed by intermittent VIO

In addition to IP before CPM, two clinical studies also compared the effect of IP (10 min ischemia, 10 min reperfusion) followed by IPM (IP-IPM) to IPM alone (also see *Table 7*) (50,51). One study randomly assigned 84 patients to either IP-IPM (group 1) or IPM (group 2) (50). Ischemia times (mean ± SD) were similar in both study arms (45.0±19.6 and 52.4±27.7 min, respectively). Moreover, there were no differences in the number as well as the severity of postoperative complications or hepatocellular injury markers (e.g., ALT). The second study evaluated the clinical feasibility of IP-IPM (51), postulating that the additional 20 min operating time inherent to IP should be avoided when the therapeutic efficacy of IP-IPM is subpar. Thirty-two patients were therefore divided into 2 experimental groups (N=16/group) based on the planned resection (i.e., major or minor liver resection). Thereafter, each group was randomly divided into 2 groups, receiving either IP-IPM or IPM alone, resulting in 4 groups (N=8/study arm). Microdialysis analysis showed that IP-IPM reduced the hepatic glycogenic activity and lactate formation during and directly after surgery, suggesting that IP alleviated the ischemia-induced metabolic perturbations seen in the IPM-only groups. However, since clinical outcome parameters such as serum liver injury markers (AST, ALT), serum liver function markers (bilirubin, prothrombin time), and postoperative complications were similar amongst all experimental groups, the therapeutic value of IP-IPM remains questionable.

Discussion

Hepatic I/R injury is still a main concern in liver surgery and a balance between blood loss and I/R injury must be established for every liver resection. VIO effectively reduces blood loss (6) yet induces I/R injury when used for prolonged periods (10,11,14,52,53). In light of this critical trade-off, there is still uncertainty on the maximal duration of VIO that the liver can withstand. This debate is sparked by multiple reports on the safe use of ischemia times of >300 min (20,22,24).

Cirrhotic livers seem to benefit more from IPM. Wu *et al.* (27) performed liver resections in cirrhotic livers using intermittent VIO up to 204 min, whereas Kim *et al.* (39) reported a maximum of 75 min of continuous VIO in cirrhotic patients. Despite that Capussotti *et al.* (29) did not find any differences in clinical outcomes between intermittent and continuous VIO in cirrhotic patients, evidence from animal studies suggests that intermittent VIO in a 15/5 min cycle provides the best protection against hepatocellular injury when the total ischemia time is 60 min (54).

Intermittent VIO has a complication rate that is comparable to continuous VIO (28). The highest complication rates are seen with >60 min of ischemia.

Studies presenting data using continuous VIO report a complication rate of 53-56% (25,37). When IPM was used, complications were seen in 20-65% of patients (18,21,24). A recent systematic review, however, indicated that the complication rate was similar for intermittent and continuous VIO *vs.* no VIO (6). However, no comparison was made between studies with ischemia times of >60 or <60 min, so a meta-analysis should be performed to assess whether intermittent or continuous VIO is preferred for prolonged ischemia times.

Another possibility to decrease I/R injury is IP, which was first described by Clavien *et al.* (35) and was shown to attenuate surgery-induced liver injury in several randomized clinical trials (43,46). In spite of these beneficial effects, combining IP with VIO durations of >60 min seems to be hazardous (13,48) and it is therefore advised to only use IP when parenchymal transection is expected to last <60 min.

Diseased (e.g., cirrhotic or steatotic) livers seem to benefit more from IP than livers with uncompromised parenchyma (55). The ischemia times used in the latter study, however, were extremely short (<20 min). In cirrhotic mice, a protective effect was noted for ischemia times of up to 60 min compared with CPM alone (56). IP has a protective effect before CPM in pre-damaged livers, but should not be used when ischemia times are >60 min.

VIO might lose ground in liver surgery, as some large centers reported using the Pringle maneuver in only 17% of liver resections since 1999 as well as a 35% decrease in its use compared to before 1999 (57). Although 17% is exceptionally low when compared with other studies performed in the last decade (58-60), the routine use of VIO may be omitted in the future. One should, however, note that bleeding complications can occur, in which case the use of VIO is an important tool in order to regain hemodynamic control. VIO will therefore always have a role in liver surgery, although one should always be aware of the consequences of prolonged ischemia. Further evaluation of the pathophysiology of I/R injury and its consequences therefore remains important (61,62), as well as the development of better interventional strategies (53).

There moreover seem to be no strict limitations regarding the duration of ischemia in healthy livers, for ischemia times of more than 300 min have been reported (20-22). Considering that only 3 patients have been exposed to VIO durations of such caliber, it is however difficult to draw definitive conclusions from these reports. These results are nevertheless promising in view of the ongoing progress in hepatic surgery. Furthermore, these data should be kept in mind when complex hepatic resections are planned and one should not withhold immediately when ischemia times of >120 min are expected during hepatectomies.

To establish the upper limit of hepatic ischemia, more data should be obtained from prolonged ischemia periods in the clinical setting. Since most hepatectomies can be performed within 30-40 min of VIO, it is not feasible to derive these data from randomized controlled trials. The maximum duration of VIO will therefore likely be determined based on case reports and small retrospective studies.

Overall conclusions

Prolonged (≥60 min) hepatic VIO (38) can be safely applied using both continuous and intermittent VIO regimens. The latter showed a benefit in terms of intra-operative blood loss and blood transfusion requirements, but did not reduce mortality and morbidity rates (6). Intermittent VIO can safely be applied for >120 min in healthy livers and may even be extended to 300 min when absolutely necessary. In well-selected cirrhotic livers, a cumulative ischemia time of 120 min is considered safe, with an upper limit of at least 200 min. Considering that most parenchymal transections can be completed within 30-40 min, clamping of the hepatic pedicle therefore does not appear to cause additional harm to the liver remnant.

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Footnote

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References

1. Pringle JH. V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. Ann Surg 1908;48:541-9.
2. Huguet C, Nordlinger B, Bloch P, et al. Tolerance of the human liver to prolonged normothermic ischemia. A biological study of 20 patients submitted to extensive hepatectomy. Arch Surg 1978;113:1448-51.
3. Huguet C, Nordlinger B, Galopin J, et al. Normothermic hepatic vascular exclusion for extensive hepatectomy. Surg Gynecol Obstet 1978;147:689-93.

4. Delva E, Camus Y, Nordlinger B, et al. Vascular Occlusion for Liver Resections. Operative management and tolerance to hepatic ischemia: 142 Cases. Ann Surg 1989;209:211-8.
5. Makuuchi M, Mori T, Gunvén P, et al. Safety of hemihepatic vascular occlusion during resection of the liver. Surg Gynecol Obstet 1987;164:155-8.
6. Gurusamy KS, Kumar Y, Ramamoorthy R, et al. Vascular occlusion for elective liver resections. Cochrane Database Syst Rev 2009;(1):CD007530.
7. Asahara T, Katayama K, Itamoto T, et al. Perioperative blood transfusion as a prognostic indicator in patients with hepatocellular carcinoma. World J Surg 1999;23:676-80.
8. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406.
9. Sitzmann JV, Greene PS. Perioperative predictors of morbidity following hepatic resection for neoplasm. A multivariate analysis of a single surgeon experience with 105 patients. Ann Surg 1994;219:13-7.
10. van Golen RF, van Gulik TM, Heger M. The sterile immune response during hepatic ischemia/reperfusion. Cytokine Growth Factor Rev 2012;23:69-84.
11. Reiniers MJ, van Golen RF, van Gulik TM, et al. Reactive Oxygen and Nitrogen Species in Steatotic Hepatocytes: A Molecular Perspective on the Pathophysiology of Ischemia-Reperfusion Injury in the Fatty Liver. Antioxid Redox Signal 2014;21:1119-42.
12. van Golen RF, Reiniers MJ, Vrisekoop N, et al. The mechanisms and physiological relevance of glycocalyx degradation in hepatic ischemia/reperfusion injury. Antioxid Redox Signal 2014;21:1098-118.
13. Rüdiger HA, Kang KJ, Sindram D, et al. Comparison of ischemic preconditioning and intermittent and continuous inflow occlusion in the murine liver. Ann Surg 2002;235:400-7.
14. van Golen RF, Reiniers MJ, Heger M, et al. Solutions to the discrepancies in the extent of liver damage following ischemia/reperfusion in standard mouse models. J Hepatol 2015;62:975-7.
15. Veteläinen R, van Vliet A, Gouma DJ, et al. Steatosis as a risk factor in liver surgery. Ann Surg 2007;245:20-30.
16. Kim YI. Ischemia-reperfusion injury of the human liver during hepatic resection. J Hepatobiliary Pancreat Surg 2003;10:195-9.
17. Delva E, Camus Y, Paugam C, et al. Hemodynamic Effects of Portal Triad Clamping in Humans. Anesth Analg 1987;66:864-8.
18. Elias D, Desruennes E, Lasser P. Prolonged intermittent clamping of the portal triad during hepatectomy. Br J Surg 1991;78:42-4.
19. Man K, Fan ST, Ng IO, et al. Prospective evaluation of Pringle maneuver in hepatectomy for liver tumors by a randomized study. Ann Surg 1997;226:704-11.
20. Sakamoto Y, Makuuchi M, Takayama T, et al. Pringle maneuver lasting 322 min. Hepatogastroenterology 1999;46:457-8.
21. Ishizaki Y, Yoshimoto J, Miwa K, et al. Safety of prolonged intermittent pringle maneuver during hepatic resection. Arch Surg 2006;141:649-53.
22. Procopio F, Torzilli G. Forty-nine colorectal cancer liver metastases in one-stage hepatectomy with cumulative Pringle time lasting 348 min. Updates Surg 2012;64:241-3.
23. Man K, Fan ST, Ng IO, et al. Tolerance of the liver to intermittent pringle maneuver in hepatectomy for liver tumors. Arch Surg 1999;134:533-9.
24. Torzilli G, Procopio F, Donadon M, et al. Safety of intermittent Pringle maneuver cumulative time exceeding 120 minutes in liver resection: a further step in favor of the "radical but conservative" policy. Ann Surg 2012;255:270-80.
25. Hannoun L, Borie D, Delva E, et al. Liver resection with normothermic ischemia exceeding 1 h. Br J Surg 1993;80:1161-5.
26. Nishimura T, Nakahara M, Kobayashi S, et al. Ischemic injury in cirrhotic livers: an experimental study of the temporary arrest of hepatic circulation. J Surg Res 1992;53:227-33.
27. Wu CC, Hwang CR, Liu TJ, et al. Effects and limitations of prolonged intermittent ischaemia for hepatic resection of the cirrhotic liver. Br J Surg 1996;83:121-4.
28. Belghiti J, Noun R, Malafosse R, et al. Continuous Versus Intermittent Portal Triad Clamping for Liver Resection. Ann Surg 1999;229:369-75.
29. Capussotti L, Nuzzo G, Polastri R, et al. Continuous versus intermittent portal triad clamping during hepatectomy in cirrhosis. Results of a prospective, randomized clinical trial. Hepatogastroenterology 2003;50:1073-7.
30. van Gulik TM, de Graaf W, Dinant S, et al. Vascular occlusion techniques during liver resection. Dig Surg 2007;24:274-81.
31. Lau WY, Lai EC, Lau SH. Methods of vascular control technique during liver resection: a comprehensive review. Hepatobiliary Pancreat Dis Int 2010;9:473-81.

32. Huguet C, Addario-Chieco P, Gavelli A, et al. Technique of hepatic vascular exclusion for extensive liver resection. Am J Surg 1992;163:602-5.
33. Smyrniotis V, Farantos C, Kostopanagiotou G, et al. Vascular control during hepatectomy: review of methods and results. World J Surg 2005;29:1384-96.
34. Cherqui D, Malassagne B, Colau P, et al. Hepatic Vascular Exclusion With Preservation of the Caval Flow for Liver Resections. Ann Surg 1999;230:24-30.
35. Clavien PA, Yadav S, Sindram D, et al. Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans. Ann Surg 2000;232:155-62.
36. Boyko VV, Pisetska ME, Tyshchenko OM, et al. Role of ischemic preconditioning in hepatic ischemia-reperfusion injury. Hepatobiliary Surg Nutr 2014;3:179-84.
37. Huguet C, Gavelli A, Addario Chieco P, et al. Liver ischemia for hepatic resection: where is the limit? Surgery 1992;111:251-9.
38. Huguet C, Gavelli A, Bona S. Hepatic resection with ischemia of the liver exceeding one hour. J Am Coll Surg 1994;178:454-8.
39. Kim YI, Nakashima K, Tada I, et al. Prolonged normothermic ischaemia of human cirrhotic liver during hepatectomy: a preliminary report. Br J Surg 1993;80:1566-70.
40. Capussotti L, Muratore A, Ferrero A, et al. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. Br J Surg 2006;93:685-9.
41. van Wagensveld BA, van Gulik TM, Gelderblom HC, et al. Prolonged continuous or intermittent vascular inflow occlusion during hemihepatectomy in pigs. Ann Surg 1999;229:376-84.
42. Chiappa A, Makuuchi M, Zbar A, et al. Comparison of continuous versus intermittent hepatic pedicle clamping in an experimental model. Hepatogastroenterology 2001;48:1416-20.
43. Clavien PA, Selzner M, Rüdiger HA, et al. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. Ann Surg 2003;238:843-50.
44. Nuzzo G, Giuliante F, Vellone M, et al. Pedicle clamping with ischemic preconditioning in liver resection. Liver Transpl 2004;10:S53-7.
45. Azoulay D, Lucidi V, Andreani P, et al. Ischemic preconditioning for major liver resection under vascular exclusion of the liver preserving the caval flow: a randomized prospective study. J Am Coll Surg 2006;202:203-11.
46. Heizmann O, Loehe F, Volk A, et al. Ischemic preconditioning improves postopeartive outcome after liver resections: A randomized controlled study. Eur J Med Res 2008;13:79-86.
47. Arkadopoulos N, Kostopanagiotou G, Theodoraki K, et al. Ischemic preconditioning confers antiapoptotic protection during major hepatectomies performed under combined inflow and outflow exclusion of the liver. A randomized clinical trial. World J Surg 2009;33:1909-15.
48. Smyrniotis V, Kostopanagiotou G, Theodoraki K, et al. Ischemic preconditioning versus intermittent vascular inflow control during major liver resection in pigs. World J Surg 2005;29:930-4.
49. Seyama Y, Imamura H, Inagaki Y, et al. Intermittent clamping is superior to ischemic preconditioning and its effect is more marked with shorter clamping cycles in the rat liver. J Gastroenterol 2013;48:115-24.
50. Scatton O, Zalinski S, Jegou D, et al. Randomized clinical trial of ischaemic preconditioning in major liver resection with intermittent Pringle manoeuvre. Br J Surg 2011;98:1236-43.
51. Winbladh A, Björnsson B, Trulsson L, et al. Ischemic preconditioning prior to intermittent Pringle maneuver in liver resections. J Hepatobiliary Pancreat Sci 2012;19:159-70.
52. Bhogal RH, Curbishley SM, Weston CJ, et al. Reactive Oxygen Species Mediate Human Hepatocyte Injury During Hypoxia / Reoxygenation. Liver transpl 2010;16:1303-13.
53. van Golen RF, Reiniers MJ, Olthof PB, et al. Sterile inflammation in hepatic ischemia/reperfusion injury: present concepts and potential therapeutics. J Gastroenterol Hepatol 2013;28:394-400.
54. Lei DX, Peng CH, Peng SY, et al. Safe upper limit of intermittent hepatic inflow occlusion for liver resection in cirrhotic rats. World J Gastroenterol 2001;7:713-7.
55. Li SQ, Liang LJ, Huang JF, et al. Ischemic preconditioning protects liver from hepatectomy under hepatic inflow occlusion for hepatocellular carcinoma patients with cirrhosis. World J Gastroenterol 2004;10:2580-4.
56. Jang JH, Kang KJ, Kang Y, et al. Ischemic preconditioning and intermittent clamping confer protection against ischemic injury in the cirrhotic mouse liver. Liver Transpl 2008;14:980-8.
57. Fan ST, Mau Lo C, Poon RTP, et al. Continuous

improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg 2011;253:745-58.
58. Weiss MJ, Ito H, Araujo RLC, et al. Hepatic pedicle clamping during hepatic resection for colorectal liver metastases: no impact on survival or hepatic recurrence. Ann Surg Oncol 2013;20:285-94.
59. Millet G, Truant S, Leteurtre E, et al. Volumetric analysis of remnant liver regeneration after major hepatectomy in bevacizumab-treated patients: a case-matched study in 82 patients. Ann Surg 2012;256:755-61; discussion 761-2.
60. Nobili C, Marzano E, Oussoultzoglou E, et al. Multivariate analysis of risk factors for pulmonary complications after hepatic resection. Ann Surg 2012;255:540-50.
61. van Golen RF, Reiniers MJ, van Gulik TM, et al. Organ cooling in liver transplantation and resection: how low should we go? Hepatology 2015;61:395-9.
62. Heger M, Reiniers MJ, van Golen R. Mitochondrial Metabolomics Unravel the Primordial Trigger of Ischemia/Reperfusion Injury. Gastroenterology 2015;148:1071-3.

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Hepatic Surgical Technique

Liver resection using total vascular exclusion of the liver preserving the caval flow, *in situ* hypothermic portal perfusion and temporary porta-caval shunt: a new technique for central tumors

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Abstract: Standard total vascular exclusion (TVE) of the liver is indicated for resection of tumors involving or adjacent to the vena cava and/or the confluence of the hepatic veins. The duration of liver ischemia can be prolonged by combined portal hypothermic perfusion of the liver (*in* or *ex situ*). The use of a venovenous bypass (VVB) during standard TVE maintains stable hemodynamics as well as optimal renal and splanchnic venous drainage. When the hepatic veins can be controlled, TVE preserving the caval flow negates the need for VVB. However this technique remains limited in duration as it is performed under warm ischemia (so-called normothermia) of the liver. To prolong the ischemia time, we have designed a modification of TVE with preservation of the caval flow including the use of temporary porta-caval shunt (PCS) and hypothermic perfusion of the liver. We describe here the first two cases of this new technique. Two patients underwent left hepatectomy extended to segments 5 and 8 (also called extended left hepatectomy) for large centrally located tumors. TVE lasted seventy-two and seventy-nine minutes, respectively. The postoperative course was uneventful and both patients were discharged on day ten and day twenty-five respectively. Both are alive without recurrence at ten and seven months following surgery. Provided the roots of the hepatic veins can be controlled, this technique combines the advantages of standard TVE with *in situ* hypothermic perfusion and VVB and obviates the need and the subsequent risks of the latter.

Keywords: Total vascular exclusion (TVE); hypothermic perfusion; porta-caval shunt (PCS); venovenous bypass (VVB)

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Background

Standard total vascular exclusion (standard TVE) of the liver includes clamping of the portal triad and the vena cava below and above the liver (1). It is indicated for the resection of tumors involving or adjacent to the vena cava and/or to the confluence of the hepatic veins.

With portal hypothermic perfusion, the duration of TVE can be prolonged to up to several hours (2,3). In the vast majority of cases of standard TVE with hypothermic perfusion of the liver, a venovenous bypass (VVB) is installed (usually cavo-porto jugular) to maintain stable hemodynamics and prevent kidneys and splanchnic venous congestion. Some centrally located tumors with intimate contact with larges branches of the hepatic veins but still not invading their roots into the inferior vena cava need TVE to be resected safely. In this situation it is possible to perform the resection under TVE while preserving the caval flow by clamping the portal pedicle and the hepatic veins extra-hepatically (4). This technique obviates both the detrimental hemodynamic effects and the kidneys venous congestion of standard TVE. However, as for the latter, it is limited in duration and it is associated with splanchnic

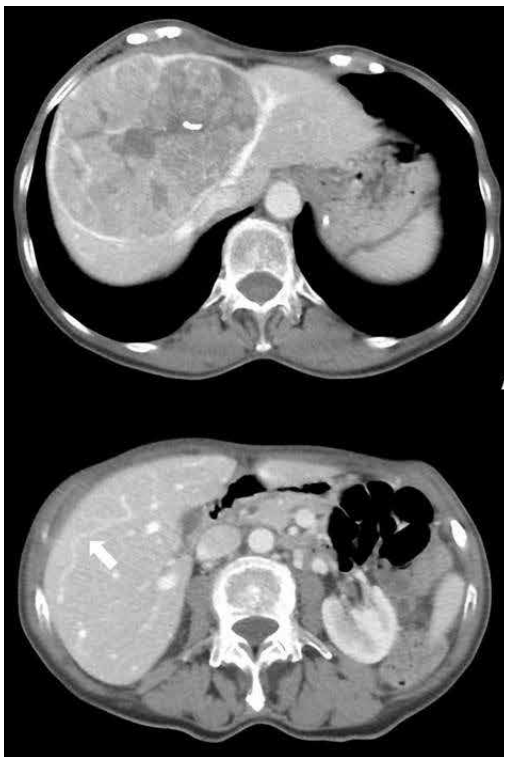

Figure 1 Preoperative CT revealed a huge tumor that involves the left and middle hepatic veins below their common root into the vena cava (case 1), and the presence of a communicating vein (white arrow) between the middle and the right hepatic veins.

congestion due to portal clamping. We report here the two first cases of a new technique of TVE with a temporary porta-caval shunt (PCS) and *in situ* portal hypothermic perfusion of the liver. In these cases the use of VVB and its subsequent risks are obviated.

Methods

Case 1

A 72-year-old female underwent a left hepatectomy extended to segments 5 and 8 for a huge (13 cm) hepatocellular carcinoma (HCC) located in segments 4, 5 and 8 of the liver and involving the left and middle hepatic veins below their common root into the vena cava. Tumor and non-tumor liver biopsies confirmed the diagnosis of HCC and normal underlying liver parenchyma, respectively. The liver and kidney function tests were normal. Alpha fetoprotein serum level (AFP) was 1,904 ng/mL. The remnant liver to body weight ratio was 0.88 on computed tomography (CT) volumetry. In addition, CT scan showed the presence of large intra-parenchyma hepatic veins collateral circulation between the middle and the right hepatic vein territory (*Figure 1*). The TVE was predicted to last potentially longer than 60 minutes and therefore the patient had TVE of the liver with *in situ* hypothermic portal perfusion with the technique described below.

Surgery was accomplished through a bilateral subcostal abdominal incision with upper midline extension. The liver attachments and the left branch of the hepatic artery and the portal vein were divided. The proximal stump of the divided left portal vein, sufficiently long in this case, was anastomosed end-to-side to the infra-hepatic vena cava. The common trunk of the left and middle hepatic veins was stapled. All minor hepatic veins as well as the hepatocaval ligament were ligated and divided. The main bile duct, the proper hepatic artery, the right portal vein above the PCS and the right hepatic vein were then clamped. The right portal vein was catheterized above the portal clamp and University of Wisconsin solution chilled at 4 ℃ was used for hypothermic perfusion of the liver (2 L were perfused). A venotomy was made immediately below the clamp on the right hepatic vein to drain the perfusate.

The liver temperature (3) dropped to a minimum of 17 ℃. The transection of the liver was completed with ultrasonic dissector to the left of the right hepatic vein leaving the segments 6 and 7 intact. The liver was then flushed with 500 mL of serum albumin via the portal vein. The portal cannula was removed. Perfusate inflow and outflow incisions were sutured transversally to prevent stenosis with interrupted nonabsorbable sutures and the PCS was divided and closed. The total ischemia time was 72 minutes. The patient received 7 units of packed red blood cells and 5 units of fresh frozen plasma. The weight of the specimen was 964 grams. Histopathological examination showed a huge, well differentiated, encapsulated HCC with macrovascular invasion of the middle hepatic vein and a R0 resection margin. The postoperative course was uneventful and the patient was discharged on postoperative day 10. She is alive and well 10 months after surgery with no evidence of recurrent disease.

Case 2

A 57-year-old male underwent a left hepatectomy extended to segments 5, 8 and 1 for a 8.5 cm intra hepatic cholangiocarcinoma (IHCC) involving the left hepatic duct and the left branch of the portal vein. Large collaterality

from the middle and left hepatic veins territory to the right hepatic vein territory was demonstrated on pre-operative CT scan. Tumor and non-tumor liver biopsies confirmed the diagnosis of IHCC and 40% macrovacuolar steatosis of the underlying liver parenchyma.

Liver and kidney function tests were normal as well as tumor markers (i.e., AFP and CA19-9). A preoperative embolization of the left portal vein and of the right anterior portal branch was performed because of the underlying liver steatosis. Following this, the remnant liver to body weight ratio increased from 0.80 to 1.09 on CT scan volumetry. As the duration of TVE was planned to last more than 60 minutes, hypothermic perfusion was performed.

A bilateral subcostal abdominal incision with upper midline extension was performed, as previously described. The left portal vein and the common trunk of left and middle hepatic veins were dissected free. Next, they were clamped and transected, and a side-to-side PCS was performed between the portal trunk and the infrahepatic vena cava. The latter shunt was chosen as the left portal vein was too short. The procedure was then conducted as for the first patient. In that case, a large right inferior hepatic vein was preserved and clamped. The liver temperature dropped to a minimum of 24 ℃ and the total ischemia time was 79 minutes. Five units of packed red cells were transfused. The postoperative course was uneventful and the patient was discharged on postoperative day 25. Histopathological examination of the specimen confirmed the diagnosis of IHCC and a R0 resection margin. At the time of writing, the patient is alive and well seven months after surgery without any evidence of recurrence.

Results and discussion

With the advance in surgical technique, liver resection under hypothermic perfusion remains rare (<1% of liver resections) and is dedicated to tumours invading the cavo-hepatic junction (and/or associated with intrahepatic hepatic veins collateral circulation) and if vascular resection-reconstruction is required for the remnant liver. The majority of patients with "limited vascular invasion" can nowadays be operated safely with intermittent occlusion of the hepatic pedicle and the most difficult part of the resection can be done under short TVE or isolated occlusion of the infra hepatic vena cava (5). This new technique is very important because resection can be performed safely under hypothermic perfusion without VVB.

Indications

This novel approach should be limited to large, centrally located tumors in contact with large branches of the hepatic veins but not involving their roots into the vena cava particularly when large intrahepatic collaterality between hepatic veins imposes early vascular exclusion. More experience with the presented technique, including right sided hepatectomies, is needed to ascertain its impact on ischemia-reperfusion injury, postoperative morbidity and mortality. For other indications of TVE needing hypothermic perfusion the standard TVE with VVB remains safer (3).

Technical aspects

Other options to operate the type of tumors discussed here could be to start the hepatic transection under intermittent clamping of the hepatic pedicle and apply short standard TVE when approaching the vascular contact (5). We decided to resort to the technique described here as there was, in both cases, a significant risk of bleeding from large interhepatic veins collateral circulation encountered usually from the beginning of the transection. Another approach recently described could have been used (6).

The temporary-portocaval shunt is a straightforward procedure particularly in units specialized in liver transplantation (7). This shunt can be performed in different ways including those described here. Other options include the construction of a temporary mesenterico-caval or spleno-renal shunt.

During TVE special attention must be paid to the assurance that the liver is completely excluded. An unknown patency of an accessory hepatic vein during hypothermic perfusion could cause cold perfusion to the heart of the patient with consequent cardioplegy. All minor hepatic veins should be divided and any inferior large hepatic vein to be preserved should be clamped during the liver hypothermic perfusion.

Advantages and drawbacks of this technique with reference to resection under other types of vascular occlusion without hypothermic perfusion

One of the major advantages of this new technique (schematized in *Figures 2* and *3*) as compared to the conventional techniques is to combine the advantages

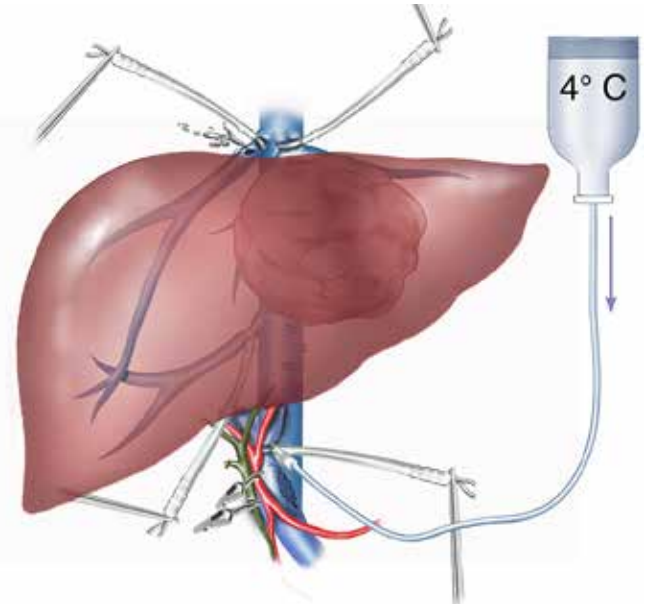

Figure 2 Schematisation of extended left hepatectomy. Vascular exclusion preserving the caval flow, temporary porta-caval shunt (PCS), *in situ* portal hypothermic perfusion.

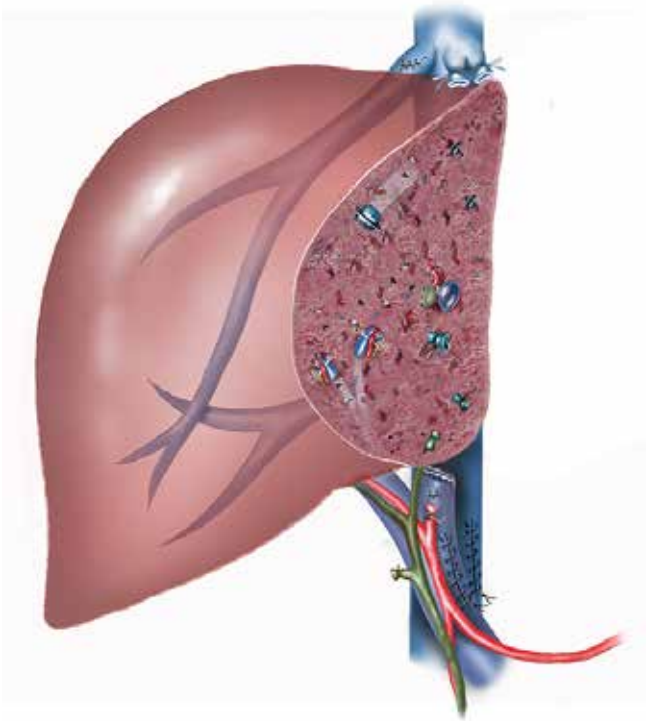

Figure 3 Extended left hepatectomy completed. The porta-caval shunt (PCS) has been divided. The holes in the portal vein and the hepatic vein for perfusate inflow and outflow have been sutured.

of standard TVE with *in situ* hypothermic perfusion of the liver with those of VVB (3). This achieves stable hemodynamics and optimal venous drainage of the kidneys via the preservation of the caval flow; and prevents splanchnic congestion via the PCS while obviating the specific risks of VVB. The latter are significant and include bleeding from vascular injury, air embolism, hemomediastinum, hypotension, atrial fibrillation, seromas or lymphoceles, wound infections and nerve injuries (8,9). In addition, extracoporeal circulation might favor tumor cell dissemination and jeopardize the oncologic outcome of these patients (10).

One of the major disadvantage of this technique is an increased risk of postoperative mortality and morbidity, as shown by the fact that these patients had been transfused of 7 and 5 units of blood, respectively.

Conclusions

When the indication for surgery is for tumors not invading or not strictly involving the hepatic vein confluence or the vena cava and with an expected TVE time ≥60 minutes, we propose an alternative technique to TVE with caval clamping, hypothermic perfusion and VVB.

Our new technique, successfully employed in two patients, consists in a TVE preserving the caval flow with *in situ* hypothermic perfusion with an end-to-side or a side-to-side temporary PCS obviating the need for extracorporeal VVB and its specific risks.

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References

1. Huguet C, Nordlinger B, Galopin JJ, et al. Normothermic hepatic vascular exclusion for extensive hepatectomy. Surg Gynecol Obstet 1978;147:689-93.
2. Pichlmayr R, Grosse H, Hauss J, et al. Technique and preliminary results of extracorporeal liver surgery (bench procedure) and of surgery on the in situ perfused liver. Br J Surg 1990;77:21-6.
3. Azoulay D, Eshkenazy R, Andreani P, et al. In situ hypothermic perfusion of the liver versus standard total vascular exclusion for complex liver resection. Ann Surg

2005;241:277-85.
4. Elias D, Lasser P, Debaene B, et al. Intermittent vascular exclusion of the liver (without vena cava clamping) during major hepatectomy. Br J Surg 1995;82:1535-9.
5. Berney T, Mentha G, Morel P. Total vascular exclusion of the liver for the resection of lesions in contact with the vena cava or the hepatic veins. Br J Surg 1998;85:485-8.
6. Reiniers MJ, van Golen RF, Heger M, et al. In situ hypothermic perfusion with retrograde outflow during right hemihepatectomy: first experiences with a new technique. J Am Coll Surg 2014;218:e7-16.
7. Tzakis AG, Reyes J, Nour B, et al. Temporary end to side portacaval shunt in orthotopic hepatic transplantation in humans. Surg Gynecol Obstet 1993;176:180-2.
8. Budd JM, Isaac JL, Bennett J, et al. Morbidity and mortality associated with large-bore percutaneous venovenous bypass cannulation for 312 orthotopic liver transplantations. Liver Transpl 2001;7:359-62.
9. Sakai T, Planinsic RM, Hilmi IA, et al. Complications associated with percutaneous placement of venous return cannula for venovenous bypass in adult orthotopic liver transplantation. Liver Transpl 2007;13:961-5.
10. Kauffmann M, Krüger T, Aebert H. Surgery on extracorporeal circulation in early and advanced non-small cell lung cancer. Thorac Cardiovasc Surg 2013;61:103-8.

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Pre-resectional inflow vascular control: extrafascial dissection of Glissonean pedicle in liver resections

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Background/aims: We are evaluated technique of anatomic major and minor hepatic resections using suprahilar-extrafascial dissection of Glissonean pedicle with vascular stapling device for transection of hepatic vessels intending to minimize operative time, and blood loss.

Methodology: We prospectively analyzed the clinical records of 170 patients who underwent hepatic resection by suprahilar-extrafascial pedicle isolation and stapling technique in our clinic for emergency surgery in Belgrade. Patients who underwent hilar extrahepatic intrafascial dissection were excluded from the study.

Results: We performed 102 minor liver resections and 68 major hepatectomies. The minor liver resections were associated with significantly shorter surgery duration (95.1±31.1 *vs.* 186.6±56.5) and transection time (35.9±14.5 *vs.* 65.3±17.2) than major hepatectomies (P<0.001 for all). The mean blood loss was 255.6±129.9 mL in minor resection and 385.7±200.1 mL in major resection (P=0.003). The mean blood transfusion requirement was 300.8±99.5 mL for the patients with minor hepatectomy and 450.9±89.6 mL for those with major liver resection (P=0.067). There was no significant difference in morbidity and mortality between the groups (P=0.989; P=0.920). Major as well as minor liver resection were a superior oncologic operation with no significant difference in the 3-year overall survival rates.

Conclusions: Extrafascial dissection of Glissonean pedicle with vascular stapling represents both an effective and safe surgical technique of anatomical liver resection. Presented approach allows early and easy ischemic delineation of appropriate anatomical liver territory to be removed (hemiliver, section, segment) with selective inflow vascular control. Also, it is not time consuming and it is very useful in re-resection, as well as oncologically reasonable.

Keywords: Liver resection; segmented orientated liver resection; Glissonean approach (GA); Glissonean pedicle stapling; vascular stapler; extrafascial dissection

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Introduction

Hepatic resection had an impressive growth, both by broadening the range of its indications and the occurrence of changes and technical tricks in order to reduce postoperative mortality and morbidity (1). Although the criteria for liver tumors resectability are expanded today, hepatectomies are still demanding procedures due to risk of hemorrhage and hepatic failure (2-6). During the last decades surgical techniques for hepatectomy have changed dramatically (2-10). All improvements in liver surgery have the same goals, to preserve the maximum amount of liver parenchyma with minimum blood loss (1-10). The blunt liver dissection has been widely replaced by various time-consuming methods, such as the cavitron ultrasonic surgical aspirator (CUSA), followed by the development of tools for safe approach, isolation and transection of vascular and biliary structures during transection of liver parenchyma (8,9).

In 1949, Honjo (Kyoto University) and later in 1952, Lortat-Jacob and Robert were performed the first anatomical right hepatectomy with classical intrafascial-extrahepatic approach so-called "classic" hilar dissection (HD) of the hepatic artery, portal vein and bile duct in the hepatoduodenal ligament (7,8,10). Nevertheless, the potential disadvantages of this approach are reflected in the cases of extensive scarring due to previous surgery, the risk of incidental lesion of anomalous hepatic vessels or the contralateral biliary duct (11-14).

The observations of Glisson and Couinaud that elements of portal triad are contained within a thick connective tissue and are surrounded by a fibrous sheet (Glissonean pedicle) were the basis for the initial proposal by Couinaud in 1957, that suprahilar vascular control of Glissonean pedicle could serve as an important alternative to classical HD for controlling vascular inflow to the liver. This technique includes the extrafascial dissection of the whole sheath of the pedicle and its division "en masse" (15). Anterior intrahepatic extrafascial approach proposed by Couinaud, Thung and Quang, uses anatomical fissures as door's of the liver. By splitting the liver substance down along the appropriate fissure could be approach to the pedicle of interest (15,16). The extrafascial dissection of left Glissonean pedicle at the hepatic hilus without liver transection, for the left hepatectomy, was previously reported by Couinaud in 1985 and later by Lazorthes in 1993 (17,18). Takasaki in 1986 described the surgical technique called "Glissonean pedicle transection method". Technique is based on detachment of the hilar plate and extrafascial-extrahepatic dissection of the main left and right, as well as both right sectional pedicles, without opening the liver parenchyma (19,20). Galperin in 1989 described a digital "hooking" technique for the isolation of portal pedicles through an extrafascial-intrahepatic approach after division of a substantial amount of the hepatic tissue (21). In 1992 Launois and Jamieson proposed the posterior intrahepatic approach to the appropriate Glissonean pedicle, through the dorsal fissure of the liver, after making proper perihilar hepatotomies (22). Machado's modifications of the posterior approach include making small incisions around the hilar plate and strictly instrumental isolation of the pedicle (23-25). It has been reported that the Glissonean approach (GA) can reduce the portal triad closure time, expedite the transection of the liver and reduce intraoperative hemorrhage, as well as the risk of injury to the vasculature or the biliary drainage of the contralateral liver (26,27).

A step forward in achieving security is the introduction of vascular staplers in liver surgery (8,28-31). Vascular staplers offer speed and safety when dividing hepatic veins and portal branches during hepatectomy, which minimizes blood loss (8,31). Previous studies compared classical HD *vs.* extrahepatic Glissonian stapling of the pedicle for major hepatectomies with acceptable morbidity (7,32).

Using technique of the suprahilar-extrafascial Glissonean pedicle dissection, with endo-GIA vascular stapling device transection of the pedicle, and appropriate hepatic vein, we have performed 170 liver resections for malignant and benign tumors, with intent of minimal blood loss. Here we review our experience gained with liver resections and compare the clinical, perioperative and postoperative results (complications, disease-free survival and overall survival) of the patients who have undergone either segmental resection of different volume, or major hepatectomy.

Methodology

We prospectively analyzed the clinical records of 170 patients who underwent hepatic resection by suprahilar-extrafascial pedicle isolation and stapling technique in our clinic for emergency surgery in Belgrade, between January 2007 and December 2011. Patients who underwent hilar extrahepatic intrafascial dissection were excluded from the study. All procedures were performed by the same operating team.

The protocol received the approval of the research review board of our hospital, and informed written consent was obtained from each patient before surgery. Before operation, all patients underwent a thorough physical examination, blood tests and radiologic evaluation. Liver function was evaluated by Child-Pugh-Turcotte (CPT) classification using prothrombin time (PT), albumin, bilirubin and clinical findings of ascites and encephalopathy. CPT score was stratified as classes A [5-6], B [7-9], and C [10-15]. Only CPT class C is considered an absolute contraindication for surgical treatment. Liver resections were defined according to the International Hepato-Pancreato-Biliary Association terminology derived from Couinaud's classification (33). The amount of operative blood lost was measured by the volume (mL) of blood collected in the aspirator container and the ultrasonic dissector and by the weight of the soaked gauzes.

Perioperative data were operative duration (min), transection time (min), intraoperative blood loss (mL), transfusion requirement (intraoperative and postoperative within the first 48 h) and intermittent vascular occlusion

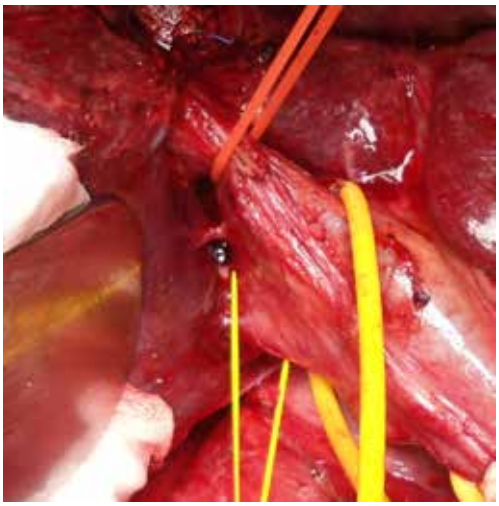

Figure 1 Takasaki's technique of extrahepatic-extrafascial dissection and isolation of the right main Glissonean (RMP) and both right anterior (RAP) and right posterior (RPP) sectional pedicles.

(IVO) duration (min). Transection time was defined as the duration between the beginning and the end of the liver parenchyma transection. The amount of operative blood lost was measured by the volume (mL) of blood collected in the aspirator container and by the weight of the soaked gauzes (assuming that 1 mL of blood =1 g). The indications for blood transfusion were massive hemorrhage with hematocrit decreasing to approximately <25% or hemoglobin level <70 g/L. Cumulative clamping time was calculated according to cumulative period of vascular occlusion.

Postoperative data included postoperative liver injury, ICU and hospital stay (days), morbidity and mortality and disease-free survival and overall survival. The patients were subjected to postoperative follow-up by blood test, ultrasonography or computed tomography (CT) scans. The degree of postoperative hepatic injury was assessed by measuring the postoperative serum values of the aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, albumin, PT and international normalized ratio (INR) on postoperative days 1, 3, 5 and 7.

Postoperatively were followed in the outpatient clinic at 1, 3, and every 6 months thereafter with blood biochemistry and spiral CT scans of the abdomen. Post-operative mortality was defined as any death occurring within 30 days after surgery. Postoperative bleeding, liver ischemia, bile leakage, or perihepatic abscess formation were considered surgical complications. Biliary leak was defined as any drainage through the catheter with a bilirubin content 2× higher than the plasma levels.

Surgical technique

Makuuchi's "J"-shaped laparotomy was used for all patients. Liver was mobilized using standard technique. Intra-operative ultrasound (IOUS) was performed to redefine tumor localization in relation to major vascular structures and to determine the transection plane. Extra hepatic "outflow" control was performed after dissection and isolation of major hepatic veins above the liver, whenever it was possible. Ischemic preconditioning (IP) was done to minimize ischemic-reperfusion injury of the liver (IRI). The liver tissue was transected under intermittent hepatic inflow vascular occlusion (IVO) which involves periods of inflow clamping for 15 minutes followed by periods of unclamping for five minutes (mode 15/5). In order to minimize bleeding in minor hepatectomies, selective vascular clamping (SVO) was used as the preferred method of inflow occlusion, particularly in patients with underlying chronic liver disease. Central venous pressure (CPV) was maintained at 0-5 mmHg to help reduce back bleeding from hepatic veins. After the transectional line was marked, the liver capsule was divided with diathermy or harmonic scalpel. Transection of the liver tissue was performed using the cavitron ultrasonic dissecting aspirator ("CUSA Excel"; Valleylab Inc., Boulder, CO, USA). During dissection, small vessels/bile ducts were ligated, coagulated or clipped to achieved hemostasis and biliostasis. The major hepatic veins were divided extrahepatically using vascular surgical stapler (Endo GIA Ultra stapler 3.0; Covidien, USA). Suprahilar vascular control of the appropriate Glissonean pedicle was achieved by Machado's modification of the posterior intrahepatic approach (23,24), or using Takasaki's technique (19) (*Figure 1*). Clamping the taped Glissonean pedicle, demonstrated the further demarcation of the appropriate anatomical territory of the liver as well as delineation of resectional plan (*Figure 2*). Pedicle was divided at the end of the resectional procedure using endo-GIA vascular stapling device (Endo GIA Ultra stapler 3.0; Covidien) (*Figure 3*). Firm counter traction on the tape was applied during application of the stapler to ensure that the contralateral pedicle was not accidentally ligated.

For the right main Glissonean pedicle (RMP) isolation maneuver, after cholecystectomy, "detachment" of the medial section of the liver (S4) was performed, by lowering the hilar plate and small anterior hepatotomy was made

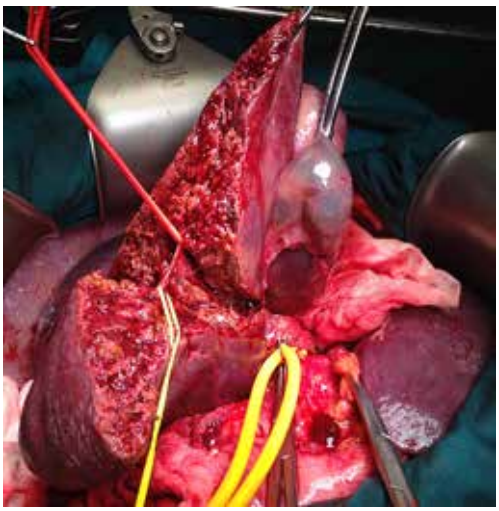

Figure 2 Mesohepatectomy: resectional plan along the right sagital fissure of the liver with isolated right anterior (RAP) and right posterior (RPP) sectional pedicles.

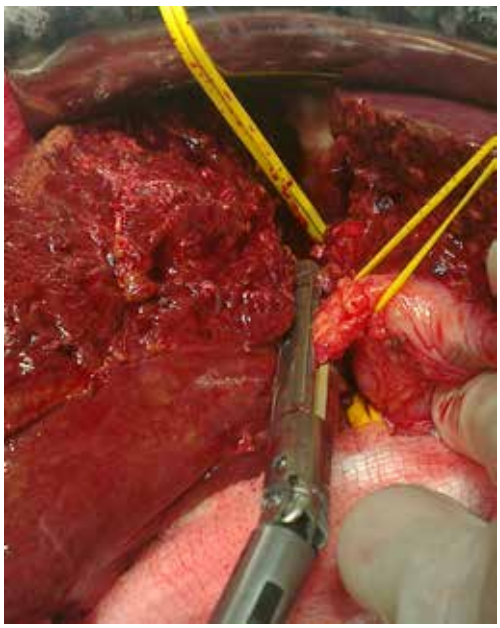

Figure 3 Right hepatectomy: transection of the right main Glissonean pedicle using endo-GIA vascular stapling device.

in front of the hilum. A second incision was performed perpendicular to the hepatic hilum, between segment S7 and caudate lobe (S1). Curved clamp then was inserted through the first hepatotomy with a 30° angle reaching the second incision. Vascular tape was then placed around the RMP. Tape was pulled down and medially to provide better exposure of the intrahepatic pedicle and to retract the left biliary tree and portal vein away from the area to be clamped or stapled. A third incision performed on the right edge of the gallbladder bed permitted access to the right anterior (RAP) and right posterior (RPP) sectional pedicles, by combining the previously mentioned incisions. In short course of the right main pedicle, the RAP and RPP were ligated and divided separately. The further, distal intrahepatic dissection of the isolated sectional pedicles, allowed the parenchymal isolation of the appropriate (S5-S8) segmental pedicle.

For the left main Glissonean pedicle (LMP) isolation, the lesser omentum was divided, exposing the Arantius venous ligament, which was then dissected and divided. The proximal stump enabled the infero-posterior approach to the left hepatic vein and common trunk. The caudal stump of the ligament was dissected towards the left portal vein. This maneuver disclosed the posterior aspect of the left Glissonean pedicle. A small anterior incision (4-5 mm) was performed on the left side of the hilum and a curved clamp was introduced behind the caudal stump of the Arantius ligament, allowing the encircling and exposure of the left main pedicle. This approach spared the caudate lobe (S1) portal branches. The round ligament was retracted upward, exposing the umbilical fissure between segments S3 and S4. If a parenchymal bridge connecting these two segments exists, it must be divided. Using the round ligament as a guide, two small incisions are performed on the left and right margins of the round ligament where it is possible to identify the anterior aspect of the Glissonean pedicle for segment S4 on its right side and segment S3 on its left side. With a clamp introduced through the anterior incision in front of the hilum and the basis of the round ligament on the right side, it is possible to isolate the Glissonean pedicle for the left medial section or segment S4. By combining incisions from the caudal stump of the Arantius ligament to the left side of the basis of the round ligament, it is possible to isolate the Glissonean pedicles for the left lateral section (segments S2 and S3).

During pedicle clamping, the color of the area changes and the tumor location is confirmed by IOUS. Pedicle is divided at the end of resectional procedure using vascular surgical stapler (Endo GIA Ultra stapler 3.0; Covidien). After completed resection, the monopolar irrigated electrocautery was applied to stop minor oozing. The raw surface of the liver was sealed using fibrin glue. Closed suction drainage was used in all patients.

Table 1 Type of minor liver resection

Type of liver resection	n (%)
Segmentectomy 1	2 (1.9)
Segmentectomy 2	4 (3.9)
Segmentectomy 3	6 (5.8)
Left lateral sectionectomy	23 (22.5)
Left medial sectionectomy (segment 4)	8 (7.8)
Segmentectomy 5	5 (4.9)
Segmentectomy 6	4 (3.9)
Segmentectomy 7	4 (3.9)
Segmentectomy 8	2 (1.9)
Right posterior sectionectomy	15 (14.7)
Right anterior sectionectomy	8 (7.8)
Bisegmentectomy 4b, 5	5 (4.9)
Bisegmentectomy 3, 4b	4 (3.9)
Right cranial bisegmentectomy 7, 8	4 (3.9)
Right caudal bisegmentectomy 5, 6	8 (7.8)
Total	102 (100.0)

Table 2 Type of major liver resection

Type of liver resection	n (%)
Extended right hepatectomy	3 (4.4)
Extended left hepatectomy	1 (1.5)
Right hepatectomy	24 (35.3)
Left hepatectomy	27 (39.7)
Mesohepatectomy	4 (5.8)
Central transversal hepatectomy (S3,S4b,S5)	4 (5.8)
Right inferior transversal hepatectomy (S4b,S5,S6)	5 (7.3)
Total	68 (100.0)

Statistical analysis

Data were expressed as mean with SD or median with interquartile range, as appropriate. Categorical data are presented by absolute numbers with percentages. Differences between groups were compared with parametric Student's *t*-test or nonparametric Mann-Whitney test. Repeated measures of liver function indicated by serum level of bilirubin, AST, ALT, albumin and PT was assessed by general linear model. For qualitative variables, comparisons between groups were performed by the χ^2 test or Fisher exact test, when needed. In all tests, P value <0.05 was considered to be statistically significant. All the calculations were performed with the SPSS 17.0 statistical package (SPSS, Inc., Chicago, IL, USA).

Results

A total of 170 anatomical hepatectomies were performed by suprahilar-extrafascial Glissonean pedicle dissection and stapling technique, including 68 (40.0%) major and 102 (60.0%) minor liver resections (*Tables 1* and *2*).

Demographics and preoperative data for all patients are shown in *Table 3*. There were no significant differences between the two groups in terms of age, gender, comorbid conditions, Child-Pugh score, indications and number of tumoral lesions (*Table 3*). Twenty-eight patients in minor resection group (27.4%) were classified as CPT class B and 9 (13.2%) patients in major resection group as CPT class B.

Indications for minor liver resection were metastases of colorectal carcinoma (CRC) in 50 (49.02%), hepatocellular carcinoma (HCC) in 10 (9.80%), cholangiocellular carcinoma in 4 (3.92%), non-colorectal liver metastases in 8 (7.84%), gall bladder carcinoma in 7 (6.86%), hemangioma hepatis in 13 (12.74%) and adenoma hepatis in 10 (9.80%) patients. Indications for major hepatectomies were colorectal liver metastases (CRC LM) in 33 (48.5%); non-colorectal liver metastases (non-CRC LM) in 7 (10.3%); HCC in 22 (32.3%); gall bladder carcinoma in 3 (4.4%) patients and liver hemangioma in 3 (4.4%).

Intraoperative data for those patients undergoing hepatectomy, hospital stay and outcome are provided in *Table 4*. There were a significant difference in overall operative time, liver transection time and ischemic duration between minor and major resections (P<0.001 for all) (*Table 4*). Intraoperative blood loss was significantly higher in the major resection group (P=0.003) (*Table 4*). Intraoperative transfusion was performed in 46 (27.1%) patients of all and there was no significant difference between minor and major resections (P=0.395). The intraoperative blood transfusion is expressed as the amount of blood volume (mL), there was no significant difference between minor and major resections (P=0.067) (*Table 4*). In 124 (72.9%) patients of all liver resection were performed without any blood transfusion.

Degree of liver damage presented by sequential postoperative serum values of AST, ALT, Bilirubin and PT. The changes in postoperative serum values of liver function markers were not significantly different between major and minor resection (P>0.05) Nevertheless, statistical analysis of the total serum AST, ALT, bilirubin, and PT values found significance in the specified period of time. Total AST and ALT values were significantly decreased on the

Table 3 Clinical characteristics and preoperative biochemical evaluations of patients included in the study

Characteristics	Minor resections (n=102)	Major resections (n=68)	P
Male*	62 (60.78%)	36 (52.9%)	0.561
Age (years)**	62.52±15.29	61.65±13.58	0.778
Comorbidity*	54 (52.94%)	35 (51.5%)	0.881
Malignant indications*	79 (77.45%)	58 (85.3%)	0.345
No. of tumours lesions**	1.71±1.10	2.23±1.28	0.053
CPT score A	74 (72.5%)	59 (86.7%)	0.649
Bilirubin (μmol/L)	20.12±12.27	22.73±14.66	>0.05
AST (U/L)	35.89±13.21	33.36±15.81	>0.05
ALT (U/L)	59.04±35.40	49.66±28.54	>0.05
Albumin (g/L)	30.39±6.59	30.49±6.91	>0.05
INR†	1.21±0.19	1.24±0.21	>0.05
PT (s)	13.72±1.68	13.22±2.32	>0.05

*, characteristics are presented as numbers of patients and percentage, n (%); **, characteristics are presented as mean ± SD, standard deviation; †, international normalized ratio.

Table 4 Perioperative characteristics of patients included in the study

Characteristics	Minor resections (n=102)	Major resections (n=68)	P
Operative time, (min)**	95.1±31.1	186.6±56.5	<0.001
Transection time, (min)**	35.9±14.5	65.3±17.2	<0.001
Blood loss, (mL)**	255.6±129.9	385.7±200.1	0.003
Ischaemic duration, (min)†	15 [15]	30 [30]	<0.001
CVP (0-5 mmHg)†	2.00 [2]	3.00 [2]	0.291
Blood transfusion inraop. (mL)**	300.8±99.5	450.9±89.6	0.067
Resection R0, n (%)*	96 (94.1%)	63 (92.6%)	0.833
Hospital stay (days)†	8 [3]	8 [4]	0.745
ICU stay (days)	1.00 [2]	1.00 [3]	0.441
Morbidity*	37 (36.3%)	25 (36.7%)	0.989
Mortality rate*	1 (0.9%)	2 (2.9%)	0.920
Overall survival rates for CRC°	53%	46%	0.744
Overall survival rates for HCC°	60%	69%	0.744

*, characteristics are presented as numbers of patients and percentage, n (%); **, characteristics are presented as mean ± SD; †, characteristics are presented as median (range); °, follow-up 36 months.

third postoperative day (P<0.001; P<0.001). Total bilirubin value was significantly lower on the 5th postoperative day (P<0.001). Total PT value was significantly reduced on the 5th postoperative day (P=0.001).

There was no significant difference in ICU stay, hospital stay and complications rate between the groups (*Table 4*). In minor resection group complications rate was 37 (36.3%). According to Clavien's classification, grade 1-2 complications were recorded in 27 (26.5%): 5 (4.9%) had cardiac complication, 10 (9.8%) had pleural effusion, 5 (4.9%) had atelectasis, 6 of them (5.9%) had wound infections and 1 (0.9%) bronchopneumonia. Total of 10 (9.8%) patients experienced grade ≥3 surgery complications: 4 (3.9%) intra-abdominal fluid collection, 2 (1.9%) biliary fistula, and 4 (3.9%) partial wound dehiscence. In major resection group according to Clavien's classification, grade

1-2 complications were recorded in 21 (30.9%): 5 (7.3%) had cardiac complication, 11 (16.2%) had respiratory complications and 5 (7.3%) had wound infections. There were 4 (5.9%) grade ≥3 surgery complications: 2 (2.9%) intra-abdominal fluid collection and 2 (2.9%) biliary fistula. The majority of complications were treated conservatively, or radiological intervention/percutaneous drainage and no patients underwent reoperation. In all cases of the biliary fistula there was spontaneous healing

Mortality between groups did not reach a significant difference (P=0.920). The hospital morbidity rate in major resection group was 2.9%. All deaths were caused by non-surgical complications. In both patients there were a history of cardiac disorders, and mortality was caused by an acute myocardial infarction, after the seventh postoperative day in both cases.

One patient who treated by minor liver resection died due to thromboembolic complications and pulmonary embolism, on postoperative day 3, despite regular anticoagulant therapy.

The 1- and 3-year disease-free survival rates in group with minor resections were 75% for patients with colorectal metastases (74% for patients with HCC) and 46% for patients with colorectal metastases (49% HCC patients), respectively. These results were similar to those observed in group with major resections (76% for CRC patients; 80% for HCC patients) and (50% for CRC patients; 52% HCC patients), respectively. There was no significant difference in the disease-free survival rates between both groups (P=0.066).

The overall survival rates after 1 year and 3 years were found to be 81% for patients with colorectal metastases (90% for patients with HCC) and 53% for patients with colorectal metastases (60% for patients with HCC) in group with minor liver resections and 83% for patients with colorectal metastases (92% for patients with HCC) and 49% for patients with colorectal metastases (69% for patients with HCC) in group with major hepatectomies, respectively. There was no significant difference in the overall survival rates between both groups (P=0.744).

Discussion

Liver resections are complex procedures that requires detailed knowledge of liver anatomy, precise "bloodless" surgical technique and sufficient volume of the remnant liver (1-8,34).

Since the late 1970s, when operative mortality was more than 20% for major liver resections, much effort has been done to intraoperative control of blood loss and reduce intraoperative hemorrhage (34,35). Excessive blood loss is associated with increased perioperative morbidity and, in cases of colorectal metastases, a shorter disease-free interval (34,36). Technical refinements are focused on minimizing hemorrhage during transection of hepatic parenchyma and safe dissection of the major hepatic veins and pedicles (34-36).

The extrafascial dissection of Glissonean pedicle is a very important technique that can be extremely useful in particular circumstances during liver surgery, such as in multi-operated patients or in patients with cirrhotic liver or anomalous vascular and biliary variations. Regarding this technique some terminology confusion still exists (*Glissonean approach*, *extra-Glissonean approach*, *Glissonean pedicle transection method*, *posterior intrahepatic approach*, *suprahilar vascular control*, *perihilar posterior approach*, *superficialisation of Glissonean pedicles*) (20,37). Nevertheless, despite many titles the main surgical concept is the same, and it's based on the anatomical fact and observation of Couinaud that portal triad elements inside the liver substance, are enveloped with fibrous Glissonean sheet, thus representing an important structure of internal architecture of the liver (15,17). The extrafascial Glissonean pedicle approach in liver surgery provides new knowledge of the surgical anatomy of the liver and advances the technique of liver surgery (38). Opposite to "classic" intrafascial dissection, this technique includes extrafascial isolation of the whole sheet of Glissonean pedicle and it's division "en masse". Glissonean pedicles can be approached intrahepatically or extrahepatically. The use of vascular staplers in this situation allows quick and safe transection of the pedicle, as well as appropriate hepatic vein (39). The second advantage of this technique presents the quick and easy definition of the anatomic territory of the liver to be removed. Selective clamping of the appropriate isolated pedicle demonstrates the further ischemic demarcation of anatomical liver part of interest (hemiliver, section or even segment) as well as delineation of resectional planes (21-25). Recent advances of presented surgical technique includes liver hanging maneuver and some modifications with two tapes to control the main fissure of the liver or various liver resections using hanging maneuver by three Glisson's pedicles and three hepatic veins (40,41). The first prospective randomized study which compared extrafascial GA *vs.* "classic" HD in major hepatectomies, was performed by the group of Figueras, showed that "*en bloc*" stapling transection of the pedicle was safe and faster than "classic" approach (7). The other studies

have shown similar results for the safety and operative duration (42-46). Also, the aim of our previous study was to analyze the efficiency and safety of the Glissonean pedicle approach *vs*. classical HD in major hepatectomies (32). The extrafascial dissection was associated with significantly shorter surgery duration, transection time and ischemic duration than intrafascial HD, while amount of blood loss was significantly lower in GA (32). Extrafascial isolation of Glissonean pedicle saves time comparing with difficult and some time hazardous intrafascial HD. Dissection above hepatic hilum significantly reduces the risk of the potentially injury of the contra-laterally sided vasculature and bile ducts (47). Smyrniotis *et al*. showed that intrahepatic dissection is safe as extrahepatic hilar division in terms of intraoperative blood requirements and morbidity; but biliary complications are more severe in patients undergoing extrahepatic division of the portal pedicle (43).

Advantages of anatomic segment orientated resections include prevention of postoperative liver failure especially in elderly or patients with underlying liver disease, reduction of blood loss as well as lower postoperative mortality and morbidity rates. The question, whether to perform a segmental or a major resection if both procedures are technically feasible, is still under debate. The presented surgical technique of suprahilar extrafascial control of the Glissonean pedicle, is very useful in performing of sectionectomies and segmentectomies. Couinaud and, more recently, Takasaki, Galperin and Launois have noted that the Glissonean capsule continues within the liver parenchyma up to the segmental divisions (19-22). Although the intersegmental planes were not visible on the surface of the liver, the segments were defined by occluding the inflow pedicle to that segment.

This study describes our experiences with the extrafascial pedicle dissection and stapling technique during major liver resection and minor hepatectomy: vascular staplers were used to divided pedicles and major hepatic veins while parenchyma transection was performed by CUSA, under IPM or selective vascular occlusion (SVO). The study was not designed to demonstrate the superiority of one major hepatic resection over the minor. Rather, it is the authors' intention to demonstrate the efficiency of the GA in major as well as in minor hepatectomy.

In our study, bisegmentectomies occupy the greatest relative share in minor liver resection group, since left lateral sectionectomies dominates. In major liver resection group, right hepatectomy and left hepatectomy had the greatest rate. The minor liver resections were associated with significantly shorter surgery duration and transection time than major hepatectomies. Intraoperative transfusion rate was no significant difference between minor and major resections. The changes in postoperative serum values of liver function markers were not significantly different between major and minor resections. There was no significant difference in ICU stay, hospital stay and complications rate between the groups. Major hepatectomy as well as minor liver resection are a superior oncologic operation with no significant difference in the 1- and 3-year disease-free survival rates and overall survival rates between both groups in our study.

Stewart registered a significant difference between the groups with extended resections and segmental ones in terms of operative blood loss and post-operative stay as major post-operative complications are less following segmental resection (48).

Intermittent Pringle maneuver (IPM) during transection of liver parenchyma is simple and safe technique that may reduce bleeding from hepatic inflow, and the total clamping time can be extended to 120 minutes in normal livers and 60 minutes in pathological livers (30,36). The disadvantage of IPM is that bleeding occurs from the liver transection surface during the unclamping period and, thus, the overall transection time is prolonged as more time is spent in achieving hemostasis. The presented surgical technique allows the use of SVO during parenchymal transection.

Selective clamping it is also important from the haemodynamic point of view because there is no splanchnic stasis and low fluid replacement. A previous randomized study demonstrated that the clinical advantages of selective clamping are more significant in patients with chronic liver disease, particularly in very difficult resections in patients in whom lengthy pedicular clamping is anticipated as a result of portal hypertension or in whom very large areas of transection are necessary (49). By contrast, selective clamping or hemihepatic vascular occlusion, as described by Makuuchi *et al*. does not increase venous portal pressure or cause fluid overload or a consequent increase in CVP (50).

Expected, in our study results showed shorter operation time, transection time, ischemic duration and less blood loss for minor hepatectomies compared to major liver resections. However our results showed that major hepatic resections are safe procedures with outcome results non-significantly different from minor resections. Further development of sophisticated techniques and instruments in order to reduce bleeding during liver resection led to the introduction of

vascular stapler in liver surgery in the last decade of the twentieth century. Recent publications reporting a number of techniques using stapling devices in liver surgery showed them to be extraordinarily useful in the safe ligation of inflow and outflow vessels (51). Application of vascular staplers to selectively divide major intrahepatic blood vessels for hepatic inflow and outflow vascular control during liver resection, has been shown to achieve excellent results, reducing blood loss, warm ischemia time and operative time (24,26,29). However, there are a few of potential dangers in using the stapler. Serious blood loss can theoretically occur when the stapler has sealed only half the diameter of the vessel or after misfire of the devise although we did not experience such a situation.

Another potential danger from the use of staplers in the liver is tearing a major hepatic vein or vena cava, while placing the instrument. Usually after encircling of the hepatic vein, the articulated and rotating Endo-GIA vascular stapler is passed gently around the hepatic vein to staple and divide it. The thinner blade of the stapler is inserted in preference to the thicker blade because the space available is limited. As the thinner blade is not on the same axis as the instrument, difficulty may be encountered if the tip of the blade and tearing of the vein may occur. In order to avoid this complication, we used a right-angle clamp to grab the thinner blade and guide its insertion into the space between the liver parenchyma and major vein. This technique is also reported by other centers (28).

Morbidity and mortality are correlated with the amount of blood loss during hepatectomy (34,36). Despite all technological advancing for liver resections, an intraoperative hemorrhage rate ranging from 700 to 1,200 mL is reported with a postoperative morbidity rate ranging from 23% to 46% and a surgical death rate ranging from 4% to 5% (34,36). Jarnagin *et al.* reported of a moderate blood loss of 600 mL and in major hepatectomy their investigations led to a blood loss of more than 1,000 mL; while 700 to 800 mL observed in the cases of stapler hepatectomy (35,52).

Specific complications after liver are all associated with high morbidity in terms of sepsis, liver failure, longer hospital stay, as well as postoperative mortality (53,54). Complications such as biliary leaks continue to be reported with incidences in the range of 2.6-15.6%, in our study 1.7% (53,54). Carefully checking the resection line and completing hemo- and bilistasis, even in a modified cirrhotic liver parenchyma, we obtained literature accepted percentages in resection line related complications (biliary fistulas, postoperative bleeding). Capussotti *et al.* published a study on 610 patients with liver resection, where biliary fistulas occurred in 3.6% of cases, and our rate of 2.3% of all being consistent with these data (53). Treatment is not easy and a number of non-surgical strategies have been proposed. However, surgical intervention should be considered for patients in whom non-surgical interventions are either unsuccessful or not feasible. In this study no patients underwent reoperation, all complications treated successfully by non-operative interventional and radiological techniques. In our series, no hemorrhage, ischemic damage or postoperative liver function was observed.

Our experience in study of 170 patients who underwent hepatectomy with stapling of the pedicle shows that this technique is applicable in a routine clinical setting based on both its feasibility and safety. Mortality of 1.7% seen in our group is consistent with the data published in the literature. In the present series, both mortality and morbidity were as low as in a recently published large series of non-selected patients who underwent liver resection in other high-volume surgical centers (1,35,52).

Conclusions

Extrafascial dissection of Glissonean pedicle with vascular stapling represents both an effective and safe surgical technique of anatomical liver resection. Presented approach allows early and easy ischemic delineation of appropriate anatomical liver territory to be removed (hemiliver, section, segment) with selective inflow vascular control. Also, it is not time consuming and it is very useful in re-resection. From the oncological point of view technique is reasonable: early initial ligation of Glissonean pedicle avoid dissemination of neoplastic cells, while anatomical concept of resection allows removal of micrometastases at the root of the pedicle with adequate resectional margin. We have demonstrated that segment-orientated liver resections offers disease-free and overall survival rates similar to those after major resection. However, the patients should be judiciously selected. Finally, according to our opinion, extrafascial GA should be a part of knowledge and skills of HPB surgeon.

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References

1. Dan RG, Creţu OM, Mazilu O, et al. Postoperative morbidity and mortality after liver resection. Retrospective study on 133 patients. Chirurgia (Bucur) 2012;107:737-41.
2. Chirica M, Scatton O, Massault PP, et al. Treatment of stage IVA hepatocellular carcinoma: should we reappraise the role of surgery? Arch Surg 2008;143:538-43; discussion 543.
3. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for respectability of colorectal liver metastases. Oncologist 2008;13:51-64.
4. González HD, Figueras J. Practical questions in liver metastases of colorectal cancer: general principles of treatment. HPB (Oxford) 2007;9:251-8.
5. Minagawa M, Yamamoto J, Miwa S, et al. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. Arch Surg 2006;141:1006-12; discussion 1013.
6. Nuzzo G, Giuliante F, Ardito F, et al. Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. J Gastrointest Surg 2007;11:318-24.
7. Figueras J, Lopez-Ben S, Lladó L, et al. Hilar dissection versus the 'Glissonian' approach and stapling of the pedicle for major hepatectomies: a prospective, randomized trial. Ann Surg 2003;238:111-9.
8. Aragon RJ, Solomon NL. Techniques of hepatic resection. J Gastrointest Oncol 2012;3:28-40.
9. Doklestic K, Karamarkovic A, Stefanovic B, et al. The efficacy of three transection techniques of the liver resection: a randomized clinical trial. Hepatogastroenterology 2012;59:1501-6.
10. Lortat-Jacob JL, Robert HG. Hepatectomie droite reglé. Press Med 1952;60:549-51.
11. Meunier B, Lakehal M, Tay KH, et al. Surgical complications and treatment during resection for malignancy of the high bile duct. World J Surg 2001;25:1284-8.
12. Lo CM, Fan ST, Liu CL, et al. Biliary complications after hepatic resection: risk factors, management and outcome. Arch Surg 1998;133:156-61.
13. Miyagawa S, Makuuchi M, Kawasaki S, et al. Criteria for safe hepatic resection. Am J Surg 1995;169:589-94.
14. Icoz G, Kilic M, Zeytunlu M, et al. Biliary reconstructions and complications encountered in 50 consecutive right-lobe living donor liver transplantation. Liver Transpl 2003;9:575-80.
15. Couinaud C. Le foie. Études Anatomiques et Chirugicales. Paris: Masson, 1957.
16. Tung TT. Les Résections Majeures et Mineures du Fois. Paris: Masson & Cie, 1957.
17. Couinaud CM. A simplified method for controlled left hepatectomy. Surgery 1985;97:358-61.
18. Lazorthes F, Chiotasso P, Chevreau P, et al. Hepatectomy with initial suprahilar control of intrahepatic portal pedicles. Surgery 1993;113:103-8.
19. Takasaki K. eds. Glissonean pedicle transection method for hepatic resection. Tokyo: Springer, 2007.
20. Takasaki K. Glissonean pedicle transection method for hepatic resection: a new concept of liver segmentation. J Hepatobiliary Pancreat Surg 1998;5:286-91.
21. Galperin EI, Karagiulian SR. A new simplified method of selective exposure of hepatic pedicles for controlled hepatectomies. HPB Surgery 1989;1:119-30.
22. Launois B, Jamieson GG. The importance of Glisson's capsule and its sheaths in the intrahepatic approach to resection of the liver. Surg Gynecol Obstet 1992;174:7-10.
23. Machado MA, Herman P, Machado MC. A standardized technique for right segmental liver resections. Arch Surg 2003;138:918-20.
24. Machado MA, Herman P, Machado MC. Anatomical resection of left liver segments. Arch Surg 2004;139:1346-9.
25. Machado MA, Herman P, Meirelles RF Jr, et al. How I do it: bi-segmentectomy V-VIII as alternative to right hepatectomy: an intrahepatic approach. J Surg Oncol 2005;90:43-5.
26. Fong Y, Blumgart L. Useful stapling techniques in liver surgery. J Am Coll Surg 1997;185:93-100.
27. Ramacciato G, Aurello P, D'Angelo F, et al. Effective vascular endostapler techniques in hepatic resection. Int Surg 1998;83:317-23.
28. Wang WX, Fan ST. Use of the Endo-GIA vascular stapler for hepatic resection. Asian J Surg 2003;26:193-6.
29. DeMatteo RP, Fong Y, Jarnagin WR, et al. Recent advances in hepatic resection. Semin Surg Oncol 2000;19:200-7.
30. Schemmer P, Friess H, Hinz U, et al. Stapler hepatectomy is a safe dissection technique: analysis of 300 patients. World J Surg 2006;30:419-30.
31. Bagul A, McMahon G, Alam F, et al. Safely dealing with the right hepatic vein during a right hepectomy. Ann R Coll Surg Engl 2010;92:442-3.
32. Karamarković A, Doklestić K, Milić N, et al. Glissonean pedicle approach in major liver resections. Hepatogastroenterology 2012;59:1896-901.
33. Pang YY. The Brisbane 2000 terminology of liver anatomy

and resections. HPB 2000; 2:333-39. HPB (Oxford) 2002;4:99; author reply 99-100.
34. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240:698-708; discussion 708-10.
35. Poon RT. Current techniques of liver transection. HPB (Oxford) 2007;9:166-73.
36. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred fourty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191:38-46.
37. Bismuth H. Surgical anatomy and anatomical surgery of the liver. World J Surg 1982;6:3-9.
38. Yamamoto M, Katagiri S, Ariizumi S, et al. Glissonean pedicle transection method for liver surgery. J Hepatobiliary Pancreat Sci 2012;19:3-8.
39. Nanashima A, Sumida Y, Oikawa M, et al. Vascular transection using endovascular stapling in hepatic resection. Hepatogastroenterology 2009;56:498-500.
40. Boudjema K, Veilhan LA, Dupont-Bierre E, et al. Two tapes to control the main fissure of the liver. Ann Chir 2002;127:149-53.
41. Kim SH, Park SJ, Lee SA, et al. Various liver resections using hanging maneuver by three Glisson's pedicles and three hepatic veins. Ann Surg 2007;245:201-5.
42. Cresswell AB, Welsh FK, John TG, et al. Evaluation of intrahepatic, extra-Glissonian stapling of the right porta hepatis vs. classical extrahepatic dissection during right hepatectomy. HPB (Oxford) 2009;11:493-8.
43. Smyrniotis V, Arkadopoulos N, Theodoraki K, et al. Association between biliary complications and technique of hilar division (extrahepatic vs. intrahepatic) in major liver resections. World J Surg Oncol 2006;4:59.
44. Giordano M, Lopez-Ben S, Codina-Barreras A, et al. Extra-Glissonian approach in liver resection. HPB (Oxford) 2010;12:94-100.
45. Mouly C, Fuks D, Browet F, et al. Feasibility of the Glissonian approach during right hepatectomy. HPB (Oxford) 2013;15:638-45.
46. Yamamoto M, Katagiri S, Ariizumi SI, et al. Tips for anatomical hepatectomy for hepatocellular carcinoma by the Glissonean pedicle approach. J Hepatobiliary Pancreat Sci 2014;21:E53-6.
47. Launois B. General principles of liver surgery. In: Launois B, Jamieson G. eds. The posterior intrahepatic approach in Liver surgery. New York, USA: Springer, 2013.
48. Stewart GD, O'Súilleabháin CB, Madhavan KK, et al. The extent of resection influences outcome following hepatectomy for colorectal liver metastases. Eur J Surg Oncol 2004;30:370-6.
49. Figueras J, Llado L, Ruiz D, et al. Complete versus selective portal triad clamping for minor liver resections. A prospective randomized trial. Ann Surg 2005;241:582-90.
50. Makuuchi M, Mori T, Gunvén P, et al. Safety of hemihepatic vascular occlusion during resection of the liver. Surg Gynecol Obstet 1987;164:155-8.
51. Delis SG, Bakoyiannis A, Karakaxas D, et al. Hepatic parenchyma resection using stapling devices: peri-operative and long-term outcome. HPB (Oxford) 2009;11:38-44.
52. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection. Analysis of 1803 consecutive cases over the past decade. Ann Surg 2002;236:397-406; discussion 406-7.
53. Capussotti L, Ferrero A, Vigano L, et al. Bile leakage and liver resection: where is the risk? Arch Surg 2006;141:690-4; discussion 695.
54. Nagano Y, Togo S, Tanaka K, et al. Risk factors and management of bile leakage after hepatic resection. World J Surg 2003;27:695-8.

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Clinical application of indocyanine green-fluorescence imaging during hepatectomy

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Abstract: In hepatobiliary surgery, the fluorescence and bile excretion of indocyanine green (ICG) can be used for real-time visualization of biological structure. Fluorescence cholangiography is used to obtain fluorescence images of the bile ducts following intrabiliary injection of 0.025–0.5 mg/mL ICG or intravenous injection of 2.5 mg ICG. Recently, the latter technique has been used in laparoscopic/robotic cholecystectomy. Intraoperative fluorescence imaging can be used to identify subcapsular hepatic tumors. Primary and secondary hepatic malignancy can be identified by intraoperative fluorescence imaging using preoperative intravenous injection of ICG through biliary excretion disorders that exist in cancerous tissues of hepatocellular carcinoma (HCC) and in non-cancerous hepatic parenchyma around adenocarcinoma foci. Intraoperative fluorescence imaging may help detect tumors to be removed, especially during laparoscopic hepatectomy, in which visual inspection and palpation are limited, compared with open surgery. Fluorescence imaging can also be used to identify hepatic segments. Boundaries of hepatic segments can be visualized following injection of 0.25–2.5 mg/mL ICG into the portal veins or by intravenous injection of 2.5 mg ICG following closure of the proximal portal pedicle toward hepatic regions to be removed. These techniques enable identification of hepatic segments before hepatectomy and during parenchymal transection for anatomic resection. Advances in imaging systems will increase the use of fluorescence imaging as an intraoperative navigation tool that can enhance the safety and accuracy of open and laparoscopic/robotic hepatobiliary surgery.

Keywords: Indocyanine green (ICG); fluorescence imaging; intraoperative cholangiography; hepatocellular carcinoma (HCC); colorectal liver metastasis (CRLM); liver resection

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Overview of intraoperative fluorescence imaging using indocyanine green (ICG)

Since approval by the U.S. Food and Drug Administration (FDA) in 1954, ICG has been used clinically to estimate cardiac output and liver function. In the 1970s, protein-bound ICG was found to emit fluorescence, peaking at about 840 nm, under illumination with near-infrared light (750–810 nm) (1). Because little light at 840 nm is absorbed by hemoglobin or water, fluorescence signals emitted by protein-bound ICG can be visualized through connective tissue 5–10 mm thick. ICG was first used clinically for fundus angiography in the early 1990s (2).

In the 21st century, fluorescence imaging using ICG has

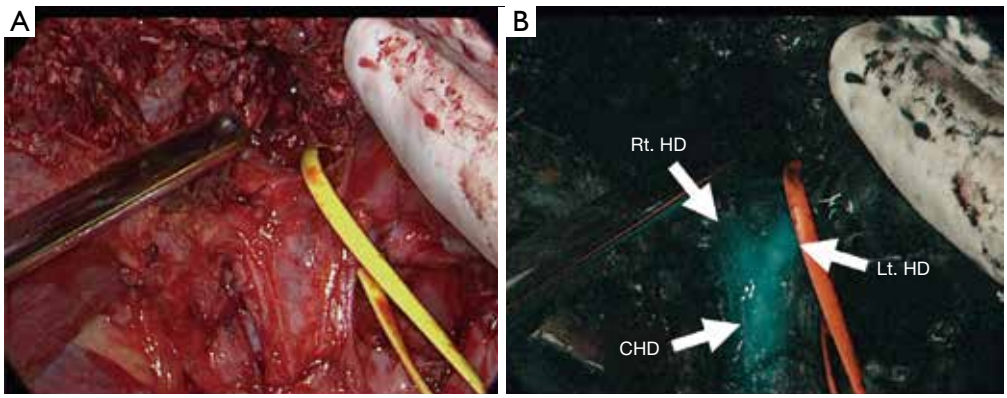

Figure 1 Fluorescence cholangiography following intraoperative intravenous injection of indocyanine green (2.5 mg) shows the confluence of the right and let hepatic ducts, enabling surgeons to determine the division point of the Lt.HD during left hepatectomy. Lt.HD, left hepatic duct; Rt.HD, right hepatic duct; CHD, common hepatic duct.

become widespread as an intraoperative navigation tool to detect lymphatic flow in the extremities (3); sentinel lymph nodes in patients with breast (4) and gastric (5) cancers; and blood flow during coronary artery bypass grafting (6) and clipping of cerebral artery aneurysms (7). In hepatobiliary surgery, however, little attention was paid to the fluorescence of ICG until, in the late 2000s, Japanese surgeons used ICG-fluorescence imaging to visualize hepatobiliary structures (8-11). This is probably because liver surgeons regarded ICG as a reagent for estimation of hepatic function.

Potentially, ICG-fluorescence imaging is highly suitable for hepatobiliary surgery, because the fluorescence of ICG and its biliary excretion can be used for the intraoperative identification of biological structures. In 2009, the first report of fluorescence cholangiography during laparoscopic cholecystectomy described using ICG excreted into bile following preoperative intravenous injection as the source of fluorescence (12). During the development of fluorescence cholangiography for hepatic tumors, it was found that ICG accumulated in cancerous tissues of hepatocellular carcinoma (HCC) and in non-cancerous hepatic parenchyma around adenocarcinoma foci (13,14). Recently, this technique has been used clinically to identify hepatic tumors during laparoscopic hepatectomy (15), and during open surgery. Refinements in imaging techniques have enabled the use of ICG-fluorescence imaging for visualization of hepatic segments, enabling more accurate anatomic resection of the liver (16,17).

Fluorescence cholangiography

Because human bile contains proteins such as albumin and lipoproteins that bind ICG (18), fluorescent images of the biliary tract can be obtained by intrabiliary injection of ICG (11). The fluorescence intensity of protein-bound ICG was found to correlate with its concentrations to approximately 0.25 mg/mL, decreasing at higher concentrations because of the absorption of near-infrared light by ICG (9). Thus, to obtain clear fluorescence images of the bile ducts following intrabiliary injection of ICG, diluted ICG solution (approximately 0.025 mg/mL) should be used for imaging (11). It is also important to aspirate a small amount of bile into the syringe before injection to promote binding of ICG to proteins. When the intrahepatic bile duct anatomy and the extrahepatic biliary system must be identified, ICG should be diluted with radiographic contrast agents, enabling radiographic cholangiography easily and immediately following fluorescence cholangiography (19).

Fluorescence cholangiography could also be performed following intravenous injection of ICG, because ICG excreted into bile can act as a source of fluorescence (*Figure 1*) (7). This technique involves the intravenous injection of small amounts of ICG, usually 2.5 mg, diluted into 1 mL solution (12,20). Although biliary excretion of ICG begins within minutes after intravenous injection (21), ICG should be administered at least 15 minutes before imaging to obtain better signal-to-background contrast. Indeed, ICG fluorescence in the extrahepatic bile ducts continues up to 6 hours after injection (12). Intravenous

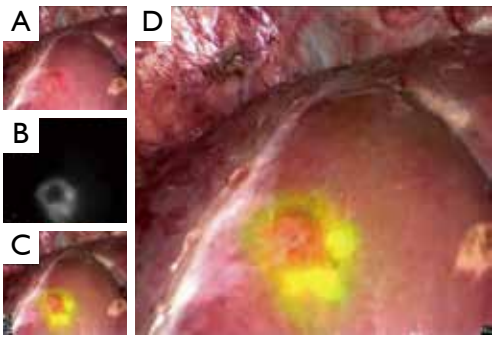

Figure 2 Fluorescence imaging of hepatic tumor (CRLM). Fluorescence imaging following preoperative intravenous injection of indocyanine green (ICG), clearly showing a CLRM located in hepatic segment VIII as a rim-fluorescing lesion during laparoscopic hepatectomy. (A) White-light color image; (B) monochromatic fluorescence image; (C,D) pseudocolor fusion images of a fluorescence and a white-light color image.

injection of ICG has potential advantages over conventional radiographic cholangiography in saving time and avoiding bile duct injury associated with the catheterization required for injection of contrast materials. Although fluorescence cholangiography has a limitation in detecting small stones floating in the common bile duct, the present technique has recently gained attention as a novel and easy-to-use navigation tool that provides a roadmap of the extrahepatic ducts, enhancing safety (22) during laparoscopic (23-28) and robotic (29,30) cholecystectomy and reducing the need for intraoperative radiographic cholangiography.

Fluorescence imaging of hepatic tumors

In a previous study of 37 patients with HCC and 12 with colorectal liver metastasis (CRLM), fluorescence imaging following preoperative intravenous injection of 0.5 mg/kg ICG identified all of the microscopically confirmed HCCs and CRLM on the cut surfaces of the resected specimens (13). The fluorescence patterns of these tumors could be classified into three types: total fluorescence, in which all tumor tissue showed uniform fluorescence; partial fluorescence, in which some tumor tissues showed fluorescence; and rim fluorescence, in which the cancer tissues were negative for fluorescence, but the surrounding liver parenchyma showed fluorescence. These fluorescence patterns were closely associated with the characteristics of the liver cancers. Total fluorescence-type tumors included all well-differentiated HCCs, whereas rim fluorescence-type-tumors consisted only of poorly differentiated HCCs and CRLM.

Recently, the mechanism of ICG-fluorescence imaging of HCCs was elucidated by immunohistochemical staining and gene expression analysis (14). In differentiated HCC tissues, the expression levels of portal uptake transporters of ICG [organic anion-transporting polypeptide 8 and Na+/taurocholate cotransporting polypeptide (31)] were well preserved, but functional or morphological biliary excretion disorders were present, leading to retention of ICG in cancerous tissues at the time of surgery, following preoperative intravenous injection. In poorly-differentiated HCCs, however, the portal uptake transporters were downregulated in cancerous tissues but biliary excretion of ICG by surrounding non-cancerous hepatic parenchyma was also disordered, resulting in rim-type fluorescence. The rim-type fluorescence signal in CRLM has been reported to be caused by immature hepatocytes with decreased bile excretion ability that surrounds the tumor (32). ICG fluorescence of HCC tissues was found associated with a risk of recurrence after hepatectomy (33).

Irrespective of their fluorescence patterns, subcapsular hepatic tumors can be identified on the liver surfaces by intraoperative fluorescence imaging, following preoperative intravenous injection of ICG. In this technique, ICG (0.5 mg/kg body weight) is administered intravenously, usually within two weeks before surgery. This method can also be used to detect biliary congestion caused by tumor invasion (34), micrometastases from pancreatic cancer (35), and extrahepatic spread of HCC (36). The intraoperative ICG-fluorescence imaging of hepatic tumors is simple and is especially useful for identifying subcapsular lesions for removal during laparoscopic hepatectomy, in which visual inspection and palpation are limited compared with open surgery (*Figure 2*) (15).

This technique has potential drawbacks, however, including a relatively high false-positive rate [around 40% (13,14)]. Lesions newly detected by ICG-fluorescence imaging should be resected only when other modalities, such as palpation and intraoperative ultrasonography, identify them as tumors to be removed. The incidence of false-positives can be reduced by not administering ICG on the day before surgery, especially in patients with decreased liver function due to cirrhosis or preoperative chemotherapy (13).

Fluorescence imaging of hepatic segments

Anatomic segmentectomy is the essential surgical

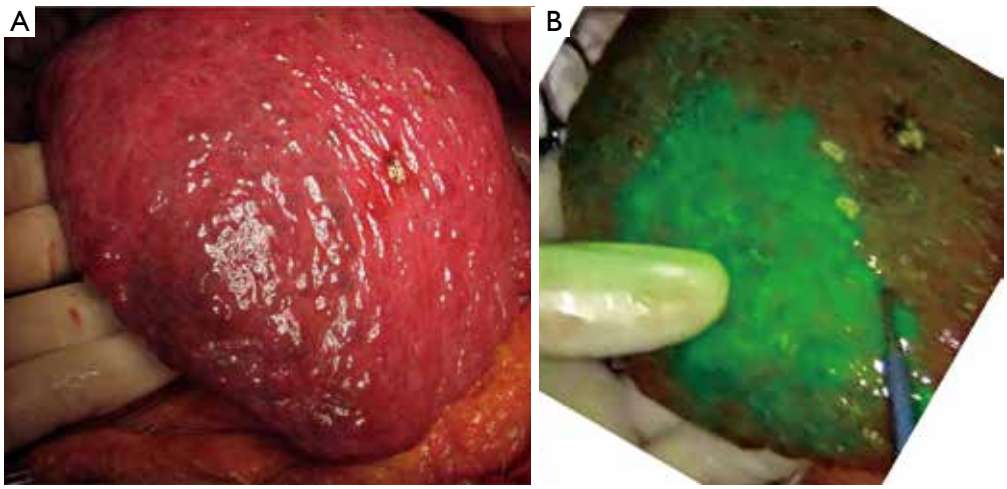

Figure 3 Identification of hepatic segments by dye-staining technique with concomitant use of indigo-carmine and indocyanine green. Fusion pseudocolor fluorescence image on color image (right), clearly showing the boundaries of hepatic segment VI. The blue stain on the liver surface is unclear because of fibrosis and the irregular surface of the liver due to cirrhosis. In this case, a laparoscopic fluorescence imaging system was used during open hepatectomy.

technique in hepatectomy, balancing cancer curability and postoperative hepatic function (37). Boundaries of hepatic segments prior to anatomic resection can be identified by a dye-staining technique, in which indigo-carmine solution is injected into the corresponding portal branch under ultrasound guidance, with positivity defined as blue staining of hepatic surfaces. In 2008, fluorescence imaging following portal injection of ICG was first used in the intraoperative identification of hepatic segments (10). This technique was later refined (16) by using a more diluted solution of ICG (2.5 mg) as a source of fluorescence and an imaging system enabling fusion of fluorescence images on color images. The concomitant injection of indigo-carmine solution with a small amount of ICG (0.25 mg) could enhance the success rate of hepatic segment identification, especially in patients with cirrhosis and/or those having livers covered by thick connective tissues owing to previous surgery (17) (*Figure 3*).

In addition to identifying hepatic segments for removal following portal injection of ICG solution (positive staining technique), hepatic segments can be identified as ischemic regions by intravenous injection of ICG (2.5 mg) following closure/division of the corresponding portal pedicle (negative staining technique) (16,38). The latter technique is especially useful in laparoscopic hepatic segmentectomy, in which injection of ICG solution into the portal vein is technically difficult (38,39). Intraoperative fluorescence imaging can also be used to estimate portal uptake function in veno-occlusive regions of the liver during hepatectomy or living-donor liver transplantation, by measuring trends of fluorescence intensity of the hepatic surfaces following injection of ICG (40,41).

Future prospects of ICG-fluorescence imaging in hepatobiliary surgery

In laparoscopic and robotic surgery, surgical procedures are based on operation fields displayed on a monitor. Thus, it is not surprising that fluorescence imaging was rapidly applied to these minimally-invasive methods. Laparoscopic and robotic fluorescence imaging systems have become commercially available (*Figure 4A*). In the near future, three-dimensional and ultra-high definition imaging (4K) may be delivered to clinical settings. Further technological innovations, however, are need to improve the feasibility of fluorescence imaging during open surgery, enabling surgeons to operate without having to switch from operation fields to a TV monitor (*Figure 4B*).

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Figure 4 Fluorescence imaging systems in laparoscopic and open surgery. (A) In laparoscopic surgery, surgeons always watch a TV monitor to obtain white-light and fluorescence images, when needed; (B) during open surgery, surgeons must look from the field of operation to each monitor used for intraoperative diagnosis, such as intraoperative ultrasonography (white arrow) and fluorescence imaging (yellow arrow). Use of a laparoscopic imaging system equipped with a short-length laparoscope during open surgery (yellow arrowhead).

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Footnote

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

References

1. Landsman ML, Kwant G, Mook GA, et al. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. J Appl Physiol 1976;40:575-83.
2. Guyer DR, Puliafito CA, Monés JM, et al. Digital indocyanine-green angiography in chorioretinal disorders. Ophthalmology 1992;99:287-91.
3. Ogata F, Azuma R, Kikuchi M, et al. Novel lymphography using indocyanine green dye for near-infrared fluorescence labeling. Ann Plast Surg 2007;58:652-5.
4. Kitai T, Inomoto T, Miwa M, et al. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. Breast Cancer 2005;12:211-5.
5. Kusano M, Tajima Y, Yamazaki K, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. Dig Surg 2008;25:103-8.
6. Rubens FD, Ruel M, Fremes SE. A new and simplified method for coronary and graft imaging during CABG. Heart Surg Forum 2002;5:141-4.
7. Raabe A, Nakaji P, Beck J, et al. Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography during aneurysm surgery. J Neurosurg 2005;103:982-9.
8. Kubota K, Kita J, Shimoda M, et al. Intraoperative assessment of reconstructed vessels in living-donor liver transplantation, using a novel fluorescence imaging technique. J Hepatobiliary Pancreat Surg 2006;13:100-4.
9. Mitsuhashi N, Kimura F, Shimizu H, et al. Usefulness of intraoperative fluorescence imaging to evaluate local anatomy in hepatobiliary surgery. J Hepatobiliary Pancreat Surg 2008;15:508-14.
10. Aoki T, Yasuda D, Shimizu Y, et al. Image-guided liver mapping using fluorescence navigation system with indocyanine green for anatomical hepatic resection. World J Surg 2008;32:1763-7.
11. Ishizawa T, Tamura S, Masuda K, et al. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. J Am Coll Surg 2009;208:e1-4.
12. Ishizawa T, Bandai Y, Kokudo N. Fluorescent

cholangiography using indocyanine green for laparoscopic cholecystectomy: an initial experience. Arch Surg 2009;144:381-2.
13. Ishizawa T, Fukushima N, Shibahara J, et al. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer 2009;115:2491-504.
14. Ishizawa T, Masuda K, Urano Y, et al. Mechanistic background and clinical applications of indocyanine green fluorescence imaging of hepatocellular carcinoma. Ann Surg Oncol 2014;21:440-8.
15. Kudo H, Ishizawa T, Tani K, et al. Visualization of subcapsular hepatic malignancy by indocyanine-green fluorescence imaging during laparoscopic hepatectomy. Surg Endosc 2014;28:2504-8.
16. Inoue Y, Arita J, Sakamoto T, et al. Anatomical liver resections guided by 3-dimensional parenchymal staining using fusion indocyanine green fluorescence imaging. Ann Surg 2015;262:105-11.
17. Miyata A, Ishizawa T, Tani K, et al. Reappraisal of a dye-staining technique for anatomic hepatectomy by the concomitant use of indocyanine green fluorescence imaging. J Am Coll Surg 2015;221:e27-36.
18. Mullock BM, Shaw LJ, Fitzharris B, et al. Sources of proteins in human bile. Gut 1985;26:500-9.
19. Ishizawa T, Kokudo N. Fluorescence imaging of human bile and biliary anatomy. In: Fong Y, Giulianotti PC, Lewis J, et al, editors. Imaging and visualization in the modern operating room. New York: Springer, 2015:271-8.
20. Ishizawa T, Bandai Y, Ijichi M, et al. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg 2010;97:1369-77.
21. Cherrick GR, Stein SW, Leevy CM, et al. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. J Clin Invest 1960;39:592-600.
22. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 1995;180:101-25.
23. Tagaya N, Shimoda M, Kato M, et al. Intraoperative exploration of biliary anatomy using fluorescence imaging of indocyanine green in experimental and clinical cholecystectomies. J Hepatobiliary Pancreat Sci 2010;17:595-600.
24. Sherwinter DA. Identification of anomolous biliary anatomy using near-infrared cholangiography. J Gastrointest Surg 2012;16:1814-5.
25. Osayi SN, Wendling MR, Drosdeck JM, et al. Near-infrared fluorescent cholangiography facilitates identification of biliary anatomy during laparoscopic cholecystectomy. Surg Endosc 2015;29:368-75.
26. Schols RM, Bouvy ND, van Dam RM, et al. Combined vascular and biliary fluorescence imaging in laparoscopic cholecystectomy. Surg Endosc 2013;27:4511-7.
27. Verbeek FP, Schaafsma BE, Tummer QR, et al. Optimization of near-infrared fluorescence cholangiography for open and laparoscopic surgery. Surg Endosc 2014;28:1076-82.
28. Dip F, Roy M, Lo Menzo E, et al. Routine use of fluorescent incisionless cholangiography as a new imaging modality during laparoscopic cholecystectomy. Surg Endosc 2015;29:1621-6.
29. Spinoglio G, Priora F, Bianchi PP, et al. Real-time near-infrared (NIR) fluorescent cholangiography in single-site robotic cholecystectomy (SSRC): a single-institutional prospective study. Surg Endosc 2013;27:2156-62.
30. Daskalaki D, Fernandes E, Wang X, et al. Indocyanine green (ICG) fluorescent cholangiography during robotic cholecystectomy: results of 184 consecutive cases in a single institution. Surg Innov 2014;21:615-21.
31. de Graaf W, Häusler S, Heger M, et al. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. J Hepatol 2011;54:738-45.
32. van der Vorst JR, Schaafsma BE, Hutteman M, et al. Near-infrared fluorescence-guided resection of colorectal liver metastases. Cancer 2013;119:3411-8.
33. Shibasaki Y, Sakaguchi T, Hiraide T, et al. Expression of indocyanine green-related transporters in hepatocellular carcinoma. J Surg Res 2015;193:567-76.
34. Harada N, Ishizawa T, Muraoka A, et al. Fluorescence navigation hepatectomy by visualization of localized cholestasis from bile duct tumor infiltration. J Am Coll Surg 2010;210:e2-6.
35. Yokoyama N, Otani T, Hashidate H, et al. Real-time detection of hepatic micrometastases from pancreatic cancer by intraoperative fluorescence imaging: Preliminary results of a prospective study. Cancer 2012;118:2813-9.
36. Satou S, Ishizawa T, Kokudo N, et al. Indocyanine green fluorescent imaging for detecting extrahepatic metastasis of hepatocellular carcinoma. J Gastroenterol 2013;48:1136-43.
37. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. Surg Gynecol Obstet 1985;161:346-50.
38. Ishizawa T, Zuker NB, Kokudo N, et al. Positive and negative staining of hepatic segments by use of fluorescent

imaging techniques during laparoscopic hepatectomy. Arch Surg 2012;147:393-4.
39. Ishizawa T, Gumbs AA, Kokudo N, et al. Laparoscopic segmentectomy of the liver: from segment I to VIII. Ann Surg 2012;256:959-64.
40. Kawaguchi Y, Ishizawa T, Miyata Y, et al. Portal uptake function in veno-occlusive regions evaluated by real-time fluorescent imaging using indocyanine green. J Hepatol 2013;58:247-53.
41. Inoue Y, Saiura A, Arita J, et al. Hepatic Vein-Oriented Liver Resection Using Fusion Indocyanine Green Fluorescence Imaging. Ann Surg 2015;262:e98-9.

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Hepatic Surgical Technique

Small for size liver remnant following resection: prevention and management

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Abstract: In the latest decades an important change was registered in liver surgery, however the management of liver cirrhosis or small size hepatic remnant still remains a challenge. Currently post-hepatectomy liver failure (PLF) is the major cause of death after liver resection often associated with sepsis and ischemia-reperfusion injury (IRI). "Small-for-size" syndrome (SFSS) and PFL have similar mechanism presenting reduction of liver mass and portal hyper flow beyond a certain threshold. Few methods are described to prevent both syndromes, in the preoperative, perioperative and postoperative stages. Additionally to portal vein embolization (PVE), radiological examinations (mainly CT and/or MRI), and more recently 3D computed tomography are fundamental to quantify the liver volume (LV) at a preoperative stage. During surgery, in order to limit parenchymal damage and optimize regenerative capacity, some hepatoprotective measures may be employed, among them: intermittent portal clamping and hypothermic liver preservation. Regarding the treatment, since PLF is a quite complex disease, it is required a multi-disciplinary approach, where it management must be undertaken in conjunction with critical care, hepatology, microbiology and radiology services. The size of the liver cannot be considered the main variable in the development of liver dysfunction after extended hepatectomies. Additional characteristics should be taken into account, such as: the future liver remnant; the portal blood flow and pressure and the exploration of the potential effects of regeneration preconditioning are all promising strategies that could help to expand the indications and increase the safety of liver surgery.

Keywords: Liver surgery; small for size liver remnant; post-hepatectomy liver failure (PLF); liver resection

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Introduction

In the latest decades an important change was registered in liver surgery, related to the progress of surgical techniques, anesthesiology and postoperative treatment, allowing a sharp decrease in mortality and morbidity. However, management of liver cirrhosis or small size hepatic remnant still remains a challenge (1).

The liver presents regenerative capacity, allowing performance of repeated resections. In certain cases, when this capacity is impaired, or where extensive resections were performed with small remnant liver, these patients may develop small for size syndrome (SFSS) with the presence of reduced liver mass insufficient to maintain normal liver function.

The term SFSS was first employed in liver transplantation to describe the development of acute liver failure (ALF) (hyperbilirubinemia, coagulopathy, encephalopathy and refractory ascites) resulted from the transplantation of a donor liver that was too small for a given recipient (2). A similar syndrome, called "post-hepatectomy liver failure (PLF)" was also described in hepatic surgery involving extended resections of liver mass. The last one is characterized by postoperative liver dysfunction, with clinical signs of prolonged cholestasis, coagulopathy, portal hypertension and ascites. PLF is the major cause of death after liver resection often associated with sepsis and ischemia-

reperfusion injury (IRI) (3).

The patho-physiological mechanisms of the SFSS and PLF are very similar, both presenting reduction of liver mass and portal hyper flow beyond a certain threshold (4).

The aim of this review is to discuss applicable peri-operative methods to prevent the SFSS or PLF and highlight the main treatment types.

Pathophysiology

The liver should contain minimum amount of parenchymal hepatic cells to assure its functions and the maintenance of its regeneration capacity. The hepatic parenchyma should be able to accommodate the hemodynamic changes that occur after liver resection, avoiding venous congestion. Factors such as decrease of hepatic parenchyma cells, infection and different causes that might jeopardize regeneration should be absent (5).

Decrease in parenchymal volume results in a hyper perfusion of the liver, causing dilation of sinusoids, hemorrhagic infiltration, shear stress, centro lobular necrosis, prolonged cholestasis impaired synthetic function and inhibition of cell proliferation (6).

Hepatic resections have higher risks of infection (above 50%). The number of Kupffer cells after hepatic resection decreased and thus the liver's ability to fight against infection as well. The sepsis possesses the ability to complicate or precipitate PLF. A relative increase in the production of endotoxins in the remnant liver is beneficial, once it activates the Kupffer cells, trigging the liver regeneration. This prolonged state may cause Kupffer's cellular dysfunction, resulting in difficulty of regeneration and even liver necrosis (7).

The parenchymal damage occurs following vascular occlusion or after hemorrhagic shock, causing IRI. After a period of ischemia, the complement cascade is triggered, leading to the activation of Kupffer cells, reactive oxygen appearance of species (ROS) and endothelial cell lesion. During reperfusion a release of cytokines, cell adhesion, activation and recruitment of T cell and polymorphonuclear cell occurs, resulting in microvascular lesion, inflammation and cell death (8).

Preoperative period-prevention

Liver function tests and scores (9)

The liver function tests can be divided into three types:

Conventional tests, i.e., serum bilirubin, albumin, alkaline phosphatase, gamma glutamyl transpeptidase, prothrombin time (PT) and platelet count;

Quantitative tests, i.e., aminopyrine breath test, antipyrine clearance, caffeine clearance, lidocaine clearance, methacetin breath test, galactose elimination capacity, low-dose galactose clearance, clearance sorbitol, indocyanine green disappearance, albumin synthesis, urea synthesis and 99mTc-GSA;

Scores, i.e., Child-Turcotte-Pugh and MELD.

One of the best tests today to check liver function before surgery is liver retention of indocyanine green. Widely used since the decade of the 70 in Asian countries, and not yet widespread in the west.

Based on the decisional tree [established by Seyama *et al.* (*Figure 1*)] identify before the operation which hepatic volume can be resected in cirrhotic patients depending on their liver function (9).

Liver volume (LV) manipulation and liver parenchymal protection

The ideal volume of the hepatic remnant was exhaustively discussed in the literature and some formulas to calculate it were described (10) (*Table 1*).

The radiological examinations (mainly CT and/or MRI) before surgery are fundamental to quantify the LV. More recently 3D computed tomography reconstructions could define more accurately the hepatic volume allowing preoperative studies. Through this exam, the surgeon can simulate a resection, making possible the planning and the choice of the best way to do the procedure (15,18).

Measurement of volume ratios correlated with the etiology and severity of chronic liver disease (CLD) constitute a reliable predictors of patient survival (19). Although, the reliability of this ratio might be compromised by the presence of dilated bile ducts, multiple tumors, undetected lesions. Additionally, due to cholestasis or previous chemotherapy, cholangitis, vascular obstruction, steatosis or cirrhosis, or segmental atrophy and/or hypertrophy from tumor growth, negatively impacts the liver function (16).

Values calculated from graft weight-to-recipient body weight ratio (GRBWR), or standardized liver volume (SLV) based on recipient body surface area (BSA) are used to predict minimum adequate graft volume (15). But in presence of steatosis, particularly >30%, graft weight alone is not a suitable guide (10).

Extended resection of 80% of functional parenchyma can be performed in the absence of CLD for hepatobiliary

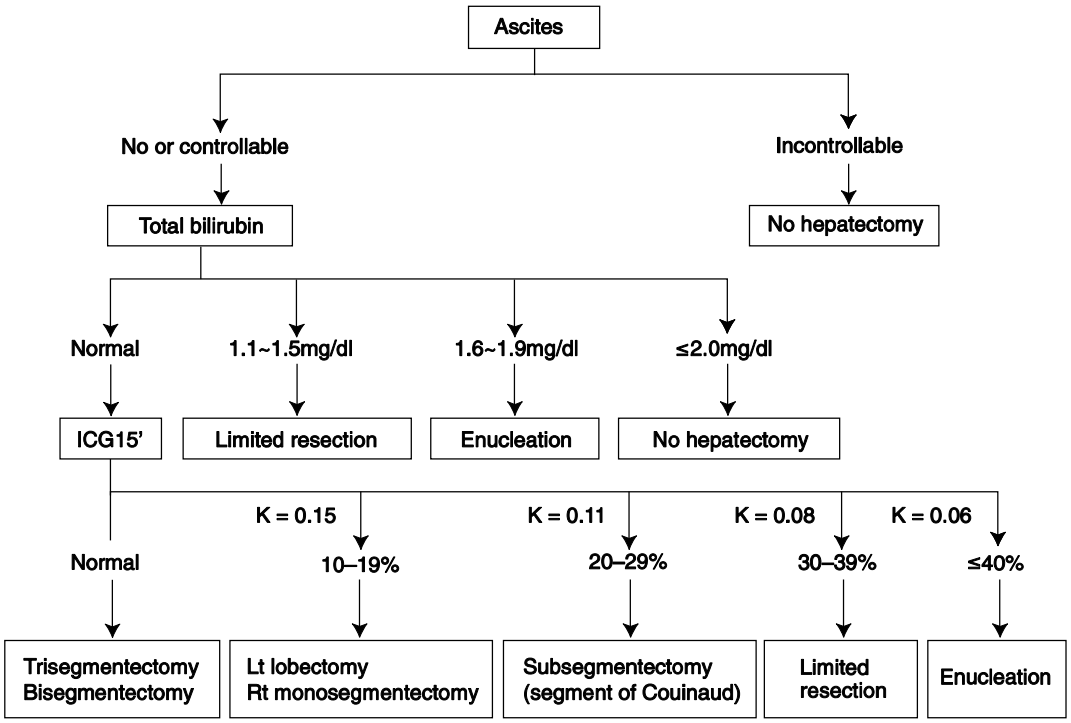

Figure 1 Decisional tree established by Seyama *et al*. (9).

Table 1 Formulas to calculate volume of the hepatic remnant

LV =706.2× BSA (m^2) +2.4 (11)
LV =[13 3 height (cm)] + [12 3 weight (kg)] –1530 (12)
LV =1072.8× BSA (m^2) –345.7 (13)
TLV =191.8+18.51× weight (kg) (14)
TLV =–794.41+1267.28× BSA (14)
VR = (LV from reconstructed CT image/predicted volume) ×100 (12)
SFLR = FLR (by CT volumetry) ÷ absolute LV (15)
ERFL = FRL ÷ (TLV – tumour volume) (16)
ERFL = (resected volume – tumour volume) ÷ (TLV – tumour volume) (16)
GRWR = graft weight ÷ recipient body weight (kg) (17)

malignancies (20). Recommended minimal functional remnant LV following extended hepatectomy is 25% in a normal liver, and 40% in a "sick" liver, with moderate to severe steatosis, cholestasis, fibrosis, cirrhosis, or following chemotherapy (15).

There are some strategies that allow volume manipulation, such as portal vein embolization (PVE) and two-stage hepatectomy (16,21). PVE is usually performed percutaneously by transhepatic PVE, but may also be achieved by surgical ligation and injection of alcohol or others products to prevent the recanalization of the portal vein. PVE increases the functional capacity of the liver remnant and can increase contralateral lobe volume by up to 20 per cent, with the peak in growth occurring within 2-4 weeks (22).

Patients, in which the liver does not have a good result after PVE are selected as no good candidates for large resections due to the difficulty of regeneration (22). Patients with bilateral tumors when proceeding PVE may stimulate of neoplastic cell growth in the non-embolized lobes, in this cases surgical treatment or ablation [radiofrequency (23,24), microwave (25) and NanoKnife® (personal experience)] of such lesions prior to the embolization are required (26). Neoadjuvant chemotherapy (27) and intra-arterial chemotherapy (28) also can be used in combination with PVE to control tumour load before resection (20,29).

Patients with bilateral liver lesions, where resection is not feasible under one procedure, the two stage hepatectomy is applied, allowing the remaining liver to be resected to achieve the suitable LV at the second stage.

Intraoperative period-prevention

In order to limit parenchymal damage and optimize regenerative capacity, two hepatoprotective measures may be employed: intermittent portal clamping and hypothermic liver preservation.

Intermittent portal clamping with intervals allowed for reperfusion is preferred to continuous clamping, usually applying a 15-min clamp-5-min release regimen (30-32).

Total vascular exclusion of the liver should be used when we have no choice to do the resection without it. When chosen, we can utilized hepatic vascular exclusion with preservation of the caval flow (33).

Hypothermic liver preservation in conjunction with total vascular exclusion attenuates IRI. The future remnant is infused with a preservative fluid and surrounded by crushed ice to maintain the liver at 4 ℃. This approach is a useful adjunct to complex resections when total vascular exclusion and vascular reconstructions are programmed (34). During surgery it is still possible to apply techniques to prevent the SFSS, if other procedures were not considered on the pre-operative period.

Association liver partition and portal vein ligation (ALPPS)

ALPPS, a newer strategy to increase resectability of hepatic malignancies, has been described for the first time in 2010 (35). This method relies on the fact (proved in clinical trials) that any closure of portal branch will be followed by a reactive perfusion through intrahepatic branches and collaterals present between two lobes. Hence, partition of the liver along the falciform ligament line, for example, will enhance regeneration compared to traditional methods. ALPPS has shown high hypertrophy rates compared to PVE/PVL (40% to 80% within a week compared to 8% to 27% within 2 to 60 days by PVL/PVE), however it is associated with high morbidity rates (16-64% of patients) and mortality rates (12-23% of patients), therefore a careful selection of surgical candidates should be done prior to surgery. Further investigation if ALPPS approach accelerates tumor growth is still required (35-37).

Recently, a number of comparisons between ALLPS and standard methods (PVE followed by liver resections) have been published (38-40). One of the proposed benefits of ALLPS, for example, is rapid removal of tumor(s), thus preventing patient dropout due to disease progression of existing liver tumors. This assumption, however, failed to achieve clinical relevance in a recent publication that compared right PVE + segment 4 to ALPPS, demonstrating mainly extra-hepatic location of metastasis in the patient's drop-out group. In addition, using PVE in this study yielded sufficient growth in 96.5% of the patients, with median hypertrophy of 62%, comparable to the FLR hypertrophy rates associated with the ALLPS approach (38).

Although none of the studies published with this technique provide measurements of portal pressure or portal blood flow, the clinical data suggest that the acceleration of the hypertrophy of the residual parenchyma occurs due to the reduction of intra-hepatic communicants, once the *in situ* split procedure leads to complete portal devascularization of segment 4, preventing formation of collaterals between the left and the right liver that could otherwise undermine the completeness of right portal vein occlusion alone (41).

A second and not mutually exclusive explanation would be the "regenerating liver" hypothesis proposed by Nagano *et al*. (42).

Modulation of portal pressure

Intraoperative Doppler ultrasonography has been used in combination with hepatic portal inflow modulation to detect and offset hyperperfusion in a small-for-size graft. Importantly, numerous interventions that modulate the portal blood flow have been shown to prevent the development of the SFSS in experimental models, such as: the performance of a portocaval anastomosis (43,44), the ligation of the splenic artery (45), banding of the portal vein (46) or the infusion of adenosine (47), somatostatin (48), pentoxifylline (49) or endothelin-1 (50). It is important to highlight that the role for inflow modulation at the time of major liver resection or as a salvage therapy in humans remains undefined.

After all these studies cited above we can conclude that the development of SFSS or PLF are not strictly determined by the "size" of the liver graft or remnant. It is determined by the hemodynamic parameters of the hepatic circulation and, specifically, by a portal blood flow that, when excessive for the volume of the liver parenchyma leads to over-pressure, sinusoidal endothelial denudation and hemorrhage. Perisinusoidal and periportal hemorrhage occurs in the first minutes after an extended hepatic resection as well as after the reperfusion of a small graft, while arterial vasoconstriction and ischemic cholangitis are observed at later stages (6).

Also, experimental and clinical studies consistently show that an increased portal blood flow relative to the weight of the liver results in an inverse relationship between portal and arterial blood flows that is known as the arterio-portal

buffer (51). The arterio-portal buffer occurs when the portal blood flow increases, the adenosine concentration in the space of mall decreases leading to arterial vasoconstriction and decrease of arterial blood flow, which is responsible for the late damage (52).

Studies performed in patients undergoing liver transplantation in which the portal and hepatic arterial blood flows were measured intra-operatively have provided further insights into the pathophysiology of the SFSS (6,53,54). A portal blood flow of 300 mL/min/100 g was established by Jiang *et al*. as the threshold above that the incidence of the SFSS increases significantly (54).

In living donor liver transplantations involving grafts with GWRW below 0.8, Troisi *et al*. showed that the construction of a portal-systemic shunt whenever the portal blood flow exceeded 250 mL/min/100 g was able to prevent the histological alterations characteristic of the SFSS and to improve the overall patient and graft survival (43,54).

Several studies indicate that additionally to blood flow, portal pressure can also be considered a good parameter for predicting the failure of the graft. For example, patients with a portal pressure higher than 20 mmHg show a decrease from 85% to 38% in their 6-month survival (55). Yagi *et al*. also described that a portal pressure above 20 mmHg was associated with the development of ascites, coagulopathy and hyperbilirubinemia as well as with an early hypertrophy of the graft, higher values of hepatocyte growth factor (HGF) and diminished levels of vascular epithelial growth factor (VEGF), suggesting that an increased portal pressure also influences liver regeneration (56). Kaido *et al*. reported their experience with small grafts (GWRW of 0.6) in combination with portal pressure control (targeting final portal pressures below 15 mmHg), showing that the survival of recipients of small grafts and standard-size grafts was similar and that the portal pressure control strategy resulted in a decreased rate of complications in the donors (57).

As in liver transplantation, studies involving extended hepatic resections also indicate that the increased portal blood flow with diminished residual parenchyma are a critical factor determining the development of PLF (47,58,59). The performance of a portocaval anastomosis in a patient with liver cirrhosis undergoing a major hepatectomy effectively prevented the syndrome, probably by reducing shear stress and damage to the sinusoids (60).

Post-operative period-treatment (61)

PLF is a quite complex disease, that requires a multi-disciplinary approach, where it management must be undertaken in conjunction with critical care, hepatology, microbiology and radiology services (1).

After liver resection, clinical and laboratory assessment should be proceeded. Normally, the level of serum bilirubin and the INR rises in the first 48-72 h after resection. It is possible to identify liver dysfunction, whenever bilirubin concentration is above 50 μmol/L (3 mg/dL) or INR greater than 1.7 beyond 5 days of surgery (3). The most sensitive variable is serum bilirubin as predictor of outcome in PLF (62). PT and INR are also relevant, but the interpretation may be compromised if patients have received clotting factors.

Serum albumin, although an indicator of hepatic synthetic function, will vary in response to inflammation and administration of intravenous fluids (63,64). Increased levels of liver enzymes are common after liver resection and do not predict outcome (3).

Ascites and hepatic encephalopathy are important markers for liver failure, although it may be difficult to assess in the immediate postoperative period. The first occurs as a result of surgery (portal hypertension, dissection, gross fluid overload), while the second is a result of mental state as collateral effect of drugs such as opiates (62).

Several studies assessed the role of postoperative functional of the liver. This task still consist a challenge, once the ICGR15 is capable to predicts PLF (65), but its value diminishes once liver failure is established, since the changes in hepatic blood flow impacts ICGR15. In the absence of controlled trials for PLF, management relies on data from experience with ALF, secondary to paracetamol toxicity (66-68).

The pattern of organ dysfunction that occurs as a result of PLF is similar to that in sepsis (1). Once the following symptoms occur: cardiovascular failure, characterized by reduced systemic vascular resistance and capillary leak; acute lung injury, due to pulmonary edema and acute respiratory distress syndrome may ensue and acute kidney injury can progress rapidly in PLF. In those cases, fluid balance should be managed judiciously with avoidance of salt and water overload (64). Identifying and treating underlying sepsis is key in managing patients with PLF. Sepsis may exacerbate PLF, and bacterial infection is present in 80 per cent of patients with PLF (69) and in 90 per cent of those with ALF (70).

Therefore, any acute deterioration should be attributed to sepsis until proven otherwise. Management of sepsis should be in accordance with the surviving sepsis guidelines (71). A trial of prophylactic antibiotics after liver

resection failed to show a reduction in liver dysfunction or infective complications (72). A study of ALF have shown that prophylactic antibiotics reduce infections, but the impact on a long-term outcome is inconclusive (70). In critically ill patients with PLF, chest radiography and cultures of blood, urine, sputum and drain site/ascitic fluid should be performed (68). Current guidelines for ALF propose that broad-spectrum antibiotics should be administered empirically to patients with progression to grade 3 or 4 of hepatic encephalopathy, renal failure and/or worsening SIRS parameters (68).

Additionally coagulopathy may occur transiently after major resection and is found in all patients with PLF. As in ALF, coagulation parameters can be used to chart the progress of PLF, provided blood products have not been given. In the absence of bleeding it is not necessary to correct clotting abnormalities, except for invasive procedures or when coagulopathy is severe. The level at which a coagulopathy should be corrected before an interventional procedure in ALF has yet to be defined (66,68,73). Vitamin K may be given, but this is not supported by clinical trials (66). Thrombocytopenia may complicate liver failure (74). Indications for platelet transfusion in ALF include bleeding, severe thrombocytopenia (less than 20×10^6/L), or when an invasive procedure is planned. A platelet count above 70×10^6/L is deemed safe for interventional procedures (75). Recombinant factor VIIa (rFVIIa) has been used to treat coagulopathy in patients with ALF (76). In a large controlled trial of rFVIIa following major liver resection, no reduction in bleeding events was observed (77). Its role in PLF is yet to be defined.

Gastrointestinal hemorrhage is a recognized complication of liver failure. In ALF, H2-receptor blockers and proton pump inhibitors (PPIs) reduce gastrointestinal ill patients ensuring euglycemia improves survival and reduces morbidity (78).

The role of imaging in PLF is to assess hepatic blood flow, identify reversible causes of liver failure and locate sites of infection. Hepatic blood flow can be evaluated using non-invasive imaging. Doppler ultrasonography may identify portal vein, hepatic artery and hepatic vein thrombosis. Contrast CT or MRI can be used to establish hepatic blood flow, provide more details of vascular abnormalities and identify sites of infection. If patency of hepatic vessels is still in doubt on cross-sectional imaging, angiography is the "gold standard" (79).

Portal vein thrombosis has also been implicated in the development of PLF. In these rare cases of inflow and outflow thrombosis with PLF, a decision must be taken regarding the benefit of surgical or radiological thrombectomy or dissolution versus anticoagulation (80,81). The use of terlipressin also can reduce the portal venous pressure helping to hepatic regeneration (82). Cerebral edema and intracranial hypertension may occur as a result of PLF. It is unlikely in patients with grade 1 or 2 of liver encephalopathy. When achieving grade 3 encephalopathy, a head CT should be performed to exclude intracranial hemorrhage or other causes of declining mental status.

In patients with established ALF and encephalopathy, enteral lactulose might prevent or treat cerebral edema, although the benefits remain unproven. Progression to grade 3/4 encephalopathy warrants ventilation and may require intracranial pressure monitoring (68).

The concept of hepatocyte transplantation has been investigated as a strategy to boost residual liver function. Intrahepatic hepatocyte transplantation (83) has been used successfully to treat patients with metabolic disorders of the liver. However, results in liver failure (including patients with PLF) have been poor due to insufficient delivery of functional cells. The potential for stem cell therapies has yet to be established (84).

The use of salvage hepatectomy and orthotopic liver transplantation for PLF has been reported in seven patients who underwent liver resection for cancer (85). Although the indications for transplantation in this study were questionable, overall 1-year (88 per cent) and 5-year (40 per cent) survival rates were promising.

Extracorporeal liver support (ELS) devices fall into two categories: artificial and bioartificial systems. Artificial devices use combinations of haemodialysis and adsorption over charcoal or albumin to detoxify plasma. Bioartificial devices use human or xenogenic hepatocytes maintained within a bioreactor to detoxify and provide synthetic function. These systems have not been evaluated extensively in patients with PLF. A recent meta-analysis and systematic review showed that ELS may improve survival in patients with ALF, but not acute-on-chronic liver failure, in comparison with standard medical therapy (86).

Conclusions

The increased use of small liver grafts and the expansion of indications of curative liver surgery in patients with hepatic tumors allows a step change in the knowledge of the mechanisms responsible for the development of the SFSS

and PLF.

It became evident that the size of the liver cannot be considered the main variable in the development of liver dysfunction after extended hepatectomies. Additional characteristics should be taken into account, such as: the future liver remnant; the portal blood flow and pressure and the exploration of the potential effects of regeneration preconditioning are all promising strategies that could help to expand the indications and increase the safety of liver surgery.

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References

1. van den Broek MA, Olde Damink SW, Dejong CH, et al. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. Liver Int 2008;28:767-80.
2. Ikegami T, Shimada M, Imura S, et al. Current concept of small-for-size grafts in living donor liver transplantation. Surg Today 2008;38:971-82.
3. Balzan S, Belghiti J, Farges O, et al. The 50-50 Criteria on Postoperative Day 5. Ann Surg 2005;242:824-8, discussion 828-9.
4. Asencio JM, Vaquero J, Olmedilla L, et al. "Small-for-flow" syndrome: shifting the "size" paradigm. Med Hypotheses 2013;80:573-7.
5. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology 2006;43:S45-53.
6. Demetris AJ, Kelly DM, Eghtesad B, et al. Pathophysiologic Observations and Histopathologic Recognition of the Portal Hyperperfusion or Small-for-size-syndrome. Am J Surg Pathol 2006;30:986-93.
7. Panis Y, McMullan DM, Emond JC. Progressive necrosis after hepatectomy and the pathophysiology of liver failure after massive resection. Surgery 1997;121:142-9.
8. Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. Am J Physiol Gastrointest Liver Physiol 2003;284:G15-26.
9. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. Hepatol Res 2009;39:107-16.
10. Tucker ON, Heaton N. The "small for size" liver syndrome. Curr Opin Crit Care 2005;11:150-5.
11. Urata K, Kawasaki S, Matsunami H. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 1995;21:1317-21.
12. Lin XZ, Sun Y, Liu Y, et al. Liver volume in patients with or without chronic liver diseases. Hepatogastroenterology 1998;45:1069-74.
13. Heinemann A, Wischhusen F, Püschel K, et al. Standard liver volume in the Caucasian population. Liver Transpl Surg 1999;5:366-8.
14. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in Western adults. Liver Transpl 2002;8:233-40.
15. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512-9.
16. Azoulay D, Castaing D, Smail A, et al. Resection of nonresectable liver metastases from colorectal cancer after percutaneous portal vein embolization. Ann Surg 2000;231:480-6.
17. Abdalla EK, Denys A, Chevalier P, et al. Total and segmental liver volume variations: implications for liver surgery. Surgery 2004;135:404-10.
18. Mise Y, Tani K, Aoki T, et al. Virtual liver resection: computer-assisted operation planning using a three-dimensional liver representation. J Hepatobiliary Pancreat Sci 2013;20:157-64.
19. Zhou XP, Lu T, Wei Y, et al. Liver volume variation in patients with virus-induced cirrhosis: findings on MDCT. AJR Am J Roentgenol 2007;189:W153-9.
20. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-80; discussion 680-1.
21. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 2000;232:777-85.
22. Farges O, Belghiti J. Portal Vein Embolization Before Right Hepatectomy Prospective clinical trial. Ann Surg 2003;237:208-17.
23. Elias D, Santoro R, Ouellet J. Simultaneous percutaneous right portal vein embolization and left liver tumor radiofrequency ablation prior to a major right hepatic resection for bilateral colorectal metastases. Hepatogastroenterology 2004;51:1788.
24. Akgül Ö, Çetinkaya E, Ersöz Ş, et al. Role of surgery in colorectal cancer liver metastases. World J Gastroenterol 2014;20:6113-22.
25. Bala MM, Riemsma RP, Wolff R, et al. Microwave coagulation for liver metastases. Cochrane Database Syst

Rev 2013;10:CD010163.
26. Hoekstra LT, van Lienden KP, Doets A, et al. Tumor progression after preoperative portal vein embolization. Ann Surg 2012;256:812-7; discussion 817-8.
27. Adam R, Delvart V, Pascal G, et al. Rescue Surgery for Unresectable Colorectal Liver Metastases Downstaged by Chemotherapy. A model to predict long term survival. Ann Surg 2004;240:644-57.
28. Selzner N, Pestalozzi BC, Kadry Z, et al. Downstaging colorectal liver metastases by concomitant unilateral portal vein ligation and selective intra-arterial chemotherapy. Br J Surg 2006;93:587-92.
29. Wicherts DA, Miller R, de Haas RJ, et al. Long-Term Results of Two-Stage Hepatectomy for Irresectable Colorectal Cancer Liver Metastases. Ann Surg 2008;248:994-1005.
30. Brooks AJ, Hammond JS, Girling K, et al. The effect of hepatic vascular inflow occlusion on liver tissue pH, carbon dioxide, and oxygen partial pressures: defining the optimal clamp/release regime for intermittent portal clamping. J Surg Res 2007;141:247-51.
31. Belghiti J, Noun R, Malafosse R. Continuous Versus Intermittent Portal Triad Clamping for Liver Resection. A Controlled study. Ann Surg 1999;229:369-75.
32. Belghiti J, Noun R, Zante E. Portal Triad Clamping or Hepatic Vascular Exclusion for Major Liver Resection. A controlled study. Ann Surg 1996;224:155-61.
33. Cherqui D, Malassagne B, Colau P. Hepatic Vascular Exclusion With Preservation of the Caval Flow for Liver Resections. Ann Surg 1999;230:24-30.
34. Azoulay D, Eshkenazy R, Andreani P, et al. In situ hypothermic perfusion of the liver versus standard total vascular exclusion for complex liver resection. Ann Surg 2005;241:277-85.
35. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.
36. Andriani OC. Long-term results with associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Ann Surg 2012;256:e5; author reply e16-9.
37. de Santibañes E, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. Ann Surg 2012;255:415-7.
38. Shindoh J, Vauthey JN, Zimmitti G, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume including a comparison to the ALPPS approach. J Am Coll Surg 2014;217:126-33; discussion 133-4.
39. Tschuor Ch, Croome KP, Sergeant G, et al. Salvage parenchymal liver transection for patients with insufficient volume increase after portal vein occlusion -- an extension of the ALPPS approach. Eur J Surg Oncol 2013;39:1230-5.
40. Schadde E, Ardiles V, Slankamenac K, et al. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. World J Surg 2014;38:1510-9.
41. Chan A, Chung PH, Poon RT. Little girl who conquered the "ALPPS". World J Gastroenterol 2014;20:10208-11.
42. Nagano Y, Nagahori K, Kamiyama M, et al. Improved functional reserve of hypertrophied contra lateral liver after portal vein ligation in rats. J Hepatol 2002;37:72-7.
43. Troisi R, Ricciardi S, Smeets P, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. Am J Transplant 2005;5:1397-404.
44. Takada Y, Ueda M, Ishikawa Y, et al. End-to-side portocaval shunting for a small-for-size graft in living donor liver transplantation. Liver Transpl 2004;10:807-10.
45. Luca A, Miraglia R, Caruso S. Effects of splenic artery occlusion on portal pressure in patients with cirrhosis and portal hypertension. Liver Transpl 2006;12:1237-43.
46. Reyal J, Uemoto S. Percutaneously adjustable portal vein banding device could prevent post-operative liver failure--artificial control of portal venous flow is the key to a new therapeutic world. Med Hypotheses 2009;73:640-50.
47. Kelly DM, Zhu X, Shiba H, et al. Adenosine restores the hepatic artery buffer response and improves survival in a porcine model of small-for-size syndrome. Liver Transpl 2009;15:1448-57.
48. Matrella E, Valatas V, Notas G, et al. Bolus somatostatin but not octreotide reduces hepatic sinusoidal pressure by a NO-independent mechanism in chronic liver disease. Aliment Pharmacol Ther 2001;15:857-64.
49. Tian Y, Jochum W. Kupffer cell-dependent TNF- signaling mediates injury in the arterialized small-for-size liver transplantation in the mouse. PNAS 2006;103:4598-603.
50. Kawachi S, Shimazu M. Efficacy of intraportal infusion of prostaglandin E1 to improve the hepatic blood flow and graft viability in porcine liver transplantation. Transplantation 1997;64:205-9.
51. Eipel C. Regulation of hepatic blood flow: The hepatic

arterial buffer response revisited. World J Gastroenterol 2010;16:6046.
52. Fondevila C, Hessheimer A. Portal hyperperfusion: Mechanism of injury and stimulus for regeneration in porcine small-for-size transplantation. Liver Transpl 2010;16:364-74.
53. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. Liver Transpl 2003;9:S36-41.
54. Jiang SM, Zhou G, Zhang R. Role of splanchnic hemodynamics in liver regeneration after living donor liver transplantation. Liver Transpl 2009;15:1043-9.
55. Boillot O, Delafosse B, Méchet I, et al. Small-for-size partial liver graft in an adult recipient; a new transplant technique. Lancet 2002;359:406-7.
56. Yagi S, Iida T, Hori T, et al. Optimal portal venous circulation for liver graft function after living-donor liver transplantation. Transplantation 2006;81:373-8.
57. Kaido T, Mori A, Ogura Y, et al. Lower limit of the graft-to-recipient weight ratio can be safely reduced to 0.6% in adult-to-adult living donor liver transplantation in combination with portal pressure control. Transplant Proc 2011;43:2391-3.
58. Hessheimer AJ, Fondevila C, Taurá P, et al. Decompression of the portal bed and twice-baseline portal inflow are necessary for the functional recovery of a "small-for-size" graft. Ann Surg 2011;253:1201-10.
59. Farantos C, Arkadopoulos N, Theodoraki K, et al. Effect of the portacaval shunt on reperfusion injury after 65% hepatectomy in pigs. Eur Surg Res 2008;40:347-53.
60. Polacco M, Vitale A, Valmasoni M, et al. Liver resection associated with mini porto-caval shunt as salvage treatment in patients with progression of hepatocellular carcinoma before liver transplantation: a case report. Transplant Proc 2010;42:1378-80.
61. Hammond JS, Guha IN, Beckingham IJ, et al. Prediction, prevention and management of postresection liver failure. Br J Surg 2011;98:1188-200.
62. Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007;204:854-62; discussion 862-4.
63. Lobo DN, Stanga Z, Aloysius MM, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. Crit Care Med 2010;38:464-70.
64. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc 2010;69:488-98.
65. de Liguori Carino N, O'Reilly DA, Dajani K, et al. Perioperative use of the LiMON method of indocyanine green elimination measurement for the prediction and early detection of post-hepatectomy liver failure. Eur J Surg Oncol 2009;35:957-62.
66. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. Hepatology 2005;41:1179-97.
67. Jalan R. Acute liver failure: current management and future prospects. J Hepatol 2005;42 Suppl:S115-23.
68. Stravitz RT, Kramer DJ. Management of acute liver failure. Nat Rev Gastroenterol Hepatol 2009;6:542-53.
69. Schindl MJ, Redhead DN, Fearon KCH, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005;54:289-96.
70. Rolando N, Gimson A, Wade J. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology 1993;17:196-201.
71. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.
72. Wu CC, Yeh DC, Lin MC, et al. Prospective randomized trial of systemic antibiotics in patients undergoing liver resection. Br J Surg 1998;85:489-93.
73. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 2004;126:11-28.
74. Schiødt FV, Balko J, Schilsky M, et al. Thrombopoietin in acute liver failure. Hepatology 2003;37:558-61.
75. Drews RE, Weinberger S. Thrombocytopenic disorders in critically ill patients. Am J Respir Crit Care Med 2000;162:347-51.
76. Shami VM, Caldwell SH, Hespenheide EE, et al. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl 2003;9:138-43.
77. Lodge JP, Jonas S. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. Anesthesiology 2005;102:269-75.
78. van Den Berghe G. Intensive insulin therapy in critically

ill patients. N Engl J Med 2001;345:1359-67.
79. DeLeve LD, Valla DC, Garcia-Tsao G. Vascular disorders of the liver. Hepatology 2009;49:1729-64.
80. Adani GL, Baccarani U, Risaliti A, et al. Percutaneous transhepatic portography for the treatment of early portal vein thrombosis after surgery. Cardiovasc Intervent Radiol 2007;30:1222-6.
81. Ozeki Y, Umemoto T. Partial portal arterialization for dearterialized liver after hepatectomy. Br J Surg 1997;84:1011.
82. Fahrner R, Patsenker E, de Gottardi A, et al. Elevated liver regeneration in response to pharmacological reduction of elevated portal venous pressure by terlipressin after partial hepatectomy. Transplantation 2014;97:892-900.
83. Fox IJ, Roy-Chowdhury J. Hepatocyte transplantation. J Hepatol 2004;40:878-86.
84. Stutchfield BM, Forbes S, Wigmore S. Prospects for stem cell transplantation in the treatment of hepatic disease. Liver Transpl 2010;16:827-36.
85. Otsuka Y, Duffy J, Saab S. Postresection hepatic failure: successful treatment with liver transplantation. Liver Transpl 2007;13:672-9.
86. Stutchfield BM, Simpson K, Wigmore SJ. Systematic review and meta-analysis of survival following extracorporeal liver support. Br J Surg 2011;98:623-31.

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Hepatic Surgical Technique

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	• UOP >0.5 mL/kg/h • BUN <150 mg/dL • >90% O_2 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	• UOP ≤0.5 mL/kg/h • BUN <150 mg/dL • <90% O_2 saturation despite oxygen supplementation • INR ≥1.5, <2.0	• 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	• UOP ≤0.5 mL/kg/h • BUN ≥150 mg/dL • ≤85% O_2 saturation despite high fraction of inspired oxygen support • INR ≥2.0	• 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

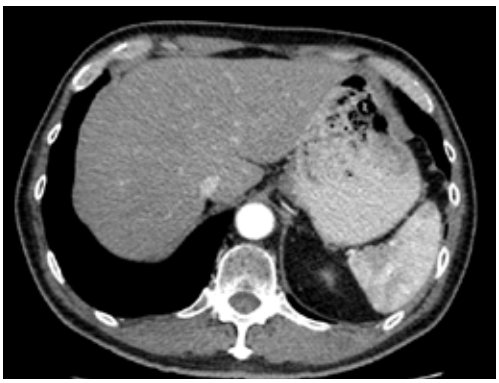

Figure 1 CT scan image of steatohepatitis, with liver attenuation lower than that of the spleen.

secondary to PHLF. Excess mortality seen in diabetic patients undergoing major hepatic resection is likely multi-factorial, 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 ≥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 ≤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).

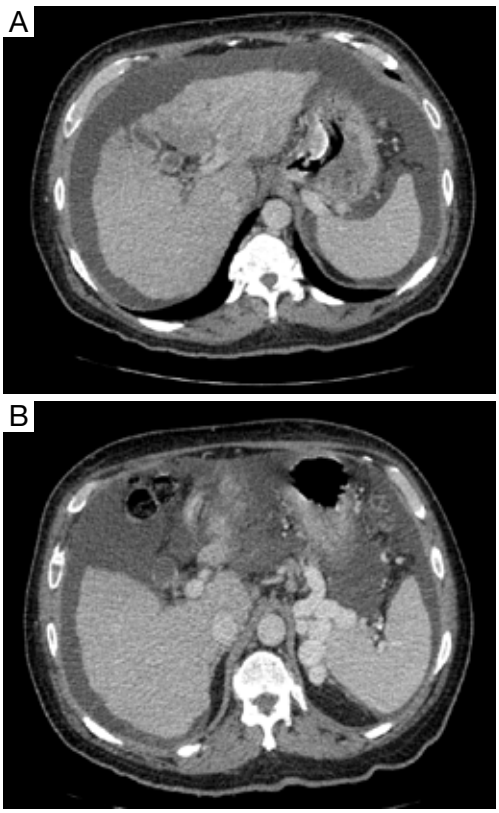

Figure 2 (A) CT scan demonstrating evidence of cirrhosis, with ascites, small liver, and splenomegaly; (B) CT scan demonstrating evidence of cirrhosis, with ascites, small liver, splenic varices, and splenomegaly.

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 μmol/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 ^{99m}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 ≥200 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 ≤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	• Predicted FLR >25% • Normal splenic size, no vascular collaterals • Indocyanine green plasma disappearance rate ≥17.6%/min	• Prothrombin activity ≥70% • Hyaluronic acid <200 ng/mL • Platelets >300,000/μL • Normal serum bilirubin level	• No history of cirrhosis • No previous hepato-toxic chemotherapy	Up to 6 (80% of functional liver volume)
High	• Predicted FLR ≤25% • Splenomegaly, presence of vascular collaterals • Steatohepatitis • Indocyanine green plasma disappearance rate <17.6%/min	• Prothrombin activity <70% • Hyaluronic acid ≥200 ng/mL • Platelets <100,000/μL • Hyperbilirubinemia	• History of cirrhosis • Previous administration of hepato-toxic chemotherapy	No more than 3 (60% of functional liver volume)

PHLF, post-hepatectomy liver failure.

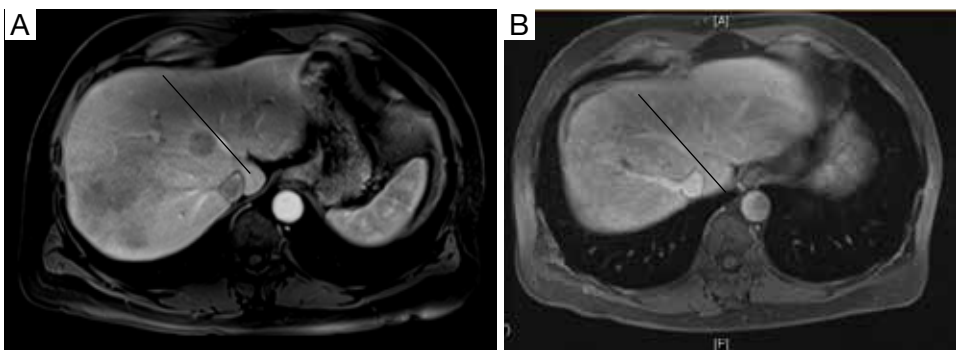

Figure 3 (A) Pre-portal vein embolization of right lobe of liver to induce hypertrophy of left lobe of liver; (B) six weeks post-portal vein embolization of right lobe of liver to induce hypertrophy of left lobe of liver. Line marks middle hepatic vein, dividing right and left hemilivers.

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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References

1. Ong GB, Lee NW. Hepatic resection. Br J Surg 1975;62:421-30.
2. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
3. Paugam-Burtz C, Janny S, Delefosse D, et al. Prospective validation of the "fifty-fifty" criteria as an early and accurate predictor of death after liver resection in intensive care unit patients. Ann Surg 2009;249:124-8.
4. Jaeck D, Bachellier P, Oussoultzoglou E, et al. Surgical resection of hepatocellular carcinoma. Post-operative outcome and long-term results in Europe: an overview. Liver Transpl 2004;10:S58-63.
5. Ren Z, Xu Y, Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. Hepatogastroenterology 2012;59:782-4.
6. Eguchi H, Umeshita K, Sakon M, et al. Presence of active hepatitis associated with liver cirrhosis is a risk factor for mortality caused by posthepatectomy liver failure. Dig Dis Sci 2000;45:1383-8.
7. Yoo HY, Edwin D, Thuluvath PJ. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. Am J Gastroenterol 2003;98:1395-9.
8. Balzan S, Belghiti J, Farges O, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. Ann Surg 2005;242:824-8, discussion 828-9.
9. Reissfelder C, Rahbari NN, Koch M, et al. Postoperative course and clinical significance of biochemical blood tests following hepatic resection. Br J Surg 2011;98:836-44.
10. Little SA, Jarnagin WR, DeMatteo RP, et al. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. J Gastrointest Surg 2002;6:88-94.
11. Fong Y, Bentrem DJ. CASH (Chemotherapy-Associated Steatohepatitis) costs. Ann Surg 2006;243:8-9.
12. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243:1-7.
13. Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 2005;200:845-53.
14. Peppercorn PD, Reznek RH, Wilson P, et al. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. Br J Cancer 1998;77:2008-11.
15. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406; discussion 406-7.
16. Tzeng CW, Cooper AB, Vauthey JN, et al. Predictors

of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB (Oxford) 2014;16:459-68.
17. Golse N, Bucur PO, Adam R, et al. New paradigms in post-hepatectomy liver failure. J Gastrointest Surg 2013;17:593-605.
18. Aloia TA, Fahy BN, Fischer CP, et al. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. HPB (Oxford) 2009;11:510-5.
19. Tomuş C, Iancu C, Bălă O, et al. Liver resection for benign hepatic lesion: mortality, morbidity and risk factors for postoperative complications. Chirurgia (Bucur) 2009;104:275-80.
20. Jin S, Fu Q, Wuyun G, et al. Management of post-hepatectomy complications. World J Gastroenterol 2013;19:7983-91.
21. Melendez J, Ferri E, Zwillman M, et al. Extended hepatic resection: a 6-year retrospective study of risk factors for perioperative mortality. J Am Coll Surg 2001;192:47-53.
22. Nanashima A, Yamaguchi H, Shibasaki S, et al. Comparative analysis of postoperative morbidity according to type and extent of hepatectomy. Hepatogastroenterology 2005;52:844-8.
23. Fujii Y, Shimada H, Endo I, et al. Risk factors of posthepatectomy liver failure after portal vein embolization. J Hepatobiliary Pancreat Surg 2003;10:226-32.
24. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointest Surg 2003;7:325-30.
25. Panicek DM, Giess CS, Schwartz LH. Qualitative assessment of liver for fatty infiltration on contrast-enhanced CT: is muscle a better standard of reference than spleen? J Comput Assist Tomogr 1997;21:699-705.
26. D'Onofrio M, De Robertis R, Demozzi E, et al. Liver volumetry: Is imaging reliable? Personal experience and review of the literature. World J Radiol 2014;6:62-71.
27. Tu R, Xia LP, Yu AL, et al. Assessment of hepatic functional reserve by cirrhosis grading and liver volume measurement using CT. World J Gastroenterol 2007;13:3956-61.
28. Torzilli G, Montorsi M, Del Fabbro D, et al. Ultrasonographically guided surgical approach to liver tumours involving the hepatic veins close to the caval confluence. Br J Surg 2006;93:1238-46.
29. Ulla M, Ardiles V, Levy-Yeyati E, et al. New surgical strategy to induce liver hypertrophy: role of MDCT-volumetry to monitor and predict liver growth. Hepatogastroenterology 2013;60:337-42.
30. Soyer P, Roche A, Elias D, et al. Hepatic metastases from colorectal cancer: influence of hepatic volumetric analysis on surgical decision making. Radiology 1992;184:695-7.
31. Suzuki K, Epstein ML, Kohlbrenner R, et al. Quantitative radiology: automated CT liver volumetry compared with interactive volumetry and manual volumetry. AJR Am J Roentgenol 2011;197:W706-12.
32. de Liguori Carino N, O'Reilly DA, Dajani K, et al. Perioperative use of the LiMON method of indocyanine green elimination measurement for the prediction and early detection of post-hepatectomy liver failure. Eur J Surg Oncol 2009;35:957-62.
33. Hoekstra LT, de Graaf W, Nibourg GA, et al. Physiological and biochemical basis of clinical liver function tests: a review. Ann Surg 2013;257:27-36.
34. Nanashima A, Tobinaga S, Abo T, et al. Reducing the incidence of post-hepatectomy hepatic complications by preoperatively applying parameters predictive of liver function. J Hepatobiliary Pancreat Sci 2010;17:871-8.
35. Thakrar PD, Madoff DC. Preoperative portal vein embolization: an approach to improve the safety of major hepatic resection. Semin Roentgenol 2011;46:142-53.
36. Shindoh J, Tzeng CW, Aloia TA, et al. Safety and efficacy of portal vein embolization before planned major or extended hepatectomy: an institutional experience of 358 patients. J Gastrointest Surg 2014;18:45-51.
37. van Lienden KP, van den Esschert JW, de Graaf W, et al. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol 2013;36:25-34.
38. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-5.
39. Ribero D, Abdalla EK, Madoff DC, et al. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94:1386-94.
40. Li J, Girotti P, Königsrainer I, et al. ALPPS in right trisectionectomy: a safe procedure to avoid postoperative liver failure? J Gastrointest Surg 2013;17:956-61.
41. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings.

Ann Surg 2012;255:405-14.
42. Vennarecci G, Laurenzi A, Levi Sandri GB, et al. The ALPPS procedure for hepatocellular carcinoma. Eur J Surg Oncol 2014;40:982-8.
43. Roberts KJ, Bharathy KG, Lodge JP. Kinetics of liver function tests after a hepatectomy for colorectal liver metastases predict post-operative liver failure as defined by the International Study Group for Liver Surgery. HPB (Oxford) 2013;15:345-51.
44. Rahman SH, Evans J, Toogood GJ, et al. Prognostic utility of postoperative C-reactive protein for posthepatectomy liver failure. Arch Surg 2008;143:247-53; discussion 253.
45. Rahbari NN, Reissfelder C, Koch M, et al. The predictive value of postoperative clinical risk scores for outcome after hepatic resection: a validation analysis in 807 patients. Ann Surg Oncol 2011;18:3640-9.
46. Hamahata N, Nagino M, Nimura Y. APACHE III, unlike APACHE II, predicts posthepatectomy mortality in patients with biliary tract carcinoma. Acute Physiology and Chronic Health Evaluation. Crit Care Med 1998;26:1671-6.
47. Chan SC, Sharr WW, Chan AC, et al. Rescue Living-donor Liver Transplantation for Liver Failure Following Hepatectomy for Hepatocellular Carcinoma. Liver Cancer 2013;2:332-7.
48. Chiarla C, Giovannini I, Giuliante F, et al. Plasma bilirubin correlations in non-obstructive cholestasis after partial hepatectomy. Clin Chem Lab Med 2008;46:1598-601.
49. Vibert E, Pittau G, Gelli M, et al. Actual incidence and long-term consequences of posthepatectomy liver failure after hepatectomy for colorectal liver metastases. Surgery 2014;155:94-105.
50. Asencio JM, García Sabrido JL, Olmedilla L. How to expand the safe limits in hepatic resections? J Hepatobiliary Pancreat Sci 2014;21:399-404.

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Learning curve in laparoscopic liver surgery: a fellow's perspective

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Abstract: The learning curve for laparoscopic liver surgery is infrequently addressed in current literature. In this paper, we explored the challenges faced in embarking on laparoscopic liver surgery in a unit that did predominantly open liver surgery. In setting up our laparoscopic liver surgery program, we adopted skills and practices learnt during fellowships at various high volume centers in North America and Australia, with modifications to suit our local patients' disease patterns. We started with simple minor resections in anterolateral segments to build confidence, which allowed us to train the surgical and nursing team before progressing to more difficult resections. Inter institutional collaboration and exchange of skills also enabled the synergistic development of techniques for safe progression to more complex surgeries. Multimedia resources and international guidelines for laparoscopic liver surgery are increasingly accessible, which further guide the practice of this emerging field, as evidence continues to validate the laparoscopic approach in well selected cases.

Keywords: Colorectal liver metastases; hepatocellular carcinoma (HCC); laparoscopic liver resection (LLR); learning curve; liver cancer

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"If I have seen further than others, it is by standing on the shoulders of giants."
—Sir Isaac Newton

Since the 1st report by Reich in 1991, there has been exponential growth in the interest and practice of laparoscopic liver resections (LLR) worldwide. Initially, only wedge resections and minor hepatectomies were attempted (1). However, with increasing experience, better optics and instrumentation, leading surgeons from large academic centers have been performing major hepatectomies, anatomical posterior segment resections, pure donor hepatectomies, and complex combined resections, such as combined major hepatectomy with pancreaticoduodenectomy laparoscopically.

Few reports, however, address the issue of mounting the learning curve in the transition from simple laparoscopic resections to more complex operations. Understandably, the learning curve for laparoscopic liver surgery is difficult to document. The techniques for liver resection differ widely depending on the location and size of the lesion, the need for parenchymal preservation versus anatomical resection, the underlying parenchymal consistency and method of preferred parenchymal transection. Furthermore, there may be the need for concomitant gastrointestinal or major vascular resection.

Each surgeon's learning curve may be influenced by his or her training background, depending on whether it is from open liver surgery to the laparoscopic approach, or from advanced laparoscopic surgery transitioning to liver surgery. For the open liver surgeon, mastering laparoscopic liver surgery can be a challenge especially with laparoscopic suturing and change in view from the anterior-posterior view of traditional open liver surgery to the caudal-cranial view of laparoscopy. In contrast, the challenge the laparoscopically trained surgeon faces may be understanding liver anatomy and its complex variations which may present a formidable initial learning curve.

Vigano *et al.* described their learning curve experience, dividing their experience into three groups of 58 patients each, who underwent LLR between 1996 and 2008 (2). In their paper, there were progressive improvements in the conversion rate, operative time, blood loss and morbidity over the time periods. Using conversion rate as their primary outcome (with adjustment for risk factors), they concluded that a learning curve of about 60 patients was required for minor hepatectomies. Abu Hilal *et al.* on the other hand suggested that improvements in the operative time and median hospital stay could be achieved after only 15 cases for their standardized procedure of laparoscopic left lateral sectionectomy (LLS) (3). In a recent article, Spampinato *et al.* demonstrated a single surgeon learning curve of only ten cases of major/complex totally LLR with improvements in operative time, median blood loss, transfusion requirement and need for intermittent Pringles maneuver. He attributes this to a solid foundation of advanced training in hepatobiliary and transplant surgery coupled with a fellowship in a high volume tertiary center specializing in laparoscopic and advanced hepatobiliary surgery (4). We recently published our initial experience in LLR and demonstrated that individual surgeon and institution volume were the main risk factors for open conversion after laparoscopic minor hepatectomy during the learning phase, albeit individual surgeon experience was the more significant factor (5). In this experience, based on conversion rates, the learning curve for an individual surgeon was about 15-20 cases for laparoscopic minor liver resection, which was lower than that reported by early studies but similar to more recent studies (2,5,6). This may suggest that with the rapid advancements in surgical technique and equipment for left hemihepatectomy (LH), the learning curve may be shortened when the surgeons collectively share their experience and actively help each other as a team in different phases of each individual's learning period. *Table 1* summarizes several studies on the learning curve for laparoscopic liver surgery.

One of the earliest LLR reported from an Eastern Hepatopancreatobiliary (HPB) unit was by Hashizume and colleagues from Japan in 1995. Here he reported a cirrhotic patient who successfully underwent laparoscopic resection of a 2 cm hepatocellular carcinoma (HCC) in Segment 5 (15). One of the first case series reported from Japan was from Kaneko and colleagues: a series of 11 patients who underwent laparoscopic partial hepatectomy or LLS with only one conversion for bleeding (16). He went on to describe the learning curve for these operations, with an improvement in operative times between the early period [1993-1998] and the later period [1999-2004] (17).

The Louisville consensus statement in 2008 provided international guidelines for laparoscopic liver surgeons and the recently concluded 2nd consensus conference held in Iwate in 2014 further added important evidence with regards to the practice and adoption of this emerging field (18,19). It was recommended in the 1st consensus statement that LLR be limited to solidary lesions (5 cm or less), in anterior segments of the liver (Segments 2,3,4b,5,6) with LLS being standard practice. In the latest consensus from the Iwate meeting, this limitation was cautiously expanded to include all minor resections being standard practice although these are generally taken not to include the "difficult" segments (Segments 1,4a,7,8). There was also a clear trend towards increasing proportion of major resections and complex resections being performed around the world with fewer conversions. Although the level of evidence was still low, it was concluded that in majority of parameters studied, the outcomes were at least not inferior in margin negativity, morbidity, perioperative mortality and overall survival. Furthermore, benefits of minimally invasive surgery (MIS) were seen with superior pain, cosmesis, blood loss and length of stay (19). While most of the evidence for LLR was based on studies without randomized control trials, they consistently show better short-term outcomes without compromise on long-term oncological outcomes. There are two randomized controlled trials underway in Norway (Oslo-CoMet) and Netherlands whose results should give us more insight on these issues (20).

The benefit of being a young laparoscopic liver surgeon in this generation is the availability of literature and videos to learn techniques, compared to our pioneering colleagues. In contrast to the lack of standardized techniques in the early years, there are currently good published techniques on the more common resections such as the LLS and even major hepatectomies (7,21). With increasing experience, technical tips on difficult resections such as isolated posterior segment resections (Segments 7/8), central hepatectomies and caudate resections are being shared (8,22-24). Laparoscopic donor hepatectomy techniques have also been described, although these surgeries are understandably performed only in a handful of high volume transplant centers (25). These are important adjuncts in helping to overcome the learning curve. However, it is important that adoption of these techniques is guided by an experienced surgeon.

Progressing to the more difficult resections should only

Table 1 Summary of laparoscopic hepatectomy studies mentioning learning curve

Author/year	Study origin	Patient number	Type of resection	Pathology	No. of patients before improvement	Parameters of improvement
Chang *et al.* 2007 (7)	W	36	LLS	Mixed	18	Operating time improved; less portal triad clamping (use and duration)
Abu Hilal *et al.* 2008 (3)	W	30	LLS	Mixed	15	Operative time improved; median hospital stay shorter
Otsuka *et al.* 2009 (8)	E	88 (90 cases)	Mixed	Mixed	45	Higher proportion of PS segments/malignancy attempted; less blood loss and shorter hospital stay
Vigano *et al.* 2009 (2)	W	174	Mixed	Mixed	60 (minor hepatectomies)	Conversion rate, operative time, blood loss, morbidity improved; less pedicle clamp applied/ time used
Cannon *et al.* 2011 (9)	W	300	Mixed	Mixed	100	Operative time improved; similar blood loss, morbidity and mortality despite increase number of segments/repeat hepatectomies
Troisi *et al.* 2011 (10)	W	36	LLS	Mixed	10	Shorter operative time, less blood loss (NS)
Robinson *et al.* 2012 (11)	W	37	Mixed	Mixed	18	Attempted more right sided resections; fewer conversions
Spampinato *et al.* 2014 (4)	W	24	Major/ complex	Mixed	10	Operative time, median blood loss, percentage requiring pedicle clamping, median units blood transfusion improved
Chan *et al.* 2014 (12)	E	98 (100 cases)	Mixed	Mixed	50	Similar operative time, blood loss despite more major resections
Goh *et al.* 2014 (5)	E	147	Minor	Mixed	15-20	Individual surgeon and institution volumes were important factors associated with open conversion after Laparoscopic minor hepatectomy
Cai *et al.* 2014 (13)	E	365	Mixed	Mixed	15-43	Stabilization of mean blood loss and operative time
Liu *et al.* 2014 (6)	E	41	LLS	Mixed	20	Median operative time and blood loss
Choi *et al.* 2015 (14)	E	46	LLS, LH, wedge PS segments	Mixed	10	Stabilized operative time and blood loss

W, Western studies; E, Eastern studies; LLS, left lateral sectionectomy; LH, left hemihepatectomy; PS, posterosuperior; NS, not significant.

be attempted after sufficient experience in the simpler resections. Cho *et al.* compared the outcome after LLR of HCC situated in the antero-lateral segment (Segments 2,3,5,6 and 4b) *vs.* those in the postero-superior segment (Segments 1,4a,7 and 8), and found that patients with postero-superior segments resected had longer operative time and a tendency towards longer median hospital stay and greater rate of intraoperative transfusion, but with no significant difference in postoperative complications or cancer recurrence (22). A recently published multicenter study in Japan on case selection for pure LLR considered scoring the difficulty of the resection according to low, intermediate and high. This score was calculated based on tumor location, extent of liver resection, tumor size,

proximity to major vessel and liver function to provide a score from 1-10 (26). Although yet to be validated by other centers outside of Japan, this paper provided a novel and practical method for predicting the technical difficulty for LLR and may provide a framework to choose resections that they can do laparoscopically consistent with their experience. In the latest consensus statement from Iwate, there was strong recommendations from the jury and expert panel that the validation and application of this novel system be carried out together with a structured training program for further safe adoption of laparoscopic liver surgery.

Personal experience

Coming from a background of predominantly open liver surgery, I decided to embark on an international fellowship in a large tertiary referral center in Australia known for its work in laparoscopic liver surgery. My supervisor Dr. Nicholas O'Rourke, and his unit at the Royal Brisbane Hospital was one of the first to publish their technique of laparoscopic right hepatectomy (27). Since 1999, they have developed an extensive experience in laparoscopic liver surgery, with over 340 laparoscopic resections to date (28,29). There was a good case mix of advanced laparoscopic hepatectomies, laparoscopic pancreatic surgery as well as complex minimally invasive biliary surgery in my training year. During my fellowship, besides laparoscopic hepatobiliary surgery, I was also exposed to advance laparoscopic revisional bariatric surgery as well as upper gastrointestinal surgery. The skills I picked up such as laparoscopic suturing and intra-corporal gastrointestinal anastomoses allowed me to have a broad based training in laparoscopic surgery. This built my confidence in handling LLR, especially in stressful situations when control of bleeding with sutures was required. I also had the opportunity to be involved in the management of many synchronous liver and colorectal resections, since the colorectal unit there was equally accomplished in advanced laparoscopic surgery.

The most important factors in embarking on safe laparoscopic liver surgery, in my experience, were the appreciation of liver anatomy from the caudal cranial view, learning laparoscopic haemostatic control and developing familiarity in using the laparoscopic ultrasound. In the initial learning process, many hours were spent assisting in laparoscopic surgeries and watching available videos to understand the various different approaches to major and minor resections in the caudal cranial perspective. While this caudal cranial view afforded excellent visualization of the infra-hepatic tunnel for securing the short hepatic veins, the orientation of the resection plane can be confusing, and access to the major hepatic veins difficult. It is crucial to be able to control bleeding and the ability to laparoscopically suture quickly at awkward locations is a skill that should be practiced till proficient even before embarking on the 1st LLR without senior supervision. The use of the laparoscopic ultrasound was a difficult technique to learn but was indispensable to continuously check on resection line, vascular anatomy deep in the liver and also margin control especially for non-anatomical resections. While there are many known techniques of parenchymal transection with a variety of energy devices, it was important to learn and be familiar with one technique consistently before embarking on other methods. Although pure laparoscopy was generally preferred, before starting operations, a potential site for hybrid or hand port was routinely marked for conversion should there be situations of difficult bleeding control or failure to progress. I did not view conversion as a failure but a necessity especially when there are concerns about oncological clearance.

After returning to Singapore, I quickly began to develop a laparoscopic liver surgery program in my institution. Starting out, it was prudent to perform only simple wedge resections of anterolateral segments and LLS within the guidelines provided by the Louisville consensus statement for minor resections. This allowed me to train my team of junior surgeons and nursing staff under less technically demanding conditions, whilst avoiding the risk of significant patient morbidity during the early days of the program.

There was also cross collaboration with other colleagues from different institutions in Singapore, one of whom was a HPB surgeon (SYL) who did a laparoscopic and liver transplant fellowship in North America with Prof. Daniel Cherqui and subsequently a surgical oncology fellowship at Memorial Sloan Kettering Cancer Center (MSKCC). The first fellowship allowed him to not only learn first-hand from one of the pioneers of laparoscopic liver surgery but provided him an unique learning opportunity and interaction with a young attending at the same unit, who was Prof. Cherqui's fellow in Paris a few years prior. This provided valuable lessons and insights how one should cautiously and appropriately embark on a laparoscopic HPB practice. The availability of an experienced mentor in challenging cases was technically helpful and morally encouraging in and out of the operating room. It also provided a unique environment where he saw how

laparoscopic surgery can be safely integrated into living donor hepatectomies to decrease donor morbidity (25). The latter MSKCC fellowship was synergistic as it allowed him to experience another perspective—the role of MIS in HPB surgical oncology. Being a cancer center, in his opinion, MSKCC did not jump on the bandwagon of pursing MIS surgery right from the start and its adoption of MIS was more calculated than other high volume tertiary centers because of the rightful concerns of MIS compromising the principles of surgical oncology (30,31). As Dr. Blake Cady once elegantly said: "*In the land of Surgical Oncology, biology is King; selection of case is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories.*" Nonetheless, because of potential benefits, culminating experience and convincing data, MIS and surgical oncology proves no longer to be mutually exclusive as long as patients are well selected and surgery performed by experienced teams (32).

In our initial experience, we worked together for major and complex hepatectomies operating with at least one other experienced laparoscopic liver surgeon (CYC). This was crucial in bringing different techniques learnt from our various training backgrounds and working to adapt these techniques to our local patients. In the Western institutions that we worked in, the majority of the resections were for colorectal liver metastases where the challenge was operating on post chemotherapy liver with the principle of parenchymal preservation. In addition, there were important lessons learnt in terms of multidisciplinary discussion and surgical approaches to combined colorectal and liver resections. In our local Asian population, we see a larger proportion of cases with HCC in cirrhotic livers (5). Besides chronic liver disease, they present additional challenges of portal hypertension with concurrent clinical coagulopathy and increased risk of bleeding. Furthermore they tolerate complications less readily and have a need for a larger future liver remnant. This has required us to adapt some techniques of liver mobilization and parenchymal transection in the setting of cirrhosis and portal hypertension. While our technique for parenchymal transection has been with hot "kelly-clysis" with a bipolar vessel sealing device, we have found the Calvitron Ultrasonic Surgical Aspirator (CUSA) (Tyco Healthcare, Mansfield, MA) as an important adjunct for careful dissection of lesions near major vascular pedicles. A roticulating energy device was also useful for non-anatomical resections and lesions higher up in the dome of the liver together with a flexible tip endoscope.

In conclusion, a solid background in open liver surgery coupled with robust training in a high volume subspecialty laparoscopic centre provided a good foundation for starting laparoscopic liver surgery. Adaptation of techniques to the local context is crucial and inter-institutional collaboration allows synergistic development of skills to mount the learning curve for more complex laparoscopic hepatobiliary surgery. The challenge remains in selecting the appropriate patient for LLR and having better guidelines and scoring systems to anticipate the difficulty of resection would undoubtedly enable us to achieve this aim.

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Footnote

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References

1. Reich H, McGlynn F, DeCaprio J, et al. Laparoscopic excision of benign liver lesions. Obstet Gynecol 1991;78:956-8.
2. Vigano L, Laurent A, Tayar C, et al. The learning curve in laparoscopic liver resection: improved feasibility and reproducibility. Ann Surg 2009;250:772-82.
3. Abu Hilal M, Pearce NW. Laparoscopic left lateral liver sectionectomy: a safe, efficient, reproducible technique. Dig Surg 2008;25:305-8.
4. Spampinato MG, Arvanitakis M, Puleo F, et al. Assessing the Learning Curve for Totally Laparoscopic Major-Complex Liver Resections: A Single Hepatobiliary Surgeon Experience. Surg Laparosc Endosc Percutan Tech 2015;25:e45-50.
5. Goh BK, Chan CY, Wong JS, et al. Factors associated with and outcomes of open conversion after laparoscopic minor hepatectomy: initial experience at a single institution. Surg Endosc 2015;29:2636-42.
6. Cai X, Li Z, Zhang Y, et al. Laparoscopic liver resection and the learning curve: a 14-year, single-center experience. Surg Endosc 2014;28:1334-41.
7. Otsuka Y, Tsuchiya M, Maeda T, et al. Laparoscopic hepatectomy for liver tumors: proposals for

standardization. J Hepatobiliary Pancreat Surg 2009;16:720-5.
8. Ishizawa T, Gumbs AA, Kokudo N, et al. Laparoscopic segmentectomy of the liver: from segment I to VIII. Ann Surg 2012;256:959-64.
9. Cannon RM, Brock GN, Marvin MR, et al. Laparoscopic liver resection: an examination of our first 300 patients. J Am Coll Surg 2011;213:501-7.
10. Troisi RI, Van Huysse J, Berrevoet F, et al. Evolution of laparoscopic left lateral sectionectomy without the Pringle maneuver: through resection of benign and malignant tumors to living liver donation. Surg Endosc 2011;25:79-87.
11. Robinson SM, Hui KY, Amer A, et al. Laparoscopic liver resection: is there a learning curve? Dig Surg 2012;29:62-9.
12. Chan FK, Cheng KC, Yeung YP. Laparoscopic liver resection: lessons learnt after 100 cases. Hong Kong Med J 2014;20:386-92.
13. Liu W, Wang Q, Huang J, et al. Laparoscopic left lateral sectionectomy -the learning curve and the role of left hepatic inflow occlusion. Hepatogastroenterology 2014;61:417-21.
14. Choi SH, Choi GH, Han DH, et al. Laparoscopic liver resection using a rubber band retraction technique: usefulness and perioperative outcome in 100 consecutive cases. Surg Endosc 2015;29:387-97.
15. Hashizume M, Takenaka K, Yanaga K, et al. Laparoscopic hepatic resection for hepatocellular carcinoma. Surg Endosc 1995;9:1289-91.
16. Kaneko H, Takagi S, Shiba T. Laparoscopic partial hepatectomy and left lateral segmentectomy: technique and results of a clinical series. Surgery 1996;120:468-75.
17. Kaneko H. Laparoscopic hepatectomy: indications and outcomes. J Hepatobiliary Pancreat Surg 2005;12:438-43.
18. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
19. Wakabayashi G, Chiriquí D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in morioka. Ann Surg 2015;261:619-29.
20. van Dam RM, Wong-Lun-Hing EM, van Breukelen GJ, et al. Open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery ERAS® programme (ORANGE II-trial): study protocol for a randomised controlled trial. Trials 2012;13:54.
21. Chang S, Laurent A, Tayar C, et al. Laparoscopy as a routine approach for left lateral sectionectomy. Br J Surg 2007;94:58-63.
22. Cho JY, Han HS, Yoon YS, et al. Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver, with a special reference to overcoming current limitations on tumor location. Surgery 2008;144:32-8.
23. Conrad C, Ogiso S, Inoue Y, et al. Laparoscopic parenchymal-sparing liver resection of lesions in the central segments: feasible, safe, and effective. Surg Endosc 2015;29:2410-7.
24. Gringeri E, Boetto R, Bassi D, et al. Totally laparoscopic caudate lobe resection: technical aspects and literature review. Surg Laparosc Endosc Percutan Tech 2014;24:e233-6.
25. Samstein B, Cherqui D, Rotellar F, et al. Totally laparoscopic full left hepatectomy for living donor liver transplantation in adolescents and adults. Am J Transplant 2013;13:2462-6.
26. Ban D, Tanabe M, Ito H, et al. A novel difficulty scoring system for laparoscopic liver resection. J Hepatobiliary Pancreat Sci 2014;21:745-53.
27. O'Rourke N, Fielding G. Laparoscopic right hepatectomy: surgical technique. J Gastrointest Surg 2004;8:213-6.
28. Chiow AK, Lewin J, Manoharan B, et al. Intercostal and transthoracic trocars enable easier laparoscopic resection of dome liver lesions. HPB (Oxford) 2015;17:299-303.
29. O'Rourke N, Shaw I, Nathanson L, et al. Laparoscopic resection of hepatic colorectal metastases. HPB (Oxford) 2004;6:230-5.
30. Ito K, Ito H, Are C, et al. Laparoscopic versus open liver resection: a matched-pair case control study. J Gastrointest Surg 2009;13:2276-83.
31. Fong Y, Jarnagin W, Conlon KC, et al. Hand-assisted laparoscopic liver resection: lessons from an initial experience. Arch Surg 2000;135:854-9.
32. Lee SY, Allen PJ, Sadot E, et al. Distal pancreatectomy: a single institution's experience in open, laparoscopic and robotic approaches. J Am Coll Surg 2015;220:18-27.

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Laparoscopic first step approach in the two stage hepatectomy

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Abstract: Resection is the gold standard therapeutic option for patients with colorectal liver metastases. However, only 20-30% of patients are resectable. In patients with a concomitant future liver remnant (FLR) less than 25-30%, a single stage resection is not feasible. The aim of this study is to evaluate the feasibility and the rates of morbidity and mortality of the laparoscopic approach in the first-step of two stage hepatectomy. From 2004 to March 2014, 73 patients underwent a two stage hepatectomy: of these, four underwent a totally laparoscopic first step [wedge left liver resection and right portal vein ligation (PVL)]. All the patients were male. Median age was 55 years. One patient underwent an atypical wedge resection of segment II-III and a laparoscopic PVL (LPVL), one patient had a first wedge resection of segment II and LPVL, and two patients underwent a wedge resection of segment III and LPVL. First step surgical mean time was 189 (range, 160-244) min, mean blood loss was 22 (range, 0-50) cc. No transfusion was required in this series. The results of our study demonstrate that the first step of hepatic resection and PVL is feasible with a laparoscopic approach in patients with bilobar liver metastases.

Keywords: Laparoscopic liver resection; two stage hepatectomy; laparoscopic portal vein ligation (LPVL)

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Introduction

Resection is the gold standard therapeutic option for patients with colorectal liver metastases. However, only 20-30% of patients are resectable (1). In recent years, different therapeutic options improved the rate of patients eligible for surgery. These results can be obtained with new chemotherapeutic regiments, new biological therapies, and with more aggressive surgical procedures such as the two-step strategy. Since the first two staged hepatectomy reports (2), liver resection indications have been implemented with new surgical procedures. In patients with colorectal or neuroendocrine bilobar liver metastases, two stage hepatectomy is nowadays routinely performed in hepatobiliary centers. In patients with a concomitant future liver remnant (FLR) less than 25-30%, in both the cases of normal liver or liver parenchyma affected by chemotherapy-related damage, a single stage resection is not feasible. In these cases patients need a first stage resection of liver metastases in the left liver with a concomitant portal vein ligation (PVL), and a second stage hepatectomy of the right lobe if the FLR has grown enough. Laparoscopy for liver resections has been demonstrated as a safe procedure in several indications (3-6).

The aim of this study is to evaluate the feasibility and the rates of morbidity and mortality of the laparoscopic approach in the first-step of two stage hepatectomy (wedge left liver resection and right PVL).

Materials and methods

We retrospectively reviewed all the patients undergoing a two stage hepatectomy for bilobar colorectal metastases, all identified from a prospectively collected database. From 2004 to March 2014, 73 patients underwent a two stage hepatectomy: of these patients, 4 underwent a totally laparoscopic first step (liver resection and PVL).

Age, gender, body mass index (BMI), number of lesions,

Table 1 Patient characteristics

Patient number	Sex	Age	First step	Time first step	Blood loss	Hospital stay	Second step	Time second step	Blood loss	Hospital stay
1	Male	60	W2-3, LPVL	244	50	4	RH	324	400	10
2	Male	57	W2, LPVL	143	0	3	RH	313	200	8
3	Male	58	W3, LPVL	210	0	5	RH	319	700	7
4	Male	45	W3, LPVL	160	40	3	RH	260	400	7

Abbreviations: LPVL, laparoscopic portal vein ligation; W2, wedge resection segment II; W3, wedge resection segment III; RH, right hepatectomy.

prior surgery, procedure time of first and second stage, length of hospital stay of first and second stage and follow up data were collected.

All patients were studied with a volumetric computed tomography (volCT) before first step and 30-40 days after PVL to confirm hypertrophy of the FLR. Second step was performed only if disease progression was excluded and FLR >30%. In this series no underlined liver disease was observed.

Surgical procedure

Patients were placed supine on the operative table with lower limbs apart, the surgeon between the legs. Access to the abdomen was gained by open technique and pneumoperitoneum was maintained at 12 mmHg. A 10-mm port at the umbilicus housed a 30° video-camera. The other three trocars were positioned usually along a semicircular line with the concavity facing the right subcostal margin. Diagnostic laparoscopy was first performed and lysis of adhesions was performed is necessary. Steep reverse Trendelenburg position was maintained. The liver was examined using laparoscopic ultrasonography (US) to confirm the extension of the lesions and their extension in the left lobe. If operability was confirmed only the right part of the pedicle was dissected. Bile duct was elevated after dissection with the intent to clearly expose the portal vein. Right portal vein was then encircled with loop (when necessary, anterior and posterior vessels were encircled separately). Wedge resection of the left metastases was performed. After completing the resection of left liver metastases, right portal vein was legated with clips or with loop ligation. A perioperative Doppler was then performed in all patients. Thirty-forty days after the first step a volCT was performed. Patients underwent the second step of the two stage hepatectomy if no progression of the disease was observed and the FLR was increased enough.

Results

Patients' characteristics are resumed in *Table 1*. All the patients were male. Median age was 55 years. One patient underwent an atypical wedge resection of segments II-III and a laparoscopic PVL (LPVL), one patient had a first wedge resection of segment II and LPVL, and two patients underwent wedge resection of segment III and LPVL. First step surgical mean time was 189 (range, 160-244) min, mean blood loss was 22 (range, 0-50) cc. No transfusion was required in this series. Mean days between the first and second step was 86 days. All second step operations consisted in an open right hepatectomy (RH). Mean surgical time was 304 (range, 260-324) min, and mean blood loss was 425 (range, 200-700) cc. For second step no transfusion was necessary. Length of hospital stay for the first step was 3, 5 (range, 3-5) days, and for the second step 8 (range, 7-10) days.

Discussion

In patients with normal liver, FLR less than 30% is considered a contraindication for surgery. Portal vein occlusion is now currently used to induce hypertrophy of the FLR before surgery. In literature the use of laparoscopy for two-stage hepatectomy has not been discussed enough, only few reports being available. The Southampton experience confirms our preliminary results that laparoscopic approach is feasible (7). However, they reported height cases with only two of them undergoing LPVL. Two studies analyzed the laparoscopic approach for PVL prior to major hepatectomy (8,9). LPVL was compared to portal vein embolization (PVE), showing the safety of LPVL and its ability in inducing an adequate FLR increase. Despite PVE is a less invasive procedure and

it has been described as superior to open PVL (10), it is affected by up to 15% of complications (11). In our series no complications were described during the laparoscopic first step procedure. Laparoscopy carries the advantages of few adhesions and shorter lengths of hospital stay respect to open approaches. Another advantage of laparoscopic approach is the rapid patient's recovery resulting in a short discontinuing of the chemotherapy regimen. The advantage concerning the immunity of laparoscopic approach is suspected but not demonstrated (12).

Conclusions

This study described a first experience of laparoscopic approach for two stage hepatectomy. Although the study included only four patients, which is not sufficient for obtaining any scientific definitive result, the evidences of our study suggest us that the first step of hepatic resection and PVL is feasible with a laparoscopic approach in patients with bilobar liver metastases. This mininvasive laparoscopic approach seems to reduce adhesions and hospital stay and should be proposed in all patients planned for a two stage hepatectomy with bilobar metastases.

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None.

Footnote

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

References

1. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49-57.
2. Adam R, Laurent A, Azoulay D, et al. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 2000;232:777-85.
3. Ettorre GM, Laurenzi A, Lionetti R, et al. Laparoscopic liver resections in normal and cirrhotic livers: a retrospective analysis in a tertiary hepato-biliary unit. Dig Liver Dis 2014;46:353-7.
4. Cherqui D, Husson E, Hammoud R, et al. Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 2000;232:753-62.
5. Cho JY, Han HS, Yoon YS, et al. Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver, with a special reference to overcoming current limitations on tumor location. Surgery 2008;144:32-8.
6. Nguyen KT, Laurent A, Dagher I, et al. Minimally invasive liver resection for metastatic colorectal cancer: a multi-institutional, international report of safety, feasibility, and early outcomes. Ann Surg 2009;250:842-8.
7. Di Fabio F, Whistance R, Rahman S, et al. Exploring the role of laparoscopic surgery in two-stage hepatectomy for bilobar colorectal liver metastases. J Laparoendosc Adv Surg Tech A 2012;22:647-50.
8. Ayiomamitis GD, Low JK, Alkari B, et al. Role of laparoscopic right portal vein ligation in planning staged or major liver resection. J Laparoendosc Adv Surg Tech A 2009;19:409-13.
9. Are C, Iacovitti S, Prete F, et al. Feasibility of laparoscopic portal vein ligation prior to major hepatectomy. HPB (Oxford) 2008;10:229-33.
10. Broering DC, Hillert C, Krupski G, et al. Portal vein embolization vs. portal vein ligation for induction of hypertrophy of the future liver remnant. J Gastrointest Surg 2002;6:905-13; discussion 913.
11. Liu H, Fu Y. Portal vein embolization before major hepatectomy. World J Gastroenterol 2005;11:2051-4.
12. Corrigan M, Cahill RA, Redmond HP. The immunomodulatory effects of laparoscopic surgery. Surg Laparosc Endosc Percutan Tech 2007;17:256-61.

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Robotic liver surgery: technical aspects and review of the literature

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Abstract: Minimally invasive surgery for liver resections has a defined role and represents an accepted alternative to open techniques for selected cases. Robotic technology can overcome some of the disadvantages of the laparoscopic technique, mainly in the most complex cases. Precise dissection and microsuturing is possible, even in narrow operative fields, allowing for a better dissection of the hepatic hilum, fine lymphadenectomy, and biliary reconstruction even with small bile ducts and easier bleeding control. This technique has the potential to allow for a greater number of major resections and difficult segmentectomies to be performed in a minimally invasive fashion. The implementation of near-infrared fluorescence with indocyanine green (ICG) also allows for a more accurate recognition of vascular and biliary anatomy. The perspectives of this kind of virtually implemented imaging are very promising and may be reflected in better outcomes. The overall data present in current literature suggests that robotic liver resections are at least comparable to both open and laparoscopic surgery in terms of perioperative and postoperative outcomes. This article provides technical details of robotic liver resections and a review of the current literature.

Keywords: Robotic liver resection; robotic hepatectomy; minimally invasive surgery

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Introduction

Minimally invasive surgery for liver resections represents an accepted alternative to open techniques for selected cases. Currently, laparoscopy is used as the only standard approach for resection of the anterior segments (II to VI) and left lateral sectionectomies (1-8).

Advantages, such as less estimated blood loss and postoperative pain, lower morbidity, shorter hospital stay and improved cosmesis, have been well established in current literature (1,7,9-11). Oncologic laparoscopic liver resections have also proven to be feasible and safe when performed in expert hands, with oncologic outcomes that are equivalent to traditional open surgery in terms of margin infiltration and local recurrence (1,2,5,10,12-17). In liver surgery, laparoscopy presents some peculiar advantages as the preservation of the abdominal wall from large subcostal incisions. This translates into better postoperative diaphragmatic function with less respiratory complications, better venous drainage in cirrhotic patients, less postoperative ascites and reduced pain. There are also long term advantages like less risk of incisional hernias and peritoneal adhesions. Furthermore, pneumoperitoneum has been shown to decrease oozing from the transection line with a positive impact on the overall blood loss.

Nonetheless, laparoscopy has some disadvantages that hinder its wider adoption, mainly in major hepatic resections and complex cases (3,6,7,18). Limited degrees of

motion of the instruments, unstable camera platform, two-dimensional vision and poor ergonomy are all factors that increase the difficulty of the procedure.

It is interesting to note that in 2008 the Louisville consensus conference limited or contraindicated the role of laparoscopy for major hepatectomies or when biliary reconstruction is needed (extended hepatectomies), when the lesion is adjacent to major vessels or in close proximity of the liver hilum. After six years, the recommendations by the last consensus conference, held in Morioka, still confirms the same indications due to a lack of evidence to generate new recommendations (19). No specific recommendations were made on robotic liver surgery, even though the studies present in current literature suggest that outcomes are not inferior to other techniques (19).

Robotic assisted liver surgery

Robotic technology, designed to overcome some of the limitations of laparoscopy, is gaining interest in this field as proven by the constantly growing number of reports in the literature. The stability of the robotic platform, combined with the three-dimensional, magnified high-definition vision, increased degrees of freedom of the instruments and tremor filtering provide higher dexterity to the surgeon and allow for the same movements of open surgery. Precise dissection and suturing is possible, even in narrow operative fields, allowing for easier dissection of the hepatic hilum, fine lymphadenectomy, biliary reconstruction even with small bile ducts and more effective bleeding control (3,4,6,20-22).

The safety and feasibility of this approach has been clearly demonstrated (1,3,4,6,10,11,20,21,23-28). The promising results suggest that Robotics has the potential to expand the indications to more complex cases such as major hepatectomies, extended hepatectomies with biliary reconstruction and difficult segmentectomies of the posterior-superior segments (4,7,22,24). Furthermore, the digital interaction with the target facilitates many potential innovations like the recent near-infrared fluorescence and the soon to come image guided surgery and augmented reality.

Near-infrared fluorescence in robotic liver surgery

The robotic platform provides additional advantages, like integrated near-infrared fluorescence imaging. Indocyanine green (ICG) is a non-toxic fluorophore that appears green when stimulated by near-infrared light. It is approved by the Food and Drug Administration (FDA) and has been used in medicine for over 40 years (29,30). Arteries and veins can be visualized 5–60 seconds after intravenous injection. ICG then accumulates in the liver and is secreted in the bile 45–60 minutes later, allowing for visualization of the biliary structures. Recognition of vascular and biliary anatomy is important in hepatic surgery, especially during dissection of the hilum. It could help to decrease intraoperative complications, especially in the presence of anatomical variations. In our practice, ICG fluorescence is used in all hepatobiliary procedures (31,32). Moreover, this technique has interesting perspectives for differentiation of hepatic lesions based on their vascular pattern. Well-differentiated hepatocarcinomas (HCC) are hyperfluorescent, while poorly-differentiated HCCs and colorectal metastases are hypofluorescent (30,33). In adjunction to preoperative imaging, this method could increase accuracy of lesion detection, or even distinction between benign and malignant masses. Future technological advancements will include new fluorophores conjugated to monoclonal antibodies, leading to a type of 'fluorescence-guided' surgery, real-time *in vivo* microscopy for evaluation of resection margins, as well as accurate identification of metastatic versus normal lymph nodes (31).

Limits of robotic liver surgery

One of the limits of robotic HPB surgery is the need for specialized training, not only for the primary surgeon, but also for the assistant surgeon and OR nurses, although in some cases, the learning curve for specific robotic procedures has proven to be shorter than the laparoscopic equivalent (17). Moreover, hepatobiliary surgeons, at the beginning of their robotic learning curve, might have a limited number of simple cases that could be used as a training model. Simulation and virtual-reality surgical training are promising, but are still under development and require validation (34,35). The robotic dual console is a teaching tool that could help accelerate proficiency (36). Another problem, more specific to liver surgery, is that currently there are only a limited number of robotic instruments for parenchymal transection. The harmonic shears are very efficient in cutting and coagulating, if properly used, but do not have all the degrees of freedom of other robotic tools. This limitation requires some adjustments during the procedure to align the instrument with the section line.

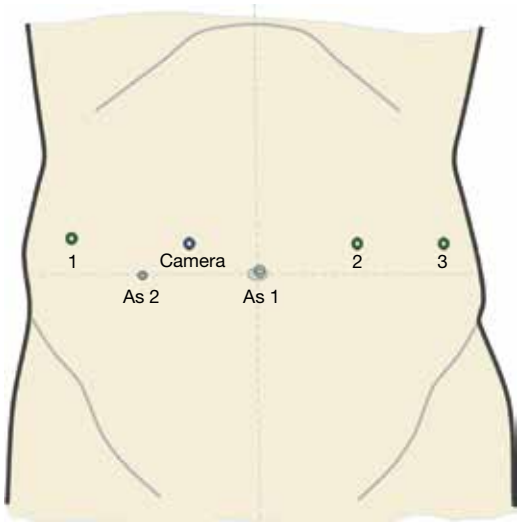

Figure 1 Port placement in robotic right hepatectomy. 1, first robotic arm; 2, second robotic arm; 3, third robotic arm; As 1, 12 mm assistant port; As 2, 5 mm assistant port.

Technique: robot-assisted right hepatectomy

Patient positioning and trocar placement

The patient is in the supine position, with parted legs in 20 degree reverse-Trendelemburg. The assistant surgeon is positioned between the patient's legs. Pneumoperitoneum is achieved with the Veress needle, preferably at the left upper quadrant. A 10–12 mm trocar is then placed above the umbilicus and is used as an assistant port during the first steps of the procedure (retraction, suction/irrigation, stapling) and as an operative port during the parenchymal transection. A 12-mm trocar is placed in the right midclavicular line (10 cm from the assistant trocar) to act as a camera port. The trocar for the first robotic arm is placed in the left midclavicular line (10 cm from the assistant trocar) and the trocar for the second robotic arm is placed in the right anterior axillary line (10 cm from the optical trocar). The third robotic arm port is placed in the left anterior axillary line and is used for retraction. The body habitus of each patient needs to be assessed, since adjustments may be needed in order to avoid arm collision and achieve optimal exposure. At this point, a diagnostic laparoscopy is performed in order to exclude the presence of metastases. An intraoperative ultrasound is also performed in order to have a better understanding of the size, number and location of the lesions, as well as to detect any contralateral nodules. The robotic cart is brought into the surgical field, coming from the patient's head, and the arms are docked (*Figure 1*).

Surgical procedure

Three steps are clearly defined. The first step is the dissection of the hepatic hilum. First, a retrograde cholecystectomy is performed. The hepatic pedicle is dissected using a combination of monopolar hooks and bipolar forceps. The right hepatic artery is dissected first and then sectioned between prolene sutures. The portal vein is completely dissected and selective stitches or ligatures are applied on the small posterior branches for segment I. The right portal vein is then divided between robotic clips and sutured with either 4-0 or 5-0 prolene. An extrahepatic dissection of the right bile duct should be performed only when the anatomy is clear and confluence of the biliary ducts is low. In such a case, when the hilar plate is lowered, the right hepatic duct is isolated and transected approximately 1 cm from the bifurcation. In other cases, the division of the right hepatic duct should be intrahepatic, during the transection of the parenchyma. ICG fluorescence can be easily used at any point and can help identify the biliary anatomy.

The second step of the procedure is the hepatocaval dissection. The falciform ligament and coronary ligament are sectioned. The lateral reflection of the peritoneum is dissected along the hepatocaval plane. The third arm is used to lift the inferior surface of the right lobe to expose the inferior vena cava (IVC). The accessory hepatic veins are sectioned between ligatures or transfixed stitches of prolene. Robotic clips can also be placed for accessory hepatic veins of minor caliber or to further secure the proximal ligature. The dissection of the IVC should proceed until the inferior aspect of the right hepatic vein is visible, close to the diaphragm. In selected cases, a true 'hanging maneuver' can be achieved.

Transection of the liver is the last step of the operation. Parenchymal transection should follow the ischemic demarcation line and start at the anterior aspect of the liver, along the cholecysto-caval line. The central venous pressure (CVP) should be lowered to less than 5 mmHg in order to reduce blood loss (37). The 2/0 prolene stay sutures are placed along the anterior border of the liver in order to retract the left lobe and expose the section line. Bipolar forceps and robotic harmonic shears are the main tools for the parenchymal transection. The transection is performed layer by layer, starting from the cortical aspect of the liver. It is important to proceed this way keeping the entire section

line always under control. Because the harmonic shears lack articulating ability, the first arm is shifted into the midline 12 mm port with a trocar in trocar technique. This allows for better alignment of the instrument with the section line. Minor bleedings can be controlled using bipolar cautery or harmonic shears, while larger vessels should be selectively sutured with prolene stitches. After the sub-cortical aspect of the liver is sectioned, the transection proceeds towards the core of the liver parenchyma. This portion of the liver includes bigger vessels, like venous branches coming from segments V and VIII, and directed to the middle hepatic vein. At this point, laparoscopic staplers are used for the parenchyma and the intracapsular control of the right hepatic vein. The bed side assistant surgeon has a key role at this stage. The liver is then completely mobilized by sectioning the remaining peritoneal attachments. The raw surface of the remaining liver should then be examined for bleeding and bile leak. Raising the CVP helps with checking the effectiveness of the hemostasis. Fluorescence can be used to detect bile leaks from the hepatic remnant, using irrigation. At the end, fibrin glue can be applied to the remaining surface as a sealant. Although some authors perform the Pringle maneuver to prevent excessive blood loss during hepatic resection, we do not find it necessary (38,39). Finally, the specimen is placed in an endoscopic bag and extracted through a small Pfannenstiel incision or through the site of a previous scar, if present. We normally place two closed suction drains in the subhepatic and subdiaphragmatic area. The robotic cart is removed from the operative field, pneumoperitoneum is stopped and the trocars are extracted under direct laparoscopic vision.

Technique: robot-assisted left hepatectomy

Patient positioning and trocar placement

The patient positioning and trocar placement are similar to the right hepatectomy. The third arm is generally kept on the left side but, in few cases, is moved on the far right to allow for more space for the operative arms on the left.

Surgical procedure

The operation begins with sectioning the round, falciform and left triangular ligaments in order to mobilize the left lobe of the liver. The left hepatic artery is identified, along the left side of the hepatoduodenal ligament, and is then dissected and sectioned between sutures after confirming the correct interpretation of the anatomy. At this point, the left portal branch is identified and sectioned between ligatures. The left hepatic biliary duct is located just above the left portal vein and divided between robotic clips and sutures. We always perform an extraparenchymal dissection of these structures.

The principles of parenchymal transection are equivalent to right hepatectomy. The transection should proceed layer by layer using the harmonic shears from the cortical aspect of the liver towards the core of the parenchyma. Stay sutures should be placed on the left side of the transection line and held by the third robotic arm in order to provide exposure of the hepatic section line. Bleeding can be managed with bipolar cautery, harmonic shears and/or selective sutures and robotic clips. The residual parenchyma and left hepatic vein are divided using a laparoscopic vascular stapler. The surface of the remnant is checked and the specimen is extracted, as described previously. Two closed suction drains are placed around the resected area.

Technique: robot-assisted segmentectomies

Patient positioning and trocar placement

The patient positioning and trocar placement can be variable depending on the segments to be resected. Trocars will be positioned very high subcostal and lateral for the posterior superior segments or closer to the transverse umbilical line for the anterior segments shifting toward the left or the right depending on the lesion location. The basic rule is to create an adequate triangulation with enough space in between the ports. The assistant ports can be placed slightly caudally from the robotic ports line to allow for more room for movements outside the abdominal cavity. Due to the limited degree of freedom of the Harmonic, correct positioning of the instrument is critical in order to follow the section line. Sometimes this might require a switch of the instrument in between the left and right operative arm.

A laparoscopic exploration of the abdominal cavity and an intraoperative laparoscopic ultrasound are performed. Those are crucial in order to assess the lesions and their relationship with the anatomical structures of the liver and plan for adequate margins.

Surgical procedure

In our experience the Pringle maneuver has been rarely used but when there is a need to secure more control on the liver inflow, the hepatic pedicle is prepared and a tourniquet

is created using an umbilical tape.

The main tool used for parenchymal transection is the robotic harmonic shears. The correct docking of the robotic arm holding the instrument is crucial in order to align the harmonic with the section line. In some cases, the robotic arm can be shifted in one of the assistant ports using a trocar-in-trocar technique. Transection is performed layer by layer, starting from the surface and proceeding towards the core. The segment/mass should be retracted very gently in order to avoid rupture of the lesion, this can be achieved with stay sutures or using the fourth robotic arm with small sponges. Once the resection is completed, hemostasis is perfected with the robotic bipolar forceps and selective stitches can be applied if needed.

Review of the literature

After searching the PubMed database with the MeSH terms: 'robotic liver resection', 'robotic hepatectomy', 'robotic hepatic resection' and 'robotic liver', we selected 12 major series that included more than ten cases with a total of 348 patients undergoing a robotic liver resection. All articles that were taken into consideration report intraoperative and postoperative outcomes. The majority of the studies also include the resection margin status (R0–R1). Two articles did not make a distinction between major and minor hepatectomies in reporting their results (19,22). We excluded two articles that reported the authors' initial experience, since the same cases were included in larger series that were later published by the same authors (23,24,39,40).

In our experience, all segments are amenable to resection. Some authors have reported that robot-assistance especially facilitates the resection of lesions located in the posterior/superior segments (38,39). Nonetheless, even though the resection of such lesions could be easier with the robotic technique instead of the laparoscopic, it can still prove to be very challenging.

Reviewing the current literature, we found that indications for robotic liver surgery included both malignant and benign disease; with the first being the most frequent, exceeding 70%. HCC was the most common indication among the neoplasms (51%), followed by colorectal metastases (35%). Of the benign lesions, 30% were hemangiomas, 20.5% focal nodular hyperplasia (FNH) and 13.7% intrahepatic duct stones.

Contraindications to the robotic approach generally included invasion of major hepatic vessels, and extension into the diaphragm, even though the latter could still be feasible in selected cases. There is no predetermined limit regarding the size of lesions, but very bulky tumors can be difficult to resect.

Major hepatectomies

Major hepatectomy is a complex procedure that requires advanced surgical knowledge and skills. Although minimally invasive resections of the liver are performed more frequently in past years, major resections are still a minority of those cases. In fact, the cases described in current literature are 149, representing 47% of total robotic liver cases (11).

The largest series of robotic hepatectomy was reported by Giulianotti *et al.* (4) in 2011 with a total of 70 hepatic resections, of which 27 were major hepatectomies. The most common procedure was right hepatectomy (n=20), followed by left hepatectomy (n=5). The most frequent indication was malignancy (60%). The mean operative time was 313 minutes with an estimated blood loss of 150 mL and a transfusion rate of 22%. The conversion-to-open rate was 3.7%. Overall morbidity was 29.6% with zero mortality. Resection margins were negative in all cases.

Our most recent experience includes 60 cases of major hepatectomy. The transfusion rate has decreased to 15% and the rate of significant postoperative complications is currently 10%. The conversion rate is 11%, reflecting the increased complexity of cases being performed. The most common reason for conversion-to-open in our series was very bulky lesions and unclear tumor margins.

Recently, Spampinato *et al.* (41) performed a retrospective study comparing the perioperative outcomes of robot-assisted major hepatectomy and laparoscopic major hepatectomy in four Italian centers. A total of 50 major hepatectomies were considered, including 25 robotic and 25 laparoscopic resections. The mean robotic operative time was 430 min, with a median EBL of 250 mL, comparable to laparoscopy. Intermittent pedicle occlusion was required only in the laparoscopic group (32 % *vs.* 0%). The ability to control bleeding effectively during parenchymal transection allows for avoidance of intermittent pedicle occlusion.

In 2014, Tsung *et al.* (7) performed a matched series comparison of surgical and postsurgical outcomes between robotic (n=57), laparoscopic (n=114), and open hepatic resections (n=21). The robotic hepatectomy series included 21 major liver resections. The authors considered the resection of 4 or more liver segments as a major resection.

Table 1 Most important series of major hepatectomies described in the literature

Author	Cases	Year	Mean age (yr)	Type of procedure	Malignant (%)	Mean operative time (min)	EBL (mL)	Transfusion rate (%)	Conversion to open rate (%)	Morbidity rate (%)	Mortality rate (%)	Mean LOS (days)	Resection margins (R0) (%)
Giulianotti *et al.*	27	2011	57	RH [20], LH [5], RT [2]	60	313#	300#	22.2	3.7	29.6	0	7	100
Spampinato *et al.*	25	2014	63#	RH [16], LH [7], ERH [1], LLS + S6 [1]	68	430#	250#	44	4	16	0	8#	100
Tsung *et al.*	21	2014	59.9	No description	71	330#	200#	5.6	19	24	0	5#	100
Wu *et al.**	20	2014	60.9	RH [12], LH [6], three S [1], LLS + S5, 6 [1]	100	380	325	–	5	8	0	7.9	–
Choi *et al.*	20	2012	52.4	RH [6], LH [14]	70	621	478	15	10	40	0	15.1	100
Lai *et al.**	10	2013	61.4	RH [7], LH [3]	100	229.4	412.6	7.1	47	7.1	0	6.2	93*

*, authors include both major and minor hepatectomy results; #, values are expressed as median. EBL, estimated blood loss; LOS, length of hospital stay; RH, right hepatectomy; LH, left hepatectomy; RT, right trisegmentectomy; ERH, extended right hepatectomy; LLS, left lateral segmentectomy; S, segmentectomy.

Mean operative time was 330 minutes with a mean EBL of 200 mL. Transfusion rate was 7% and conversion-to-open occurred in 19% of cases. Morbidity rate was 24%. Mortality and rate of positive resection margins was zero. A statistically significant difference was seen when comparing the EBL of robotic versus open surgery, as well as in the length of hospital stay. The authors concluded that laparoscopic and robotic liver resections are comparable, even with no demonstration of clear superiority of the robotic approach in terms of outcomes.

Wu *et al.* (22) reported 52 robotic hepatic resections, including 20 major hepatectomies. In their paper, they analyzed the results of 38 procedures performed for HCC, with no distinction between major and minor. They compared these cases to 41 laparoscopic cases done in the same center. Conversion to open, morbidity, and mortality rates were comparable in the two groups. However, their results showed a longer operation time (380 *vs.* 227 mL) and greater blood loss (325 *vs.* 480 mL) in the robotic group. Interestingly, they describe that the use of the robotic approach lead to a twofold increase in minimally invasive liver resections, as well as an increase of the percentage of cases of HCC performed in such a manner.

Choi *et al.* (21) published the results of 20 major liver resections. The mean operative time was 621 min, with a mean blood loss of 478 mL and 15% transfusion rate. The conversion rate was 10% and the overall morbidity rate was 40%. The authors recorded the operative time as a tool to assess their learning curve in left hepatectomies. They found a clear cutoff point after the seventh case, where the total operating and console time began to gradually decrease.

In a smaller series, Lai *et al.* (23) described 42 liver resections, of which ten were major hepatectomies. The authors did not differentiate the results between major and minor liver resections, but did observe favorable results with the robotic technique, including a 7.1% complication rate. In their experience, major anatomical dissection was feasible, and with low blood loss, due to the ability to perform accurate extraparenchymal dissection of the portal pedicles and hepatic veins before transection.

The results of the most important series of major hepatectomies are summarized in *Table 1*.

Extended liver resections have also been described in the literature. In 2010, Giulianotti *et al.* were the first to describe a case of extended right hepatectomy with biliary reconstruction for hilar cholangiocarcinoma (42). The series, published in 2011, also included two cases of right trisectionectomy (4). A case report of robotic left

hepatectomy with revision hepaticojejunostomy has also been published by Chen *et al.* (43). Spampinato *et al.* also included a case of extended right hemihepatectomy and Ji *et al.* described one case of left hemihepatectomy with caudate lobe resection (25,41). Specific results regarding these individual cases have not been reported since they are part of the larger series previously described in this review.

The number of major hepatectomies reported in the literature is still somewhat limited, although steadily increasing. The overall data suggests that this technique is comparable to both open and laparoscopic surgery in terms of perioperative and postoperative outcomes, as well as oncologic efficacy. Complex procedures, such as extender liver resections, are made feasible by the intrinsic advantages of the robotic system. Still, this type of complex procedure should be performed by skilled surgeons, specialized in both robotic and hepatobiliary surgery, while maintaining the correct indications.

Minor hepatectomies

Worldwide, the most common liver procedure performed using the robotic approach is minor hepatectomy. Anatomic and non-anatomic segmentectomies are the most frequently performed (28.6%), followed by left lateral sectionectomies (13%) and bisegmentectomies (9%).

In our 2011 series, we described the results of 43 minor hepatectomies (4). The most common resection was segmentectomy (16 cases), bisegmentectomy (10 cases) and left lateral sectionectomy (9 cases). The most frequent indication for surgery was malignancy (60%). The mean operative time was 198 min, with an EBL of 150 mL and a 20.9% transfusion rate. Conversion to open occurred in 7% of cases. The mortality was zero and the overall morbidity rate was 16%. Resection margins were all negative. Our most recent experience includes 77 cases of minor resections. The transfusion rate is 6.5% and the conversion rate has also decreased to 5%. The overall morbidity rate is currently 9%.

Troisi *et al.* (24,39) compared 223 patients who underwent laparoscopic liver resection with 38 patients who had a robotic hepatic resection. The most common resection was segmentectomy or wedge resection (15 cases) and the indication was a malignant tumor in 70% of the cases. The mean operative time and EBL was 271 and 330 mL. Mortality was zero and the morbidity rate was 12.5%. The conversion-to-open surgery was 20%. A negative resection margin was achieved in 92.5% of patients. In their experience, the robot-assisted technique allowed for a more conservative approach, with a greater number of lesions that can be resected, preserving hepatic parenchyma and avoiding major hepatic procedures. Also, in their first experience published in 2011, the same authors concluded that robot-assistance facilitates the resection of lesions localized in the posterior/superior segments, as well as lesions in contact with major liver vessels (39).

In a recent article, Tsung *et al.* performed a matched comparison of patients undergoing robotic and laparoscopic liver resection (7). Fifty-seven patients underwent robotic hepatectomy and 114 laparoscopic hepatectomy. There were 36 cases of minor hepatectomy. The median operative time was 198 min, with a median EBL of 285 mL. The transfusion rate was 2.9%. No conversions-to-open occurred in this series. Mortality was zero and morbidity was 17%. The resection margins were negative in 93% of cases.

In 2013, a prospective evaluation of robotic minor liver resection was performed in 33 patients with a diagnosis of HCC (23). The procedures performed were 12 left lateral sectionectomies, 10 wedge resections, 7 segmentectomies and 4 bisegmentectomies. The mean operative time was 202.7 min and the mean blood loss was 373.4 mL. The complication and mortality rate were 7.1% and 0% respectively, with a negative resection margin of 93%. The authors concluded that robot-assistance is not only feasible and safe, but also does not increase tumor dissemination.

Tranchart *et al.* compared 26 cases of robotic minor hepatectomy performed in an Italian center, to 26 cases of laparoscopic minor hepatectomy performed in a French center (38). Interestingly, the authors report 42% portal triad clamping in the robotic group versus 0% in the laparoscopic group. This was attributed to the surgeons' preference, which differed in the two centers. Although the two techniques had similar outcomes, the use of the robot seemed to facilitate the resection of posterior and superior liver tumors, especially when atypical resection was required.

There are several other reported cases describing robotic minor liver resections (6,25,26,44). Their results are in agreement with the aforementioned studies. Overall, postoperative outcomes are comparable to laparoscopy and the available short-term oncologic outcomes are encouraging. Robotic-assistance could definitely provide an advantage in the most complex cases, in posterior/superior segments and parenchyma-sparing resections. The results of the most important series of major hepatectomies are summarized in *Tables 2* and *3*.

Table 2 Most important series of minor hepatectomies described in the literature, intra- and postoperative outcomes

Author	Cases	Year	Mean age (yr)	Malignant (%)	Mean operative time (min)	EBL (mL)	Transfusion rate (%)	Conversion to open rate (%)	Morbidity rate (%)	Mortality rate (%)	Mean LOS (days)	Resection margins (RO) (%)
Giulianotti *et al.*	43	2011	57	60	198	150	20.9	7	16.2	0	–	100
Troisi *et al.*	38	2013	64.6	70	271	330	–	20	12.5	0	6.1	92.50
Tsung *et al.*	36	2014	59.9	69	198[#]	285[#]	2.9	0	17	0	4[#]	93
Lai *et al.*[*]	33	2013	61.4	100	229.4	412.6[#]	7.1	7.14	7.1	0	6.2	93
Tranchart *et al.*	26	2014	66.5	53.5	210	200	14.2	14.2	35.7	0	6	–
Patriti *et al.*	18	2014	62.6	79	303	376.3	42.1	–	31.5	–	6.7	89.50
Packiam *et al.*	11	2012	57	55	175	30	0	0	27	0	4	–
Yu *et al.*	10	2014	50.4	76.9	291.5	388.5	0	0	0	0	7.8	–
Choi *et al.*	10	2012	52.4	70	403	184	10	0	50	0	8	100

*, authors include both major and minor hepatectomy results; [#], values are expressed as median. EBL, estimated blood loss; LOS, length of hospital stay.

Table 3 Most important series of minor hepatectomies described in the literature and type of procedures

Author	Cases	Segmentectomy	Bisegmentectomy	Wedge resection	Left lateral segmentectomy	Non-adjacent segmentectomies	Subsegmentectomy
Giulianotti *et al.*	43	16	10	8	9	–	–
Troisi *et al.*	38	7	8	15	2	6	–
Tsung *et al.*	36	NR	NR	NR	NR	NR	NR
Lai *et al.*[*]	33	7	4	10	12	–	–
Tranchart *et al.*	26	7	1	13	5	–	–
Patriti *et al.*	18	8	3	5	–	–	2
Packiam *et al.*	11	NR	NR	NR	NR	NR	NR
Yu *et al.*	10	–	–	–	10	–	–
Choi *et al.*	10	2	–	4	4	–	–

*, authors include both major and minor hepatectomy results. NR, not reported.

Conclusions

In the last 20 years, minimally invasive surgery has gained a growing role in liver resections. It is now considered an option for the resection of the anterior and left lateral segments. This approach is also used in few highly specialized centers for major hepatectomies. Due to the limitations of the technique, laparoscopy is still not considered ideal for routine major hepatectomies, extended hepatectomies and for cases at high risk for bleeding.

Robotic surgery has the potential to overcome some of the limits of laparoscopy and, in past years, its range of applications in this field has quickly expanded. Major hepatectomies, extended right, extended left, posterior segments and living donor hepatectomies have been described in the literature (4,20,25,38,41,43,45,46). Perioperative and postoperative outcomes, as well as oncologic efficacy, are not inferior to open or laparoscopic surgery. This approach especially facilitates certain steps of the procedure, such as dissection of the hepatic hilum and hepatocaval plane, mobilization of the liver attachments, biliary anastomosis and suturing for bleeding management during the parenchymal transection. Furthermore, the robotic platform allows for easier integration of new technologies, such as the recently introduced near-infrared fluorescence, for vascular and biliary identification. Augmented reality, image-guided surgery and 3D ultrasound instruments with integrated probes for section margin assessment are all implementations, that in the near future will not only make the complex resections safer and more efficient, but also the routine resections.

There are no large, prospective studies regarding robotic hepatectomies published to date. Further investigation and multicenter trials are needed to validate the current promising results.

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Footnote

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References

1. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg 2009;250:831-41.
2. Nguyen KT, Marsh JW, Tsung A, et al. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg 2011;146:348-56.
3. Milone L, Daskalaki D, Fernandes E, et al. State of the art in robotic hepatobiliary surgery. World J Surg 2013;37:2747-55.
4. Giulianotti PC, Coratti A, Sbrana F, et al. Robotic liver surgery: results for 70 resections. Surgery 2011;149:29-39.
5. Soubrane O, Goumard C, Laurent A, et al. Laparoscopic resection of hepatocellular carcinoma: a French survey in 351 patients. HPB (Oxford) 2014;16:357-65.
6. Packiam V, Bartlett DL, Tohme S, et al. Minimally invasive liver resection: robotic versus laparoscopic left lateral sectionectomy. J Gastrointest Surg 2012;16:2233-8.
7. Tsung A, Geller DA, Sukato DC, et al. Robotic versus laparoscopic hepatectomy: a matched comparison. Ann Surg 2014;259:549-55.
8. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
9. Bhojani FD, Fox A, Pitzul K, et al. Clinical and economic comparison of laparoscopic to open liver resections using a 2-to-1 matched pair analysis: an institutional experience. J Am Coll Surg 2012;214:184-95.
10. Jackson NR, Hauch A, Hu T, et al. The Safety and Efficacy of Approaches to Liver Resection: A Meta-Analysis. JSLS 2015;19:e2014.00186.
11. Qiu J, Chen S, Chengyou D. A systematic review of robotic-assisted liver resection and meta-analysis of robotic versus laparoscopic hepatectomy for hepatic neoplasms. Surg Endosc 2016;30:862-75.
12. Vanounou T, Steel JL, Nguyen KT, et al. Comparing the clinical and economic impact of laparoscopic versus open liver resection. Ann Surg Oncol 2010;17:998-1009.
13. Memeo R, de'Angelis N, Compagnon P, et al. Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case-control study. World J Surg 2014;38:2919-26.
14. Dagher I, Belli G, Fantini C, et al. Laparoscopic hepatectomy for hepatocellular carcinoma: a European experience. J Am Coll Surg 2010;211:16-23.
15. Vibert E, Perniceni T, Levard H, et al. Laparoscopic liver resection. Br J Surg 2006;93:67-72.
16. Gobardhan PD, Subar D, Gayet B. Laparoscopic liver surgery: An overview of the literature and experiences of a single centre. Best Pract Res Clin Gastroenterol

2014;28:111-21.
17. Ocuin LM, Tsung A. Robotic liver resection for malignancy: Current status, oncologic outcomes, comparison to laparoscopy, and future applications. J Surg Oncol 2015;112:295-301.
18. Ballantyne GH. The pitfalls of laparoscopic surgery: challenges for robotics and telerobotic surgery. Surg Laparosc Endosc Percutan Tech 2002;12:1-5.
19. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-29.
20. Giulianotti PC, Sbrana F, Coratti A, et al. Totally robotic right hepatectomy: surgical technique and outcomes. Arch Surg 2011;146:844-50.
21. Choi GH, Choi SH, Kim SH, et al. Robotic liver resection: technique and results of 30 consecutive procedures. Surg Endosc 2012;26:2247-58.
22. Wu YM, Hu RH, Lai HS, et al. Robotic-assisted minimally invasive liver resection. Asian J Surg 2014;37:53-7.
23. Lai EC, Yang GP, Tang CN. Robot-assisted laparoscopic liver resection for hepatocellular carcinoma: short-term outcome. Am J Surg 2013;205:697-702.
24. Troisi RI, Patriti A, Montalti R, et al. Robot assistance in liver surgery: a real advantage over a fully laparoscopic approach? Results of a comparative bi-institutional analysis. Int J Med Robot 2013;9:160-6.
25. Ji WB, Wang HG, Zhao ZM, et al. Robotic-assisted laparoscopic anatomic hepatectomy in China: initial experience. Ann Surg 2011;253:342-8.
26. Berber E, Akyildiz HY, Aucejo F, et al. Robotic versus laparoscopic resection of liver tumours. HPB (Oxford) 2010;12:583-6.
27. Koffron AJ, Auffenberg G, Kung R, et al. Evaluation of 300 minimally invasive liver resections at a single institution: less is more. Ann Surg 2007;246:385-92; discussion 392-4.
28. Abood GJ, Tsung A. Robot-assisted surgery: improved tool for major liver resections? J Hepatobiliary Pancreat Sci 2013;20:151-6.
29. Flower RW, Hochheimer BF. Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein angiography. Johns Hopkins Med J 1976;138:33-42.
30. Hoekstra LT, de Graaf W, Nibourg GA, et al. Physiological and biochemical basis of clinical liver function tests: a review. Ann Surg 2013;257:27-36.
31. Daskalaki D, Aguilera F, Patton K, et al. Fluorescence in robotic surgery. J Surg Oncol 2015;112:250-6.
32. Daskalaki D, Fernandes E, Wang X, et al. Indocyanine green (ICG) fluorescent cholangiography during robotic cholecystectomy: results of 184 consecutive cases in a single institution. Surg Innov 2014;21:615-21.
33. Chung JJ, Kim MJ, Kim KW. Mangafodipir trisodium-enhanced MRI for the detection and characterization of focal hepatic lesions: is delayed imaging useful? J Magn Reson Imaging 2006;23:706-11.
34. Perrenot C, Perez M, Tran N, et al. The virtual reality simulator dV-Trainer((R)) is a valid assessment tool for robotic surgical skills. Surg Endosc 2012;26:2587-93.
35. Fisher RA, Dasgupta P, Mottrie A, et al. An over-view of robot assisted surgery curricula and the status of their validation. Int J Surg 2015;13:115-23.
36. Fernandes E, Elli E, Giulianotti P. The role of the dual console in robotic surgical training. Surgery 2014;155:1-4.
37. Li Z, Sun YM, Wu FX, et al. Controlled low central venous pressure reduces blood loss and transfusion requirements in hepatectomy. World J Gastroenterol 2014;20:303-9.
38. Tranchart H, Ceribelli C, Ferretti S, et al. Traditional versus robot-assisted full laparoscopic liver resection: a matched-pair comparative study. World J Surg 2014;38:2904-9.
39. Casciola L, Patriti A, Ceccarelli G, et al. Robot-assisted parenchymal-sparing liver surgery including lesions located in the posterosuperior segments. Surg Endosc 2011;25:3815-24.
40. Chan OC, Tang CN, Lai EC, et al. Robotic hepatobiliary and pancreatic surgery: a cohort study. J Hepatobiliary Pancreat Sci 2011;18:471-80.
41. Spampinato MG, Coratti A, Bianco L, et al. Perioperative outcomes of laparoscopic and robot-assisted major hepatectomies: an Italian multi-institutional comparative study. Surg Endosc 2014;28:2973-9.
42. Giulianotti PC, Sbrana F, Bianco FM, et al. Robot-assisted laparoscopic extended right hepatectomy with biliary reconstruction. J Laparoendosc Adv Surg Tech A 2010;20:159-63.
43. Chen KH, Chen SD, Chen YD, et al. Robotic left hepatectomy with revision of hepaticojejunostomy. Asian J Surg 2014;37:106-9.

44. Patriti A, Cipriani F, Ratti F, et al. Robot-assisted versus open liver resection in the right posterior section. JSLS 2014;18. pii: e2014.00040.
45. Tzvetanov I, Bejarano-Pineda L, Giulianotti PC, et al. State of the art of robotic surgery in organ transplantation. World J Surg 2013;37:2791-9.
46. Giulianotti PC, Tzvetanov I, Jeon H, et al. Robot-assisted right lobe donor hepatectomy. Transpl Int 2012;25:e5-9.

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Laparoscopic Pringle maneuver: how we do it?

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Abstract: Laparoscopic liver resection (LLR) is technically possible with new devices which allow a relatively bloodless liver parenchymal transection. Despite, the main concern remains intraoperative hemorrhage. Currently, perioperative excessive blood loss during LLR is difficult to control with necessity of laparotomy conversion. Moreover, major blood loss requires transfusion and increases postoperative morbidity and mortality. When in-flow is limited by the hepatic pedicle clamping, it reduces intraoperative blood loss. The Pringle maneuver, first described in 1908, is the simplest method of inflow occlusion and currently can be achieved during LLR. The purpose of this note was to describe two different modalities of Pringle maneuver used by two different teams during LLR.

Keywords: Pringle maneuver; laparoscopy; hepatobiliary surgery

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Introduction

Laparoscopic liver resection (LLR) is technically possible with new instruments that allow a relatively bloodless liver parenchymal transection. Despite novel tools developed for parenchymal transection, the main concern remains intraoperative hemorrhage (1). Actually, intraoperative excessive blood loss during LLR is often difficult to control and is one of the primary reasons for conversion to laparotomy (2). In addition, major blood loss requires transfusion and increases postoperative morbidity and mortality. When limiting the in-flow by occluding vascular pedicle we can severely reduce intraoperative blood loss. The Pringle maneuver (3), first described in 1908, is the simplest method of inflow occlusion and currently can be achieved during LLR. The purpose of this note was to describe two different modalities of Pringle maneuver during LLR used by two different teams.

Extracorporeal Pringle maneuver

This method is used routinely by the Reims team and is similar to the one described by Rotellar *et al.* (4) in 2012 with some peculiarities. Once the pneumoperitoneum is established the hepatoduodenal ligament is exposed and the pars flaccida of the gastrohepatic ligament is opened using a system of ultrasound energy (ultracision). A 5-mm port trocar is placed along the axillary line in the right flank (*Figure 1A*). It is important that the trocar should be positioned this way because it must be perfectly perpendicular to the hepatoduodenal ligament; so, a grasper goes behind the hepatic pedicle through the foramen of Winslow and a cotton tape is placed (*Figure 1B,C*). Then, the ends of the cotton tape are pulled out through the 5-mm port trocar with the help of the grasper. The 5-mm trocar is removed and the end of the cotton tape goes through a 20-F rubber tourniquet that is pushed inside the abdominal cavity up to the level of the hepatic pedicle, while the external end of the cotton tape remains outside of the patient (*Figure 1D*). For a lesion located in the right liver there are two options: (I) for an anterior lesion (5, 6 anterior, or segment 4b in the left liver) or in case of right hepatectomy the technique differs in the way that a 5-mm trocar is placed in the left flank, and with the help of a second grasp when the cotton

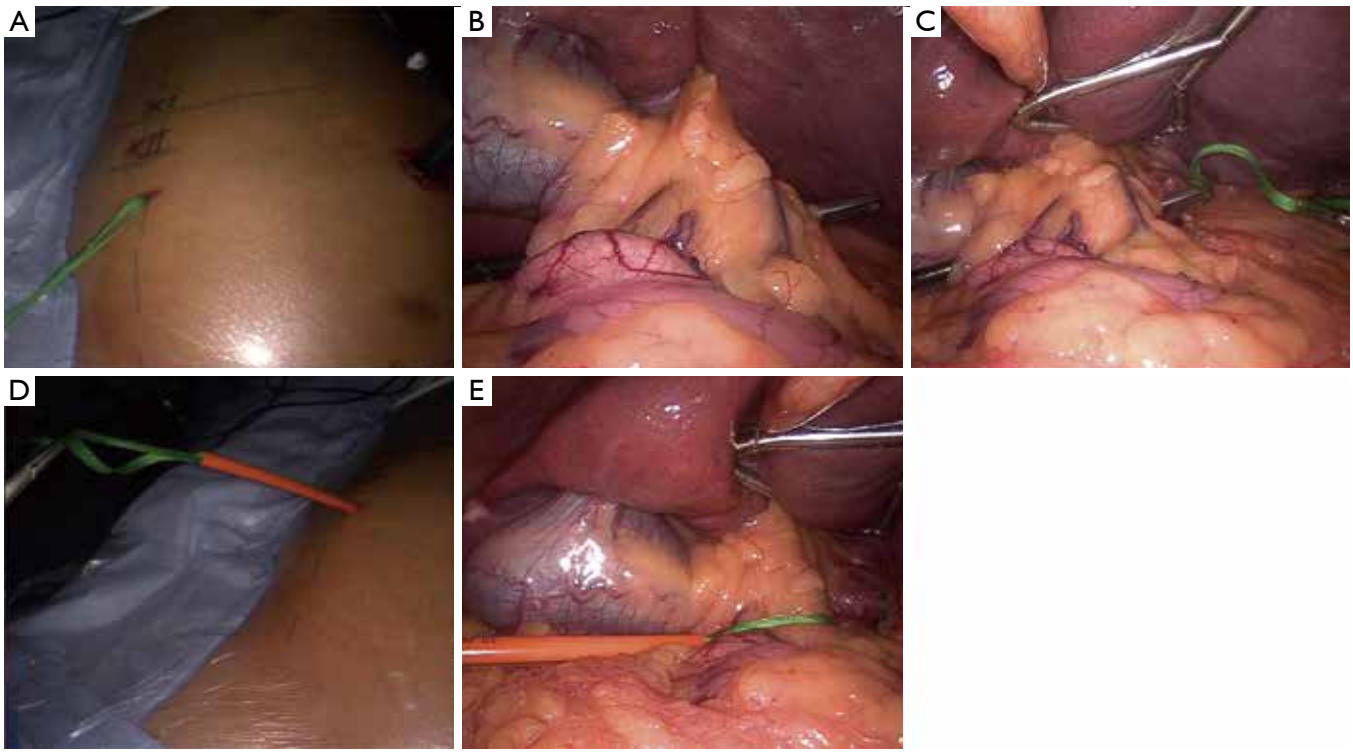

Figure 1 Pringle maneuver: external approach. (A) Trocart (5 mm diameter) is placed on the mid axillary axe, 3 fingers under the tenth coast; (B) forceps are inserted perpendicular to hepatic pedicle; (C) cord is inserted through anterior trocart to surround the hepatic pedicle; (D) cord is exited through the right lateral trocart, and a tube is placed in order to do the clampage; (E) the hepatic pedicle is surrounding and could be clamped easily at any moment by pulling the cord through the tube.

Figure 2 External and anterior approach of the laparoscopic Pringle maneuver (7). First part: external approach. Second part: anterior approach. The exhaustive procedure with their respective steps were explained in *Figures 1* and *3*.
Available online: http://www.asvide.com/articles/1006

tape goes round the hepatic pedicle, the end of the cotton tape is brought out to the left; (II) for a lateral lesion (5,6), we adopt a left lateral decubitus approach. In this case we put out the cotton tape in the right periumbilical region. The Pringle maneuver is done under direct vision in an extracorporeal manner using a Mayo clamp to tighten the tourniquet around the hepatoduodenal ligament (*Figures 1E,2*).

Intracorporeal Pringle maneuver

This method is used routinely by the Strasbourg team and is similar to the one described by Cherqui *et al.* (8) in 2009 with some peculiarities. In fact, even in this method, as we have previously described, a 5 mm trocar is positioned along the left axillary line. So a grasper goes behind the hepatic pedicle through the foramen of Winslow and a cotton tape is placed (*Figure 3A,B*). The ends of the cotton tape are put out of the trocar (10 mm) located on the left of the optic trocar and passed in a 12 F rubber tourniquet long 5 cm (*Figure 3C*). This tourniquet is pushed into the cavity and a clip is placed at the ends of the cotton tape (*Figure 3D*). The Pringle maneuver is done under direct vision in an

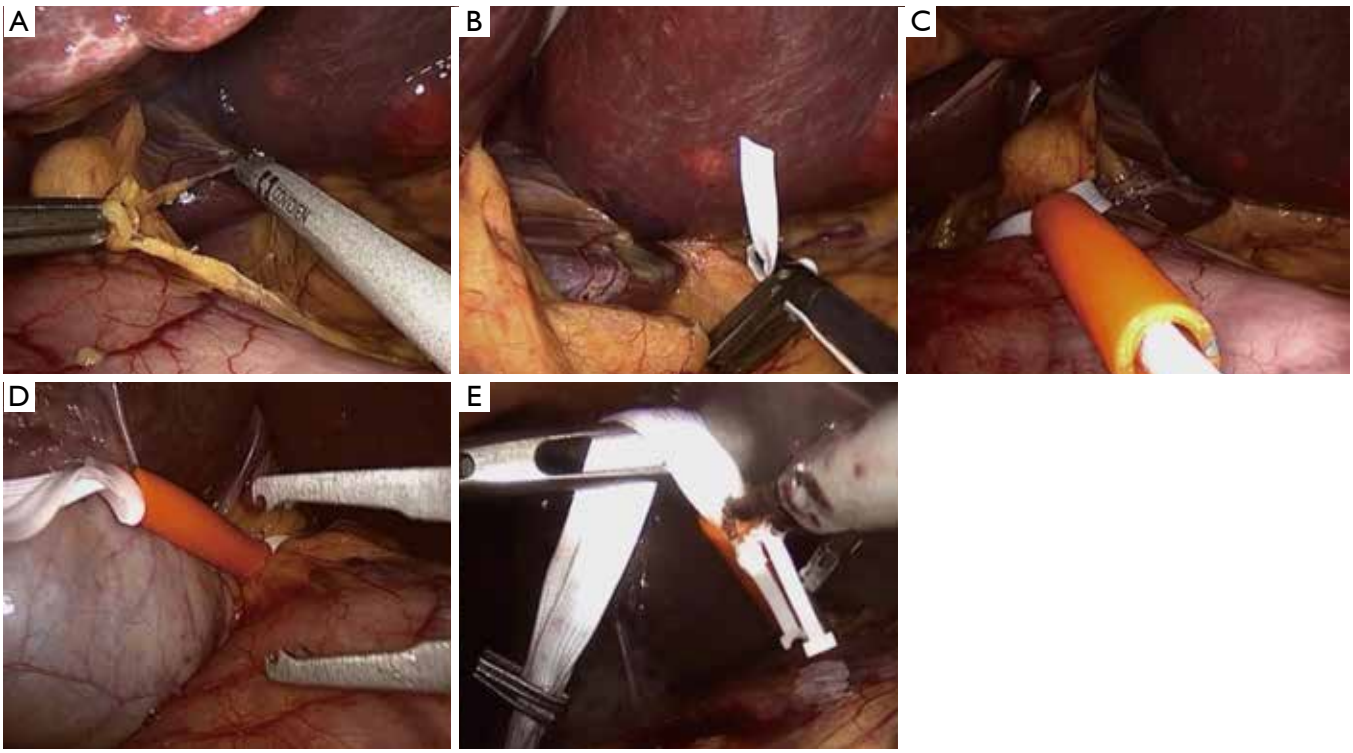

Figure 3 Pringle maneuver: anterior approach. (A) Small epiploon opening; (B) forceps are inserted parallel to hepatic pedicle. Cord is inserted parallel through anterior to posterior movement; (C) cord is exited through the anterior trocart, and a tube is placed in order to do the internal clampage; (D) the hepatic pedicle is surrounding and could be clamped easily at any moment by pulling the cord through the tube and putting an emolock; (E) declamping the hepatic pedicule using ultracision device to remove the emolock.

Table 1 Advantage and disadvantage of different Pringle technique

Pringle technique	Advantage	Disadvantage
Intracorporeal technique	Doesn't require an additional incision	Requires specific material (hemoclips)
	Easy to perform in different positions	Not easy to achieve "in critical moments"
		Elaborated at the moment of unclamping
Extracorporeal technique	Cheap and easy to reproduce	Requires an additional incision
	Quickly usable in case of major bleeding	Complex to manoeuvre in the left side and in lateral decubitus
	Declamping easy and fast	

intracorporeal manner: through the left 10 mm trocar is gripped the tail of the cotton tape while simultaneously through the trocar to the right of the umbilicus a emolock is pushed to tighten the tourniquet around the hepatic pedicle. The parenchymal reperfusion is achieved by the emolock section using a system of ultrasound energy (ultracision) (*Figures 2,3E*). In contrast to the extracorporeal method, this technique does not change according to the location of the lesion.

Discussion

The Pringle maneuver is feasible during LLR. In this technical note we described in a comprehensive way two different methods of approach to the hepatoduodenal ligament that appears easy and reproducible (*Table 1*). Adequate Pringle maneuver may be achieve via extra or intracorporeal, and the positive and negative factors can be evaluated by the surgeon based on experience and type of resection. The main criticism that can be done about

the intracorporeal technique is that it can be difficult to correctly position the emolock to have a complete occlusion of the vascular pedicle. Furthermore, there can be, in the case of intermittent clamping, an increase of the time of ischemia to the difficulty of the remove emolock with ultracision. In contrast, the extracorporeal method criticism is underlined by the fact that to have a correct view on the liver the output cotton tape should vary according to the lesion site.

Nevertheless, we believe that there is a critical point related the laparoscopic Pringle maneuver: to pass through the narrow space between the hepatoduodenal ligament and the inferior vena cava. The grasp must cross horizontally the hepatic pedicle and this is possible only with a 5-mm port trocar placed along the axillary line in the right flank as also described by Rotellar *et al.* Even in obese patients or with a severe adhesion due to a previous operation, this technique can be applied with minimal adhesiolysis using 30° camera scope and forceps. In fact, while with 30° optics we can see the right margin of the ligament with the 5-mm trocar in the right flank, we are able to open a sufficient space to pass a cotton tape. This maneuver can be laborious when we use the tocar placed at the right of the midline. Dua *et al.* in extracorporeal Pringle maneuver used to place an umbilical tape around the hepatoduodenal ligament, a 5-mm laparoscopic articulating 90° esophageal dissector localized at the right or left side of the midline. This type of dissector is necessary because the surgeon operates with a tool practically parallel to the hepatoduodenal ligament.

In literature, different modalities of vascular occlusion to decrease blood loss during LLR have been reported. A literature search for phrases like "Pringle maneuver", "inflow occlusion" and "liver laparoscopic resection" was performed in PubMed from cited English publications. Six articles were reviewed and all studies were unicentric: 3 originated from Asia, 2 from Europe and 1 from America. All publications were retrospective analyses: 2 compared Pringle *vs.* no Pringle or tourniquet method and only one reported experience in HCC. Whilst in the case of extracorporeal technique we know the difference of execution, in situations of hemorrhage clamping is easy and effective. Regarding the intracorporeal technique we appreciated the important difference in execution. The experience of Foshan's hospital (9,10) describes two different methods: the "six-loop" and the other "the lowering of hilar plate approach". Both methods appear difficult to elaborate and to perform. In the case of the "six-loop" a 1-0 vicryl was used to fix the nelaton tube onto the other end or the cross head of T-tube during the clamp period to prevent loosening of the six-loop. In this way, it is difficult to duplicate the method; the author experience reported average Pringle maneuver is 36.2 min that is maximum 2 times. In the case of lowering hilar plate approach, it could be highlighted the difficulty to dissect the hilar plate region and to lower the plate and on the other, the risk of a lesion of the bile ducts.

In conclusion, despite novel devices to do hepatic transection limiting the perioperative blood loss, the Pringle maneuver is feasible and easy to do to ensure safety and prevent major accidental blood loss. In addition, we think that is should be employed especially in case of minor hepatectomy where the axe of transection plane is not under direct vision plan, underlying a higher risk of bleeding not easily accessible to direct usual hemostasis.

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Footnote

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

Informed Consent: Written informed consent was obtained from the patient for publication of this article and any accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

References

1. Buell JF, Thomas MT, Rudich S, et al. Experience with more than 500 minimally invasive hepatic procedures. Ann Surg 2008;248:475-86.
2. Piardi T, Sommacale D, Baumert T, et al. Laparoscopic resection for hepatocellular carcinoma: comparison between Middle Eastern and Western experience. Hepatobiliary Surg Nutr 2014;3:60-72.
3. Pringle JH. V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. Ann Surg 1908;48:541-9.
4. Rotellar F, Pardo F, Bueno A, et al. Extracorporeal tourniquet method for intermittent hepatic pedicle clamping during laparoscopic liver surgery: an easy, cheap, and effective technique. Langenbecks Arch Surg 2012;397:481-5.

5. Dua MM, Worhunsky DJ, Hwa K, et al. Extracorporeal Pringle for laparoscopic liver resection. Surg Endosc 2015;29:1348-55.
6. Zhen ZJ, Lau WY, Wang FJ, et al. Laparoscopic liver resection for hepatocellular carcinoma in the left liver: Pringle maneuver versus tourniquet method. World J Surg 2010;34:314-9.
7. Piardi T, Lhuaire M, Memeo R, et al. External and anterior approach of the laparoscopic Pringle maneuver. Asvide 2016;3:246. Available online: http://www.asvide.com/articles/1006
8. Cherqui D, Husson E, Hammoud R, et al. Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 2000;232:753-62.
9. Chao YJ, Wang CJ, Shan YS. hnical notes: a self-designed, simple, secure, and safe six-loop intracorporeal Pringle's maneuver for laparoscopic liver resection. Surg Endosc 2012;26:2681-6.
10. Chen YJ, Zhen ZJ, Chen HW, et al. Laparoscopic liver resection under hemihepatic vascular inflow occlusion using the lowering of hilar plate approach. Hepatobiliary Pancreat Dis Int 2014;13:508-12.

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A totally laparoscopic associating liver partition and portal vein ligation for staged hepatectomy assisted with radiofrequency (radiofrequency assisted liver partition with portal vein ligation) for staged liver resection

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Abstract: In order to induce liver hypertrophy to enable liver resection in patients with a small future liver remnant (FLR), various methods have been proposed in addition to portal vein embolisation (PVE). Most recently, the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique has gained significant international interest. This technique is limited by the high morbidity associated with an *in situ* liver splitting and the patient undergoing two open operations. We present the case of a variant ALPPS technique performed entirely laparoscopically with no major morbidity or mortality. An increased liver volume of 57.9% was seen after 14 days. This technique is feasible to perform and compares favourably to other ALPPS methods whilst gaining the advantages of laparoscopic surgery.

Keywords: Radiofrequency assisted liver partition with portal vein ligation (RALPP); associating liver partition and portal vein ligation for staged hepatectomy (ALPPS); liver resection; two-stage; portal vein ligation; radiofrequency ablation

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Introduction

Liver resection remains the gold standard treatment modality for patients suffering from primary or secondary liver tumours. It is the only option that offers the possibility of long-term survival (1). Almost half of resectable cases require an extended hepatectomy to obtain a negative resection margin, a key determinant for long-term survival (2). However, the future liver remnant (FLR) of the liver must make up at least 25% of the total liver volume (3) and thus only 10–20% of patients are suitable for this surgery (4). In order to increase the FLR size prior to surgical resection, a number of techniques have been implemented by clinicians. This has resulted in an increase in candidates for hepatic resection (5) and a reduced risk of postoperative liver failure after major hepatectomy (6).

Traditionally, radiological portal vein embolization has become the gold standard for increasing the FLR size. However, in the last few years, there have been a number of publications centred around the surgical approach termed associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) following the original publication by Schnitzbauer *et al.* (7) in 2012. By ligating the portal vein and splitting the liver parenchyma '*in-situ*', distinct and rapid hypertrophy of the liver tissue occurs. In 2005, Dr. Jiao first introduced the concept of virtual splitting of liver parenchyma by using an energy source, a variant ALPPS technique assisted with radiofrequency named as radiofrequency assisted liver partition with portal vein ligation (RALPP) (3), whereby surgical portal vein ligation and radiofrequency ablation of the liver parenchyma

is performed, without splitting liver parenchyma to avoid complications related to ALPPS, as stage I before completion hepatectomy as stage II. A case of RALPP with both stages completed entirely laparoscopically is reported here.

Case history and technique

A 76-year-old male was referred to the senior surgeon (LR Jiao) for management of multiple synchronous colorectal liver metastases following a laparoscopic right hemicolectomy for a final histological staging of a T4N2M1 adenocarcinoma of the colon in August 2014 after 10 cycles of Folfirinox chemotherapy. Prior to chemotherapy, he had bilobar liver metastases, 3 in the left lobe and 4 in the right lobe. He had a good response to the chemotherapy with smaller tumours throughout although seven metastases remained (*Figure 1*).

After discussion at the regional liver multi-disciplinary team meeting it was decided that he was suitable for a staged liver resection for resection of his bilobar metastases (8). However, his FLR was calculated as being only 26.0% of the total liver volume. This coupled with a prolonged preoperative chemotherapy was felt to be insufficient to sustain postoperative liver function. He was considered for laparoscopic RALPP procedure to induce liver hypertrophy prior to an extended right hepatectomy. Stage I was completed laparoscopically as outlined below in March 2015. Total operative time was 1 hour and 50 minutes with minimal blood loss and no post-operative transfusion requirements. He returned to the surgical ward for routine post-operative care. He was discharged on post-operative day 1 having had no complications. He underwent updated cross sectional imaging on day 14 post stage I. At this time his FLR was calculated as 38.9% of his total liver volume with a relative increase in volume of 57.9%. He was scheduled for stage II, an extended right hepatectomy laparoscopically, as outlined below. The operative time was 4 hours and 30 minutes with 600 mL of blood loss and two units of intra-operative blood transfusion. Following routine post-surgical care he was discharged home on day 19 after a prolonged post-operative ileus. He had no other 30 day morbidity or mortality. *Figure 1* shows CT slices of his liver before and after stage I RALPP laparoscopically. Both procedures were performed by Professor Jiao.

Stage I RALPP was performed using a 5 port (2 mm × 10 mm working ports on each side of abdomen) technique. Following wedge resection of three tumours from segments II (n=2) and III (n=1) respectively (*Figure 2A*), attention was paid to hilar dissection for identification and ligation of the right portal vein. The portal vein was carefully separated from the common hepatic duct behind the right hepatic artery. The right hepatic artery was isolated and slung with a non-absorbable suture (0/0 prolene) to aid identification and ligation of this at the second stage liver resection. The right portal vein was isolated using blunt dissection and ligated using 2 Hem-o-loks (Teleflex, NC, USA). Following ligation of the right portal vein, the demarcation between the left and right lobe of the liver was clearly visible. Then, radiofrequency ablation using a laparoscopic device (Habib Sealer LH4X, Rita, USA) was performed for completion of RALPP along the demarcation line between segments V and IVa. One of the four tumours in the right lobe of the liver was situated in the junction of segments VIII and IVb along the demarcation line (*Figures 1*,*2*). To avoid going through the tumour, the line of virtual division with radiofrequency was veered to the left border of the tumour in segment IVb towards the middle hepatic vein (*Figure 2B*).

Stage II RALPP was performed laparoscopically by re-opening the same five port sites. The slung right hepatic artery was identified and ligated. Following this the right Glissonian pedicle was divided using Endo GIA 60 (Medtronic, Minneapolis, USA). The liver parenchyma was divided along the previous ablation line using Ligasure (Medtronic, Minneapolis, USA). Finally the right and middle hepatic veins were divided using the Endo GIA 60 stapler (Medtronic, Minneapolis, USA) by taking the segment IVb (*Figure 2C*).

The resected tissue was removed with Endo Catch (Medtronic, Minneapolis, USA) via a small Pfannenstiel incision.

Discussion

A variant ALPPS technique with both stages being performed successfully entirely laparoscopically is reported here. Laparoscopic surgery has well known benefits for the patient, in particular, quicker recovery, less analgesic requirements, shorter length of stay and reduced morbidity. This laparoscopic technique has been shown to be safe and feasible in patients requiring staged hepatectomy (3).

To increase the number of patients suitable for liver resection, the only proven effective method available for liver regeneration with portal vein embolisation (PVE) has been used to increase the size of the FLR before surgery. However, the rate of hypertrophy is small around

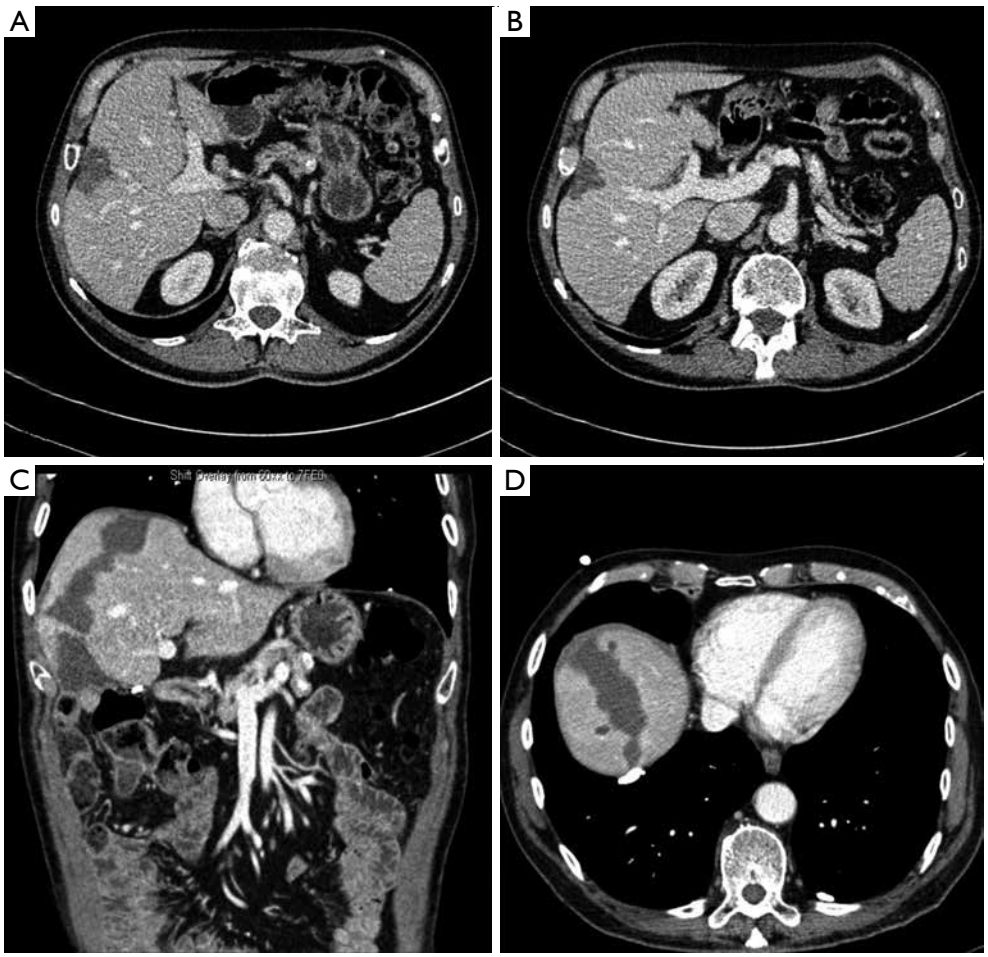

Figure 1 CT slices of case study. The segments VIII and IVb lesion is seen before chemotherapy (A) and after chemotherapy (B). (C,D) Show the radiofrequency ablation line after stage I RALPP. RALPP, radiofrequency assisted liver partition with portal vein ligation.

11.9% over a 6-week period (9). Over the last few years, a new surgical technique, ALPPS, has been reported to dramatically increase FLR volume by 74.0% in an average of around nine days (7). In comparison to PVE, ALPPS clearly has been beneficial in terms of both FLR volume (74.0% *vs.* 11.9%) and time interval to second stage (9 *vs.* 55 days). However, ALPPS is associated with morbidity rates of 33.0–64.0% (3), which, in comparison, is higher than 16.0% (9) seen after PVE. ALPPS can be accompanied by a high risk of post-operative bile leaks (20.0%) (7), which contributes to high morbidity levels. Efforts were made to reduce bile leakage by an Argentinian group (10) through the implementation of a hermetic bag being wrapped around the diseased liver. This, however, still produced a high morbidity level of 58.0% (11). High rates of bile leakage were also documented by a German study (12) performing ALPPS in nine patients. These complications were largely attributable to the direct result of splitting of liver parenchyma. A new variant ALPPS termed RALPP was thus invented and reported by senior surgeon, Professor Jiao. The major advantage of this technique was to reduce the post-operative complications related to split the liver parenchyma in stage I (bile leak rate of 0%) while capitalising the advantages of rapid liver hypertrophy (66.0%) within a short period of time (21.8 days) as seen with ALPPS.

In 2012, the first totally laparoscopic ALPPS was performed by Machado *et al.* (13) and colleagues on a 69-year-old woman with multiple bilobar colorectal liver metastases. Stage-one of their procedure involved laparoscopic partial resection of segment 3 followed by right portal vein ligation and *in situ* split. Full mobilisation of the

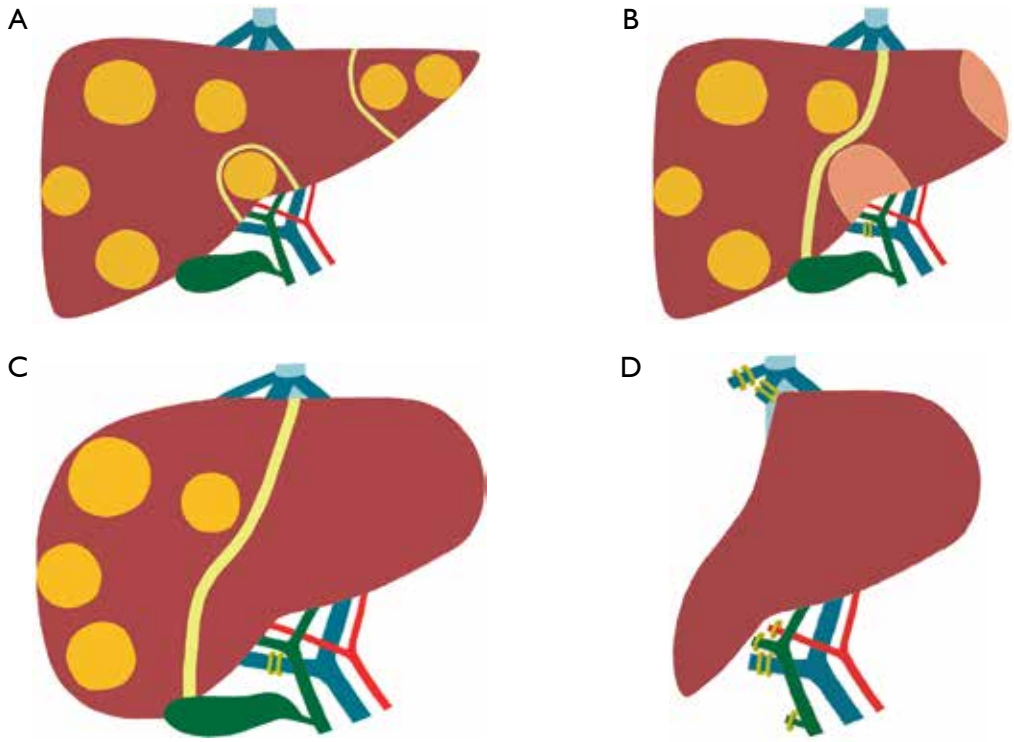

Figure 2 Techniques for laparoscopic RALPP. (A) Stage 1: laparoscopic resection of liver tumour from the left lobe of liver; (B) stage 1: laparoscopic ligation of right portal vein with division of liver parenchyma with RFA; (C,D) stage 2: laparoscopic extend right hepatectomy with resection of segment IVb. RALPP, radiofrequency assisted liver partition with portal vein ligation.

right liver was performed in the first stage. Liver transection was facilitated though the use of harmonic scalpel and vascular endoscopic stapler. Computerised tomography at the seventh postoperative day showed an 88.0% increase in FLR volume. Stage-two was performed on the ninth postoperative day. Adhesion rate was considerably lower. Division of the remaining liver parenchyma, pedicle, and right hepatic vein was done using a stapling device. The specimen was removed through a previous midline incision. Recovery was uneventful.

In 2014, Cai *et al.* (14) successfully performed totally laparoscopic ALPPS using a tourniquet technique on a 64-year-old patient with multiple hepatocellular carcinomas. This represented the first case in which the tourniquet technique was performed laparoscopically as a replacement to *in situ* splitting of the liver. Stage-one included dissection of the right hepatic artery and ligation of the right portal vein. The ligature used was a Flocare® nasogastric tube (Nutricia Flocare, Schiphol Airport, The Netherlands). The tourniquet was wrapped around the liver along the future resection boundary and both ends were passed through the abdominal wall via a small incision and through a thorax tube. The ligature was locked outside the abdominal cavity. Laparoscopic hepatectomy was performed in stage-two by curettage and aspiration. The specimen was extracted through a small incision by a retrieval bag. No bile leakage was observed and patient recovery was uneventful. Cillo *et al.* (15) subsequently reported similar results with microwave ablation in a patient with colorectal liver metastases.

This is only the third report in the literature of an ALPPS technique being performed entirely laparoscopically. This total laparoscopic approach further benefits patients by reducing adhesions, the severity and number of postoperative complications and surgical trauma for quicker recovery. Laparoscopic RALPP allows the second-stage to be performed at an optimal time for the patient without having an urgency to avoid adhesions. It compares favourably with other laparoscopic ALPPS and variant ALPPS (*Table 1*). With the advantages of open RALPP over ALPPS, the total laparoscopic RALPP will improve the outcome of major liver resection further by increasing

Table 1 Comparison of reported total laparoscopic ALPPS and variant ALPPS with laparoscopic RALPP

Reference	Method	Diagnosis (n)	FLR volume increase % mean	Time between stages (days)	Operative time [minutes]	Morbidity (%)	Mortality (%)	Bile leak
Machado *et al.* (13), 2012	Laparoscopic ALPPS	CLM (n=1)	88.0	9	N/A	0	0	0
Cai *et al.* (14), 2014	Laparoscopic ALTPS (Tourniquet)	HCC (n=1)	37.9	14	Stage 1: [315]; stage 2: [215]	0	0	0
Gall *et al.* (3), 2015	Laparoscopic RALPP followed by open stage II resection	CLM (n=5)	62.0	11	Stage 1: [165]; stage 2: [260]	20*	0	0
Cillo *et al.* (15), 2015	Laparoscopic microwave ablation and portal vein ligation for staged hepatectomy	CLM (n=1)	90.4	15	Stage 1: [170]; stage 2: [630]	0	0	0
Current case	Laparoscopic RALPP followed by laparoscopic stage II resection	CLM (n=1)	57.9	21	Stage 1: [110]; stage 2: [270]	0	0	0

*, one patient known to have PE and IVC filter inserted for colectomy developed chest related problems 2 weeks after discharge following stage I RALPP. She was readmitted to medical team for treatment although no proven new PE. ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; RALPP, radiofrequency assisted liver partition with portal vein ligation; CLM, colorectal liver metastases; HCC, hepatocellular carcinoma.

the number of cases for liver resection while keeping a low morbidity and mortality. Currently, a randomised controlled trial comparing the RALPP technique with PVE (REBIRTH trial) is ongoing in our unit to evaluate the real benefit of RALPP over PVE.

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Footnote

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

Informed Consent: Informed consent was obtained from the patient for publication of this article and any accompanying images.

References

1. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125-35.
2. Yamamoto J, Kosuge T, Takayama T, et al. Recurrence of hepatocellular carcinoma after surgery. Br J Surg 1996;83:1219-22.
3. Gall TM, Sodergren MH, Frampton AE, et al. Radio-frequency-assisted Liver Partition with Portal vein ligation (RALPP) for liver regeneration. Ann Surg 2015;261:e45-6.
4. Bismuth H, Adam R, Lévi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509-20; discussion 520-2.
5. Bertens KA, Hawel J, Lung K, et al. ALPPS: challenging the concept of unresectability--a systematic review. Int J Surg 2015;13:280-7.
6. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-80; discussion 680-1.
7. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.
8. Tsim N, Healey AJ, Frampton AE, et al. Two-stage

resection for bilobar colorectal liver metastases: R0 resection is the key. Ann Surg Oncol 2011;18:1939-46.
9. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49-57.
10. de Santibañes E, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. Ann Surg 2012;255:415-7.
11. Alvarez FA, Ardiles V, Sanchez Claria R, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): tips and tricks. J Gastrointest Surg 2013;17:814-21.
12. Li J, Girotti P, Königsrainer I, et al. ALPPS in right trisectionectomy: a safe procedure to avoid postoperative liver failure? J Gastrointest Surg 2013;17:956-61.
13. Machado MA, Makdissi FF, Surjan RC. Totally laparoscopic ALPPS is feasible and may be worthwhile. Ann Surg 2012;256:e13; author reply e16-9.
14. Cai X, Peng S, Duan L, et al. Completely laparoscopic ALPPS using round-the-liver ligation to replace parenchymal transection for a patient with multiple right liver cancers complicated with liver cirrhosis. J Laparoendosc Adv Surg Tech A 2014;24:883-6.
15. Cillo U, Gringeri E, Feltracco P, et al. Totally Laparoscopic Microwave Ablation and Portal Vein Ligation for Staged Hepatectomy : A New Minimally Invasive Two-Stage Hepatectomy. Ann Surg Oncol 2015;22:2787-8.

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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 ≤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 ≤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

Video 1 Laparoscopic liver resection: basic skills for peripheral lesions.
Available online: http://www.asvide.com/articles/636

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 (*Video 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 ≤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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References

1. Afaneh C, Kluger MD. Laparoscopic liver resection: lessons at the end of the second decade. Semin Liver Dis 2013;33:226-35.
2. Viganò L, Tayar C, Laurent A, et al. Laparoscopic liver resection: a systematic review. J Hepatobiliary Pancreat Surg 2009;16:410-21.
3. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg 2009;250:831-41.
4. Moloo H, Haggar F, Martel G, et al. The adoption of laparoscopic colorectal surgery: a national survey of general surgeons. Can J Surg 2009;52:455-62.
5. Do LV, Laplante R, Miller S, et al. Laparoscopic colon surgery performed safely by general surgeons in a community hospital: a review of 154 consecutive cases. Surg Endosc 2005;19:1533-7.
6. Singh R, Omiccioli A, Hegge SG, et al. Can community surgeons perform laparoscopic colorectal surgery with outcomes equivalent to tertiary care centers? Surg Endosc 2009;23:283-8.
7. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
8. Cucchetti A, Cescon M, Ercolani G, et al. A comprehensive meta-regression analysis on outcome of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. Ann Surg Oncol 2012;19:3697-705.
9. Zhou Y, Xu D, Wu L, et al. Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. Langenbecks Arch Surg 2011;396:1109-17.
10. Kluger MD, Cherqui D. Laparoscopic resection of hepatocellular carcinoma. Recent Results Cancer Res 2013;190:111-26.
11. Kluger MD, Vigano L, Barroso R, et al. The learning curve in laparoscopic major liver resection. J Hepatobiliary Pancreat Sci 2013;20:131-6.

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The laparoscopic liver resections—an initial experience and the literature review

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Abstract: The laparoscopic liver resection (LLR) represents a new pathway in hepatic surgery. Several studies have reported its application in both malignant and benign liver diseases. The most common liver resections performed laparoscopically are wedge, segmental resections and metastasectomy; although in large centers the laparoscopic right and left hepatectomies have begun to perform more frequently. We report the initial experience in LLRs at our department including a case of the first laparoscopic left lateral liver bisegmentectomy performed in patient with follicular nodular hyperplasia and the 15 cases of wedge laparoscopic resections of echinococcic liver cysts. According to literature the mortality rate in LLRs is up to 0.3% and morbidity rate up to 10.5%. The most common cause of the death is liver failure, while the most frequent complication is the bile leakage. Advantages for patients include smaller incisions, less blood loss, and shorter lengths of hospital stay. The LLRs in experienced hands were shown to be safe with acceptable morbidity and mortality for both minor and major hepatic resections in benign and malignant diseases.

Keywords: Laparoscopic liver resection (LLR); segmental resections; left lateral bisegmentectomy; liver echinococcic cyst laparoscopic treatment

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In general, liver surgery has seen significant advances in the last decades, particularly associated with improvements in anesthesia and critical care as well as surgical techniques. The improved understanding of the vascular anatomy of the liver based on Couinaud segments, has also led to a great reduction in morbidity and mortality associated with liver resection (1).

Clearly challenging, the laparoscopic liver resections (LLRs) were not accepted until recently due to the several reasons: the problem of intraoperative bleeding control, the technical difficulties, the learning curve and the fear of gas embolism (2). Since the first reported cases of liver resection in 1991 and 1992 (3,4), more than 3,000 cases have been reported in literature worldwide.

In general, LLR is associated with significant advantages: faster recovery, less post-operative pain, less morbidity, easier subsequent surgery and better cosmetic results (5). At first the indications limited to easily accessible tumors mostly placed at the peripheral portion of liver, the anterolateral segments (II, III, V, VI and the inferior part of IV liver segment) (6,7). The majority of initial reports suggested that LLR is poorly indicated when the lesion is located in the posterior or superior part of the liver (segments I, VII and VIII, the same as the superior part of segment IV) (8,9).

The indications for LLRs widened from solitary, small, easily approachable lesions, to more demanding procedures including the major liver resections such as left and right hepatectomies (10-14). The disease-related indications for LLRs included various conditions of benign, but also the malignant diseases especially the hepatocellular carcinoma and colorectal liver metastases (15-21).

In our department the laparoscopic surgical procedures are widespread. The laparoscopic cholecystectomies

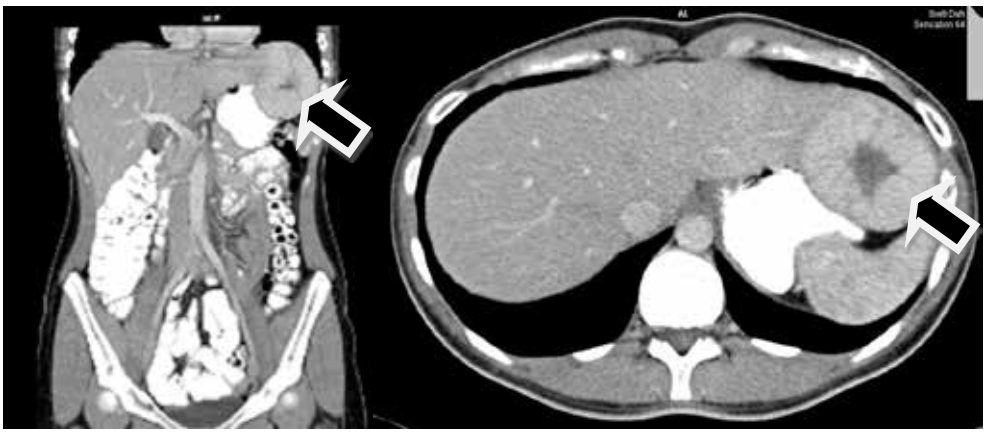

Figure 1 Magnetic resonance imaging (MRI) record of the operated patient with focal nodular hyperplasia (FNH). The tumor located in segments II and III of the liver, shown with black arrows.

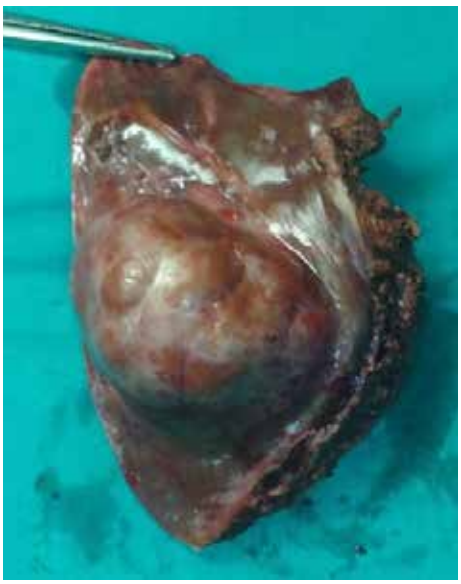

Figure 2 Resected tumor along with the segment II and III of liver.

and appendectomies are performed routinely and have outnumbered the open cholecystectomies and appendectomies that are done only in a narrow spectrum of indications. Apart from that the explorations, the ulcer perforation and hernia repair are performed laparoscopically, as well. During last 10 years the elective splenectomies and colon resections are performed laparoscopically in the high number of cases.

On the other hand, more than 100 open liver resections are performed per year. The experience in laparoscopic surgery and open liver surgery encouraged our surgeons to start performing LLRs. There have already been some reports of laparoscopic operations of the echinococcic cysts performed in our institution (1,10,11).

Through this paper we aim to report our initial experience in laparoscopic liver surgery with the emphasis on the first left lateral bisegmentectomy and to show a brief literature review onto the main problems and concems concerning the LLRs.

Report of a case

A 29 years old female patient was admitted to hospital for operative therapy of a liver tumor found on a magnetic resonance imaging (MRI) scan preformed as gastroenterological workup for symptoms related to chronic gastritis (*Figure 1*). There were no co-morbidities other than mild ankylosing spondylitis and the general clinical state was proper to the age of the patient. According to MRI record the tumor was situated at the left hepatic lobe and its diameters were 62×57 mm. There were no other tumors found inside of the abdominal and thoracic cavity. The patient underwent the laparoscopic left lateral bisegmentectomy of the 2nd and 3rd liver segments (*Figure 2*). The resection was performed throe three skin incisions (*Figure 3*), using the harmonic scalpel and the vascular structures were ligated by the endoscopic vascular staplers (35 and 45 mm). The operation lasted for an hour. The patient spent a day in intensive care unit (ICU). There were no any early complication found and the patient was released home on the third postoperative day. The pathology of the resected tumor had shown the follicular nodular hyperplasia. The consequent perioperative period passed without complications.

Figure 3 Postoperative skin incisions.

Report of laparoscopically treated patients with echinococcic liver disease

In our institution 15 laparoscopic pericistectomies were performed to date. All patients were pre-operatively treated with albendazole. Total pericystectomy without opening the cyst cavity was performed laparoscopically in seven patients, while the partials pericystectomy was done laparoscopically five patients. In another three patients the procedure started laparoscopically but were converted and completed as an open procedure. The median operative time was 67.5 minutes (range, 60.0-120.0 minutes) and the median hospital stay 5.0 days (range, 4.0-7.0 days). In one patient the echinococcic cyst was situated in 7th liver segment and another three cysts were found intraabdominaly. All of them were removed laparoscopically. There were no complication nor recurrences reported until now in laparoscopically operated patients. During the same period of time 32 patients underwent the open operation of the echinococcic liver cysts. In those patients the operation lasted longer [mean operative time 100.0 minutes (range, 60.0-210.0 minutes)]. On the other hand, the hospital stay was longer in patient that underwent the open surgical procedure [median hospital stay 8.0 days (range, 7.0-14.0 days)]. Also there was one case of recurrence in patient treated with the open procedure 3 years following the operation. There was no mortality reported until now in both groups of patients.

Discussion

As the experience and technical improvement grow the spectrum of indications expands. According to recently published study the LLR can be performed safely in selected patients with both benign and malignant liver tumors regardless to the dimensions, location or previous operating history with comparable morbidity and mortality to those in open surgical procedures (12). LLRs were concluded to be comparable or even better than open liver resection in the context of intraoperative blood loss and the length of hospital stay (13). A similar or lower mortality (0.3%) and morbidity (10.5%) were reported at LLR in comparison to open operative technique of the liver resection (14). There was no significant difference in overall and disease-free 5-year survival rate for hepatocellular carcinoma between open and laparoscopic hepatectomies (15). The conversion rates vary from 8.1% to 17.6% and the reported rate of complications was 3.6% with the postoperative bile leakage rate of 1.1% in 27 analyzed studies that included 619 patients (16).

Conclusions

In our initial experience of operated patients the performed laparoscopic surgical procedures were found safe and efficient with the acceptable operative time and hospital stay. The data found in literature are encouraging, however the proper surgical training and experience the same as well technically equipped centers are essential for performing LLRs.

Acknowledgements

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References

1. Busić Z, Lemac D, Stipancić I, et al. Surgical treatment of liver echinococcosis--the role of laparoscopy. Acta Chir Belg 2006;106:688-91.
2. Cai X, Li Z, Zhang Y, et al. Laparoscopic liver resection and the learning curve: a 14-year, single-center experience. Surg Endosc 2014;28:1334-41.
3. Reich H, McGlynn F, DeCaprio J, et al. Laparoscopic excision of benign liver lesions. Obstet Gynecol 1991;78:956-8.
4. Gagner M, Rheault M, Dubuc J. Laparoscopic partial hepatectomy for liver tumor [abstract]. Surg Endosc 1992;6:99.
5. Tranchart H, Dagher I. Laparoscopic liver resection: a review. J Visc Surg 2014;151:107-15.
6. Gigot JF, Glineur D, Santiago Azagra J, et al. Laparoscopic liver resection for malignant liver tumors: preliminary results of a multicenter European study. Ann Surg 2002;236:90-7.

7. Kaneko H, Takagi S, Shiba T. Laparoscopic partial hepatectomy and left lateral segmentectomy: technique and results of a clinical series. Surgery 1996;120:468-75.
8. Laurent A, Cherqui D, Lesurtel M, et al. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. Arch Surg 2003;138:763-9; discussion 769.
9. Dulucq JL, Wintringer P, Stabilini C, et al. Laparoscopic liver resections: a single center experience. Surg Endosc 2005;19:886-91.
10. Busić Z, Cupurdija K, Servis D, et al. Surgical treatment of liver echinococcosis--open or laparoscopic surgery? Coll Antropol 2012;36:1363-6.
11. Busić Z, Lovrić Z, Kolovrat M, et al. Laparoscopic operation of hepatic hydatid cyst with intraabdominal dissemination--a case report and literature review. Coll Antropol 2009;33 Suppl 2:181-3.
12. Han HS, Yoon YS, Cho JY, et al. Laparoscopic liver resection for hepatocellular carcinoma: korean experiences. Liver Cancer 2013;2:25-30.
13. Simillis C, Constantinides VA, Tekkis PP, et al. Laparoscopic versus open hepatic resections for benign and malignant neoplasms--a meta-analysis. Surgery 2007;141:203-11.
14. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg 2009;250:831-41.
15. Kaneko H, Takagi S, Otsuka Y, et al. Laparoscopic liver resection of hepatocellular carcinoma. Am J Surg 2005;189:190-4.
16. Laurence JM, Lam VW, Langcake ME, et al. Laparoscopic hepatectomy, a systematic review. ANZ J Surg 2007;77:948-53.
17. Jurisić I, Paradzik MT, Jurić D, et al. National program of colorectal carcinoma early detection in Brod-Posavina County (east Croatia). Coll Antropol 2013;37:1223-7.
18. Milas J, Samardzić S, Miskulin M. Neoplasms (C00-D48) in Osijek-Baranja County from 2001 to 2006, Croatia. Coll Antropol 2013;37:1209-22.
19. Samardzić S, Mihaljević S, Dmitrović B, et al. First six years of implementing colorectal cancer screening in the Osijek-Baranja County, Croatia--can we do better? Coll Antropol 2013;37:913-8.
20. Boras Z, Kondza G, Sisljagić V, et al. Prognostic factors of local recurrence and survival after curative rectal cancer surgery: a single institution experience. Coll Antropol 2012;36:1355-61.
21. Krebs B, Kozelj M, Potrc S. Rectal cancer treatment and survival--comparison of two 5-year time intervals. Coll Antropol 2012;36:419-23.

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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).

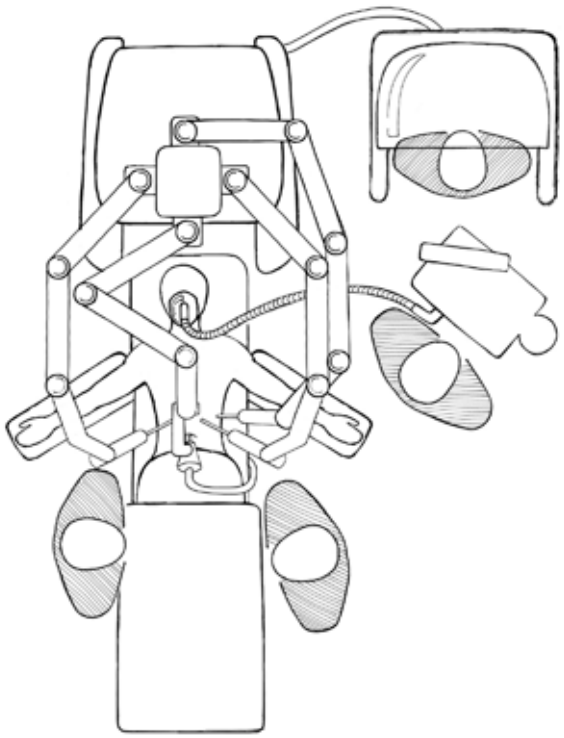

Figure 1 Typical room setup for a robotic hepatectomy.

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

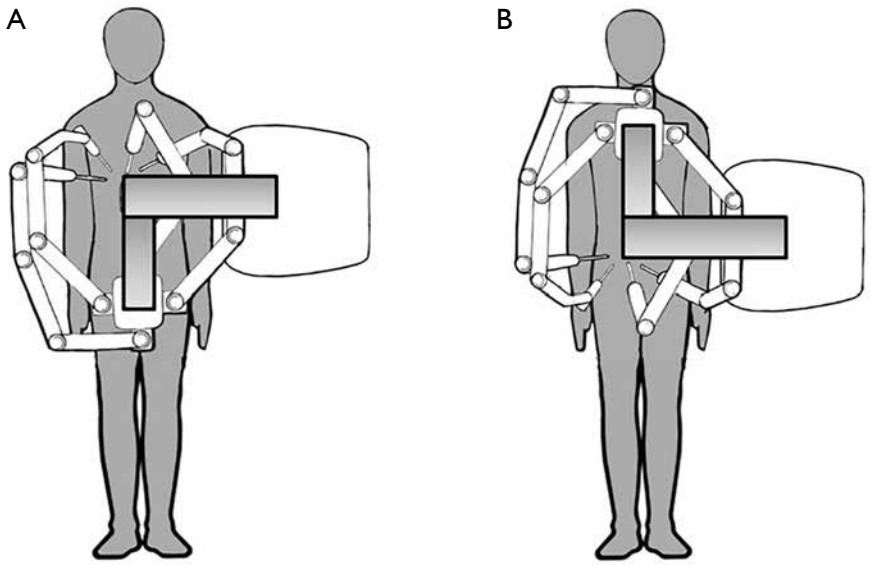

Figure 2 Flexibility for multi-field robotic surgery for the Intuitive Xi Robot. Without moving the patient, or table, or robotic tower, the working arms can be turned 180 degrees to swap from right upper quadrant work (A) to pelvic work (B). This will allow combined hepatectomy and rectal resections.

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 places 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.

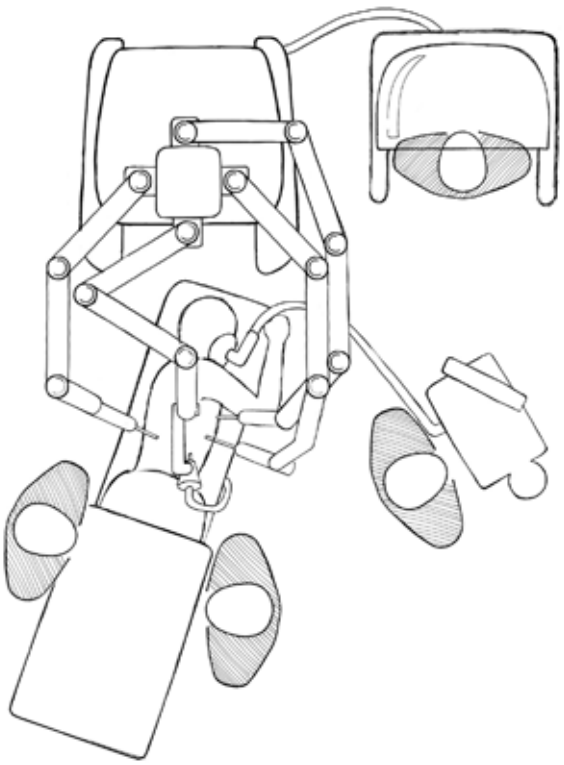

Figure 3 Positioning for robotic hepatectomy for lesions in segment 7 or 8.

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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References

1. Cherqui D, Husson E, Hammoud R, et al. Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 2000;232:753-62.
2. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
3. Shetty GS, You YK, Choi HJ, et al. Extending the limitations of liver surgery: outcomes of initial human experience in a high-volume center performing single-port laparoscopic liver resection for hepatocellular carcinoma. Surg Endosc 2012;26:1602-8.
4. Aikawa M, Miyazawa M, Okamoto K, et al. Single-port laparoscopic hepatectomy: technique, safety, and feasibility in a clinical case series. Surg Endosc 2012;26:1696-701.
5. Romanelli JR, Earle DB. Single-port laparoscopic surgery: an overview. Surg Endosc 2009;23:1419-27.
6. Hung AJ, Patil MB, Zehnder P, et al. Concurrent and predictive validation of a novel robotic surgery simulator: a prospective, randomized study. J Urol 2012;187:630-7.
7. Korets R, Mues AC, Graversen JA, et al. Validating the use of the Mimic dV-trainer for robotic surgery skill acquisition among urology residents. Urology 2011;78:1326-30.
8. Giulianotti PC, Coratti A, Angelini M, et al. Robotics in general surgery: personal experience in a large community hospital. Arch Surg 2003;138:777-84.

9. Ji WB, Wang HG, Zhao ZM, et al. Robotic-assisted laparoscopic anatomic hepatectomy in China: initial experience. Ann Surg 2011;253:342-8.
10. Lai EC, Yang GP, Tang CN. Robot-assisted laparoscopic liver resection for hepatocellular carcinoma: short-term outcome. Am J Surg 2013;205:697-702.
11. Tsung A, Geller DA, Sukato DC, et al. Robotic versus laparoscopic hepatectomy: a matched comparison. Ann Surg 2014;259:549-55.
12. Agcaoglu O, Aliyev S, Taskin HE, et al. Malfunction and failure of robotic systems during general surgical procedures. Surg Endosc 2012;26:3580-3.
13. Buchs NC, Pugin F, Volontl F, et al. Reliability of robotic system during general surgical procedures in a university hospital. Am J Surg 2014;207:84-8.
14. Kim WT, Ham WS, Jeong W, et al. Failure and malfunction of da Vinci Surgical systems during various robotic surgeries: experience from six departments at a single institute. Urology 2009;74:1234-7.
15. Steinberg PL, Merguerian PA, Bihrle W 3rd, et al. A da Vinci robot system can make sense for a mature laparoscopic prostatectomy program. JSLS 2008;12:9-12.
16. Turchetti G, Palla I, Pierotti F, et al. Economic evaluation of da Vinci-assisted robotic surgery: a systematic review. Surg Endosc 2012;26:598-606.
17. Satava RM. Surgical robotics: the early chronicles: a personal historical perspective. Surg Laparosc Endosc Percutan Tech 2002;12:6-16.
18. Lanfranco AR, Castellanos AE, Desai JP, et al. Robotic surgery: a current perspective. Ann Surg 2004;239:14-21.
19. Yates DR, Vaessen C, Roupret M. From Leonardo to da Vinci: the history of robot-assisted surgery in urology. BJU Int 2011;108:1708-13; discussion 1714.
20. Intuitive Surgical. Da Vinci Surgical Si System. Available online: http://www.intuitivesurgical.com/products/davinci_surgical_system/davinci_surgical_system_si/
21. Cho JY, Han HS, Yoon YS, et al. Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver, with a special reference to overcoming current limitations on tumor location. Surgery 2008;144:32-8.
22. Casciola L, Patriti A, Ceccarelli G, et al. Robot-assisted parenchymal-sparing liver surgery including lesions located in the posterosuperior segments. Surg Endosc 2011;25:3815-24.
23. Kingham TP, Scherer MA, Neese BW, et al. Image-guided liver surgery: intraoperative projection of computed tomography images utilizing tracked ultrasound. HPB (Oxford) 2012;14:594-603.
24. Kandil E, Noureldine SI, Saggi B, et al. Robotic liver resection: initial experience with three-arm robotic and single-port robotic technique. JSLS 2013;17:56-62.
25. Marescaux J, Leroy J, Gagner M, et al.Transatlantic robot-assisted telesurgery. Nature 2001;413:379-80.
26. Xu S, Perez M, Yang K, et al. Determination of the latency effects on surgical performance and the acceptable latency levels in telesurgery using the dV-Trainer(®) simulator. Surg Endosc 2014;28:2569-76.
27. Gagner M, Begin E, Hurteau R, et al. Robotic interactive laparoscopic cholecystectomy. Lancet 1994;343:596-7.
28. Himpens J, Leman G, Cadiere GB. Telesurgical laparoscopic cholecystectomy. Surg Endosc 1998;12:1091.
29. Chan OC, Tang CN, Lai EC, et al. Robotic hepatobiliary and pancreatic surgery: a cohort study. J Hepatobiliary Pancreat Sci 2011;18:471-80.
30. Giulianotti PC, Coratti A, Sbrana F, et al. Robotic liver surgery: results for 70 resections. Surgery 2011;149:29-39.
31. Berber E, Akyildiz HY, Aucejo F, et al. Robotic versus laparoscopic resection of liver tumours. HPB (Oxford) 2010;12:583-6.

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Laparoscopic liver resection for hepatocellular carcinoma in patients with cirrhosis

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Abstract: Liver resection for patients with cirrhosis remains a challenging operation. The presence of thrombocytopenia and portal hypertension could lead to severe bleeding during hepatectomy. The enthusiasm of laparoscopic hepatectomy has been growing and many studies have reported their initial favorable results for patients with hepatocellular carcinoma (HCC). The advancement in technology, better understanding of the use of pneumoperitoneum pressure and more experience accumulated make laparoscopic liver resection for patients with cirrhosis possible. Favorable outcome may be achieved if the patients are carefully selected and carried out in high volume centers.

Keywords: Laparoscopic liver resection; hepatocellular carcinoma (HCC); technique; cirrhosis

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Introduction

Liver resection has been considered one of the most difficult procedures to be performed by laparoscopic means. After the first cholecystectomy (1) performed more than 20 years ago, the development of laparoscopic surgery has been very enthusiastic. Unlike many medium-sized operations such as laparoscopic hernia repair, splenectomy and adrenalectomy the development of laparoscopic hepatectomy has been slow (2-4). The initial indication of laparoscopic liver resection was mainly limited to benign conditions (5). With increasing number of successful reports, nowadays the indications was been broadened to other malignant condition liver colorectal liver metastasis and hepatocellular carcinoma (HCC) (6-9).

The gold standard

Open hepatectomy has been a well-established treatment option for HCC even in patients with liver cirrhosis. In our center, we performed more than 250 cases of the liver resection per year. Amongst those, 75% of the cases were hepatitis B carrier where liver cirrhosis is a common finding during the operation. In recent 10 years, we observed a constant good results of hepatectomy for HCC despite an older patient population, a higher incidence of comorbid illness, a higher incidence of cirrhosis, and worse liver function in patients (10). The operation mortality rate nowadays for major hepatectomy in patients with cirrhosis was 4.3% and operation mortality rate for minor hepatectomy in patients with cirrhosis was 1.5% (11). It is not difficult to imagine the slow development pace of laparoscopic liver resection in the presence of well high quality performance of the open approach.

Difficulties of liver resection in patients with liver cirrhosis

Liver resection remains one of the most challenging procedures in surgery. The liver is anatomically divided into

different sections according to its complex vasculatures. Bleeding, biliary fistula, post-operative liver failure and mortality could happened even after a simple minor hepatectomy (12). In Asia, the incidence of HCC is highest in the world due to the presence of concomitant hepatitis B infection. Hepatitis B related HCC usually associated with liver cirrhosis in Asian countries. Without a proper screening program, most of the patients with HCC are considered unresectable due to the late presentation of the symptom (13). Only 25% of the patients can received live resection at the moment the diagnosis is made. The presence of portal hypertension, splenomegaly, presence of gastric or esophageal varices and thrombocytopenia make hepatectomy more difficult when compared to liver resection in the western countries (14). The major hurdle to laparoscopic liver hepatectomy is obvious. It seems very difficult if not impossible to perform such a difficult operation in difficult patients with minimally access surgery.

Technical issues

We believed that safe hepatectomy can be performed in patients with HCC even in the presence of cirrhosis. The selection criteria of laparoscopic liver resection follow exactly the same principle of open surgery. There should be absence of extrahepatic disease, absence of tumor thrombus in the main portal vein and inferior vena cava and anatomically feasible for liver resection. Liver function assessment was based largely on the result of the indocyanine green (ICG) clearance test. An ICG retention rate of 14% at 15 min after injection was considered favorable for major hepatectomy. For minor hepatectomy, the cut-off value for ICG clearance was 22% (11). In laparoscopic approach, the technique should be comparable to that of open approach. For patients receiving major liver resection, the portal pedicle will be dissected clearly from the Glisson capsule and the portal vein, hepatic artery and bile duct were separately controlled and divided. The patient was usually placed in the Lloyd-Davis position. The primary surgeon stood between the legs with one assistant on each side. Pneumoperitoneum was usually done by subumbilical incision. Three to four working ports sized between 5 and 12 mm were used. This allow the use of an ultrasonic dissector like Harmonic scalpel or Thunder beat and a CUSA for parenchymal transection (15,16). Nowadays, the new energy devices can produce good sealing effects to vessels up to 7 mm in diameters. These could assist effective liver parenchymal transection in anatomic liver resection where major bile ducts were located away from the transection plane.

Intraoperative ultrasound was performed as with the patients receiving the open approach. The small vessels were controlled with multi-fired metal clips. The major hepatic veins were controlled with vascular staplers. Hemostasis was performed using metal clips, diathermy, and suturing. The liver was delivered through an incision not larger than the largest diameter of the delivered specimen. Usually in a pfannenstiel incision were the wound would become less visible after the operation. Usually no drainage tube was placed (16).

One of the major breakthroughs in laparoscopic liver resection is the rapid development of the high definition unit of the laparoscopic camera processor. Crystal clear image with magnification make meticulous dissection of the vital structure of the liver possible. Apart from clear visualization, the application of the positive pneumoperitoneum pressure makes liver parenchymal transection less difficult (17-19).

In open approach, in order to prevent venous oozing from liver parenchymal transection, careful administration of intravenous fluid and meticulous central venous pressure control was administrated. With the help of vasodilators and diuretics, the anesthesiologist will cautiously keep the CVP at preferably less than 5 cm water. In laparoscopic approach, the venous oozing can be effectively manipulated by elevation of the pneumoperitoneum pressure (11). This is particularly important for patients with cirrhosis where venous oozing secondary to portal hypertension is a common phenomenon. It has been shown that laparoscopic hepatectomy performed in a range between 10-14 mmHg is safe (20-23). There has not been a single report of major gas embolism event that has led to a major complication (Calvien-Dindo > II) due to pneumoperitoneum (24,25).

Indications and advantages

We started with our initial laparoscopic liver resection for cancers with small peripheral lesions in patients with liver metastasis. Our initial result demonstrated that laparoscopic liver resection in selected patients can produce some favorable outcome. Comparing the laparoscopic group with the open resection group, the median operating time was 180 *vs.* 210 min (P=0.059), the median blood loss was 200 *vs.* 310 mL. Hospital stay was 4.5 *vs.* 7 days (9). The extent of resection has become wider when experience accumulated. Liver resection for HCC in cirrhotic patients is possible. In fact, laparoscopic minor resection for patients with cirrhosis may be advantageous. A large

wound could be avoided particularly when the lesion is located in the posterior section of the right side of the liver. Bleeding complication, infection of the wound, hernia formation of the wound is more common if the incision is bigger particularly in patients with cirrhosis and portal hypertension. In comparison to laparoscopic liver resection, patients with liver cirrhosis prone to developed ascites after open hepatectomy with a larger wound (26). Probably it is because laparoscopic liver resection causes fewer disturbances to the collateral vessels in the abdominal wall. It has been observed that laparoscopic liver resection will provide a less blood loss, shorter operation time and shorter hospital stay. We have reported our initial result in Annals of Surgery. With the laparoscopic group compared with the open resection group, operation time was 232.5 *vs.* 204.5 min, blood loss was 150 *vs.* 300 mL, hospital stay was 4 *vs.* 7 days, postoperative complication was 2 (6.3%) *vs.* 12 (18.8%) (16).

Currently laparoscopic left lateral sectionectomy has been considered a standard practice in many of the centers where there is expertise in hepatobiliary and laparoscopic surgery (27,28).

Laparoscopic major hepatectomy has been more controversial particularly when it involved patients with HCC and cirrhosis. The same argument applied to lesion located in more difficult location of the liver like sections 1,7,8 and superior part of section (29). This would be question of patients' safety *vs.* the advantage of patients' gain through a smaller wound. Unlike minor liver resection, at least at this moment, there is not enough evidence to show that laparoscopic liver resection is a more favorable surgical option in patients with liver cirrhosis. The median operation time was longer and the median blood loss was not less if not more (30). Although laparoscopic major liver resection is technically feasible in patients with moderate size tumor, the reported number of cases performed is still small. Since not every cases with HCC is favorable for laparoscopic resection, the experience accumulated for laparoscopic liver resection is still in its early phase and many of the reported cases series probably has not pass its learning curve phase as reflected by the number of cases performed (31).

For cancer treatment, long term survival outcome is more important than the approach of the operative technique applied. Since the principle of laparoscopic hepatectomy is to mimic the open approach without compromise, similar oncological outcome has been observed. In our center, comparing the laparoscopic group with the open resection group for colorectal liver metastasis, the median survival was 69.4 *vs.* 42.1 months, and the disease-free survival was 9.8 *vs.* 10.9 months (9). For patients with HCC, with the laparoscopic hepatectomy compared with the open resection, disease-free survival was 78.5 *vs.* 29 months, and overall survival was 92 *vs.* 71 months. The disease-free survival for stage II HCC was 22.1 *vs.* 12.4 months (16).

There are several systemic reviews and meta-analysis articles published to investigate the role of laparoscopic liver hepatectomy (30,32-36). It is generally observed that favorable outcome is observed in terms of operative blood loss, blood transfusion requirement, and length of stay in the laparoscopic hepatectomy groups. There was no difference in terms of surgical margin, overall and disease free survival when laparoscopic approach was compared to conventional open approach. There was only one meta-analysis investigating the results of laparoscopic liver resection for HCC patients with cirrhosis involving 4 nonrandomized studies (34). The results showed that laparoscopic approach has a better short term outcomes with less blood loss, wider resection margin and shorter hospital stays. However, this information has to be interpreted with caution. All of the studies involved in all these systemic review or meta-analysis are non-randomized trial. Most of the studies involved included mainly minor liver resection or technically straight forward operations. The effect of publication bias is needed to be addressed. Centers with unfavorable outcome by laparoscopic approach may not report these results. Randomized controlled trials in processes will definitely provide better reflection of actual situation.

Table 1 summarized the result of laparoscopic liver resection for HCC patients with cirrhosis performed in various center (6,7,16,26,37,38). The experience reported on laparoscopic liver resection on cirrhotic liver is still limited but undoubtedly there is an overwhelming enthusiasm on this topic. The number of published articles has been increasing throughout the year.

Conclusions

Laparoscopic liver resection in cirrhotic liver remained a technically challenging procedure. It has to be performed in centers with expertise in (I) surgeons who can performed complicated liver surgery; (II) surgeons who are experienced in laparoscopic technique; and (III) high volume center of liver surgery. Careful case selection without compromise to patients' safety is the key to success and favorable surgical outcome.

Table 1 The result of laparoscopic liver resection for HCC patients with cirrhosis performed in various center

Author	Total number of patient	LLR	OLR	Morbidity		Hospital mortality		Disease free survival		Overall survival	
				LLR (%)	OLR (%)	LLR (%)	OLR (%)	LLR (%)	OLR (%)	LLR (%)	OLR (%)
Kanazawa *et al.* (26)	56	28	28	10.7	71	0	0	NA	NA	NA	NA
Cheung *et al.* (16)	96	32	64	3	19	0	1.5	(5-year) 54	44	72	57
Belli *et al.* (6)	46	23	23	13	48	4.3	0	(2-year) 85	80	85	80
Tranchart *et al.* (7)	84	42	42	12	28	2.4	2.4	(5-year) 46	37	60	47
Truant *et al.* (37)	89	36	53	25	36	0	7.5	(5-year) 56	34	70	46
Memeo *et al.*(38)	90	45	45	20	45	0	4.5	(5-year) 19	23	59	44

HCC, hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection; NA, not available.

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Footnote

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

References

1. Mühe E. Laparoscopic cholecystectomy. Z Gastroenterol Verh 1991;26:204-6.
2. Barczyński M, Konturek A, Nowak W. Randomized clinical trial of posterior retroperitoneoscopic adrenalectomy versus lateral transperitoneal laparoscopic adrenalectomy with a 5-year follow-up. Ann Surg 2014;260:740-7; discussion 747-8.
3. Mason RJ, Moazzez A, Sohn HJ, et al. Laparoscopic versus open anterior abdominal wall hernia repair: 30-day morbidity and mortality using the ACS-NSQIP database. Ann Surg 2011;254:641-52.
4. Musallam KM, Khalife M, Sfeir PM, et al. Postoperative outcomes after laparoscopic splenectomy compared with open splenectomy. Ann Surg 2013;257:1116-23.
5. Shimada M, Hashizume M, Maehara S, et al. Laparoscopic hepatectomy for hepatocellular carcinoma. Surg Endosc 2001;15:541-4.
6. Belli G, Fantini C, D'Agostino A, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in patients with histologically proven cirrhosis: short- and middle-term results. Surg Endosc 2007;21:2004-11.
7. Tranchart H, Di Giuro G, Lainas P, et al. Laparoscopic resection for hepatocellular carcinoma: a matched-pair comparative study. Surg Endosc 2010;24:1170-6.
8. Cheung TT, Ng KK, Poon RT, et al. A case of laparoscopic hepatectomy for recurrent hepatocellular carcinoma. World J Gastroenterol 2010;16:526-30.
9. Cheung TT, Poon RT, Yuen WK, et al. Outcome of laparoscopic versus open hepatectomy for colorectal liver metastases. ANZ J Surg 2013;83:847-52.
10. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. Ann Surg 1999;229:322-30.
11. Fan ST, Mau Lo C, Poon RT, et al. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg 2011;253:745-58.
12. Ishizawa T, Mise Y, Aoki T, et al. Surgical technique: new advances for expanding indications and increasing safety in liver resection for HCC: the Eastern perspective. J Hepatobiliary Pancreat Sci 2010;17:389-93.
13. Yau T, Tang VY, Yao TJ, et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014;146:1691-700.
14. Imamura H, Sano K, Sugawara Y, et al. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg 2005;12:16-22.
15. Cheung TT, Poon RT. Synchronous resections of primary colorectal tumor and liver metastasis by laparoscopic approach. World J Hepatol 2013;5:298-301.
16. Cheung TT, Poon RT, Yuen WK, et al. Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. Ann Surg 2013;257:506-11.
17. Farges O, Goutte N, Dokmak S, et al. How surgical technology translates into practice: the model of laparoscopic liver resections performed in France. Ann

Surg 2014;260:916-21.
18. Fuks D, Cauchy F, Ftériche S, et al. Laparoscopy Decreases Pulmonary Complications in Patients Undergoing Major Liver Resection: A Propensity Score Analysis. Ann Surg 2015. [Epub ahead of print].
19. Cheung TT, Poon RT, Lo CM. Reply to Letter: "Long-term Survival Analysis of Pure Laparoscopic Versus Open Hepatectomy for Hepatocellular Carcinoma in Patients With Cirrhosis: A Single-center Experience". Ann Surg 2015;262:e20-1.
20. Honda G, Kurata M, Okuda Y, et al. Totally laparoscopic hepatectomy exposing the major vessels. J Hepatobiliary Pancreat Sci 2013;20:435-40.
21. Troisi RI, Van Huysse J, Berrevoet F, et al. Evolution of laparoscopic left lateral sectionectomy without the Pringle maneuver: through resection of benign and malignant tumors to living liver donation. Surg Endosc 2011;25:79-87.
22. Aldrighetti L, Pulitanò C, Arru M, et al. Ultrasonic-mediated laparoscopic liver transection. Am J Surg 2008;195:270-2.
23. Gayet B, Cavaliere D, Vibert E, et al. Totally laparoscopic right hepatectomy. Am J Surg 2007;194:685-9.
24. Jayaraman S, Khakhar A, Yang H, et al. The association between central venous pressure, pneumoperitoneum, and venous carbon dioxide embolism in laparoscopic hepatectomy. Surg Endosc 2009;23:2369-73.
25. Schmandra TC, Mierdl S, Hollander D, et al. Risk of gas embolism in hand-assisted versus total laparoscopic hepatic resection. Surg Technol Int 2004;12:137-43.
26. Kanazawa A, Tsukamoto T, Shimizu S, et al. Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. Surg Endosc 2013;27:2592-7.
27. Dokmak S, Raut V, Aussilhou B, et al. Laparoscopic left lateral resection is the gold standard for benign liver lesions: a case-control study. HPB (Oxford) 2014;16:183-7.
28. Hasegawa Y, Nitta H, Sasaki A, et al. Laparoscopic left lateral sectionectomy as a training procedure for surgeons learning laparoscopic hepatectomy. J Hepatobiliary Pancreat Sci 2013;20:525-30.
29. Han HS, Yoon YS, Cho JY, et al. Laparoscopic liver resection for hepatocellular carcinoma: korean experiences. Liver Cancer 2013;2:25-30.
30. Nguyen KT, Marsh JW, Tsung A, et al. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg 2011;146:348-56.
31. Hibi T, Cherqui D, Geller DA, et al. International Survey on Technical Aspects of Laparoscopic Liver Resection: a web-based study on the global diffusion of laparoscopic liver surgery prior to the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan. J Hepatobiliary Pancreat Sci 2014;21:737-44.
32. Yin Z, Fan X, Ye H, et al. Short- and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis. Ann Surg Oncol 2013;20:1203-15.
33. Xiong JJ, Altaf K, Javed MA, et al. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. World J Gastroenterol 2012;18:6657-68.
34. Twaij A, Pucher PH, Sodergren MH, et al. Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis. World J Gastroenterol 2014;20:8274-81.
35. Fancellu A, Rosman AS, Sanna V, et al. Meta-analysis of trials comparing minimally-invasive and open liver resections for hepatocellular carcinoma. J Surg Res 2011;171:e33-45.
36. Zhou YM, Shao WY, Zhao YF, et al. Meta-analysis of laparoscopic versus open resection for hepatocellular carcinoma. Dig Dis Sci 2011;56:1937-43.
37. Truant S, Bouras AF, Hebbar M, et al. Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a case-matched study. Surg Endosc 2011;25:3668-77.
38. Memeo R, de'Angelis N, Compagnon P, et al. Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case-control study. World J Surg 2014;38:2919-26.

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Liver resection for hepatocellular carcinoma in patients with portal hypertension: the role of laparoscopy

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Abstract: Liver resection (LR) for hepatocellular carcinoma (HCC) in patients with chronic liver disease (CLD) is a major issue since patients are at risk of serious intraoperative and postoperative complications. The current EASL/AASLD guidelines recommend LR only in case of patients with stage A HCC with well-preserved liver function and consider the presence of portal hypertension (PHT) as a contraindication to surgery. Nevertheless, the literature on this topic is conflicting. Recently several studies reported that favorable outcomes can be achieved with a careful patients' selection in high volume centers. Laparoscopic LR, when performed by well-trained surgeons and with appropriate indications, proved to be a valid option for the surgical treatment of HCC on cirrhosis offering similar oncologic outcomes but a reduction in surgical related morbidities. Laparoscopic LR thanks to a reduction in the incidence of post-operative liver failure and ascites development in comparison to standard open LR could, in selected cases challenge alternative treatments in the treatment of HCC patients with preserved liver function and clinical signs of mild PHT.

Keywords: Laparoscopic; liver resection (LR); hepatocellular carcinoma (HCC); portal hypertension (PHT); cirrhosis

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Introduction

Liver cancer is one of the leading causes of cancer death worldwide accounting for an estimated 745,500 deaths occurred during 2012 (1). Hepatocellular carcinoma (HCC) which is by far the most common primary liver malignancy has an increased incidence in patients with chronic liver disease (CLD), mostly owing to hepatitis B or C infections (2). Liver transplantation is a potentially curative treatment for HCC in patients with underlying CLD, but it cannot be applied on a large scale for several reasons (3). Therefore, other therapeutic options such as hepatic resection, percutaneous ablation techniques, transarterial chemoembolization (TACE) or systemic chemotherapy are widely applied worldwide. The choice of the optimal treatment has to be tailored on the single patient condition taking into account not only the oncologic staging and perspective but also the degree of CLD and hepatic decompensation. In fact, patients affected by CLD are at higher risk for development of harmful post-therapies complications (4-7). Liver resection (LR) still detains a paramount role in the curative strategy of HCC in patients with an adequate liver function but the current European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines recommend LR as preferred treatment only in case of early stage (A) single nodule of HCC in patients without signs of portal hypertension (PHT) or a bilirubin level higher than 1 mg/dL (8,9). In patients affected by CLD the development of PHT is strictly related to the degree of liver cirrhosis and its presence can complicate HCC treatment by increasing the risk of hemorrhage and liver failure. In fact, resected patients with

PHT are at higher risk of liver failure, varices rupture, and coagulation disorders caused by thrombocytopenia (7). These are all factors that can complicate the postoperative outcomes and minimize the efficacy of LR compromising the survival outcomes. Nevertheless, the literature is conflicting in considering the presence of PHT as an absolute contraindication to LR.

Current role of liver resection (LR) in patients with portal hypertension (PHT)

In Western countries the presence of PHT is widely considered as a contraindication to LR in case of HCC, on the contrary, in the East the presence of PHT is not considered as an absolute contraindication to LR and various authors demonstrated that a low rates of postoperative mortality and morbidity can be achieved if a careful preoperative liver function evaluation is performed (10,11). The EASL/AASLD guidelines are based on the Barcelona group studies (12,13) of very small sample size and are in contrast with the result of many recent studies, also coming from Western centers. In fact, several reports coming from tertiary referral centers with an high grade of expertise in the surgical treatment of HCC demonstrated that in case of cirrhotic patients with PHT and a preserved liver function, classified by the Child-Pugh or Model for End-stage Liver Disease (MELD) score or on the basis of indocyanine green retention test (ICGR 15) value, surgical resection of up to two segments can offer similar long term outcomes when compared to those of resected patients without PHT (14-19). Furthermore, it has been reported that, when performing LR, the presence of an hepatic venous pressure gradient (HVPG) ≥10 mmHg was associated to liver failure and mortality while clinical indirect signs of PHT were not (20,21). The study by Santambrogio *et al.* also demonstrated that patients with clinically significant PHT and preserved liver function (Child-Pugh A5 class) can undergo LR with the best chances of long-term survival without postoperative impairment of liver function (22). Finally, the results of two multicenter retrospective studies collecting a huge number of patients operated in different continents give strength to the need for a re-discussion on the role of PHT as absolute contraindication to LR.

The first study by Torzilli *et al.* (23) collected 2,046 patients (10% with F1 to F3 esophageal varices) and demonstrated the safety and the benefit of LR in selected patients classified as Barcelona Clinic Liver Cancer (BCLC) B and C stage even in case of PHT. The BRIDGE study (24) collected 8,656 patients (3,103 with PHT) and demonstrated that in patients submitted to OLR the presence of PHT alone (defined as the presence of either splenomegaly, platelet count <100,000/μL or varices) without ascites had no statistically significant impact on survival outcomes when compared to optimal candidate to open LR without signs of PHT. Indeed, the EASL/AASLD guidelines define the presence of PHT as the measurement of an HVPG ≥10 mmHg. Unfortunately, HVPG measurement needs technical expertise and is an invasive procedure which is not widely performed in clinical practice worldwide. Therefore, the presence of clinical signs is widely adopted as surrogates for the diagnosis of PHT. The EASL/AASLD guidelines seem to be able to select the best candidates for resection and to allocate to different treatments non-optimal patients, nevertheless there is possibly a room to expand the indication for LR to patient with moderate clinical signs of PHT.

Potential role of laparoscopic liver resection (LR)

In the decision making process guiding the choice of the appropriate treatment for HCC when considering LR nowadays clinicians have to take into account also the possibility to consider the option of laparoscopic LR. In fact, laparoscopic LR is now offered to patients, with selected indications, in many centers worldwide. HCC, which mainly occurs on the background of liver cirrhosis, is by far the most reported indication for laparoscopic LR in case of malignancy (25). This is probably due to the fact that the benefit of a minimally invasive approach seems to be more pronounced in case of cirrhotic patients. In fact, laparoscopic LR can offer additional benefit if performed in patients affected by CLD and cirrhosis by minimizing abdominal wall trauma, liver compression-manipulation and extensive liver mobilization (often no need for transection of the round ligament and the re-canalized umbilical vein or other liver suspensory ligament). These are all factors that allow to preserve collateral blood and lymphatic circulation and reduce the risk of postoperative liver failure, the development of postoperative intractable ascites (which can be per-se a life treating complication) and the rate of overall postoperative morbidity. From an analysis of the literature 21 comparative studies (26-46) focused on the comparison of open and laparoscopic LR for HCC are currently available in the English literature (47) and 11 of them analyzed post-operative ascites development and reported a reduction in its incidence associated to laparoscopic

LR. Interestingly in the study by Truant *et al.* (39), including patients affected by PHT, despite similar magnitude of LR and PHT levels patients operated on by laparoscopy showed lower morbidity and mortality in terms of severe complications related to ascites than patients operated by open approach (0% *vs.* 33% death rate) without differences in 5-year, disease-free and overall survival (OS). In addition, from the cooperative effort done in 2014 at the second international consensus conference on laparoscopic liver surgery held in Morioka-Iwate, the most updated and comprehensive systematic review and meta-analysis available in the literature (48) has been recently published highlighting a reduction in both postoperative liver failure and post-operative ascites development in case of laparoscopic LR performed for HCC complicated by CLD. From an oncologic perspective has been also demonstrated that stratifying patients for factors well known to relate with outcomes, when compared to standard open LR, laparoscopic LR for HCC on cirrhosis can offer similar long-term oncologic outcomes both in term of OS and recurrence free survival (RFS) (32,49). This has been confirmed by the meta-analysis by Morise *et al.* (48) and Xiong *et al.* (50) which did not find any difference in the oncologic outcomes between open and laparoscopic LR. The latter meta-analysis also examined ascites development and postoperative liver failure after laparoscopic LR and reported reduced incidences of both when compared to open LR for the treatment of HCC complicated by CLD.

Finally, although LR resection is strongly challenged by alternative treatment such as tumor ablation and TACE especially in terms of overall morbidity, recently new evidences on the treatment of HCC in patients with PHT appeared in the literature. In the study by Faitot *et al.* (51) the authors observed, on explanted specimens of patients submitted to liver transplant, a reduction in the efficiency of TACE (a 3-fold lower pathological response rate) in patients with PHT when compared to patients without PHT. This data raise questions on the appropriateness of TACE as preferred option in case of patients with PHT and otherwise suitable to minor laparoscopic LR which can offer a complete tumor removal with a reduced incidence of post-operative liver failure and ascites formation in comparison to open LR. In addition the study by Qiu *et al.* (52) demonstrated that when comparing by a propensity score matching analysis the outcomes of LR and tumor ablation in hepatitis B virus-related HCC patients with PHT, LR proved to offer a consistent survival benefit without increasing the incidence of grade II-IV complications (Clavien-Dindo classification). Therefore, laparoscopic LR more than alternative should be probably considered complementary to percutaneous ablation in the treatment of early HCC even in case of PHT. When adequate expertise in both open and minimally invasive liver surgery are available laparoscopic LR could be offered to patients deserving minor resections of peripherally located lesions, while percutaneous ablation could be preferred in case of small deeply located HCC. In fact, in case of peripherally located lesions percutaneous ablation can carry a high risk of tumor seeding while laparoscopic LR can be safely carried out in dedicated centers and can offer the possibility of an accurate pathological and genetic assessment of tumor biology and surrounding liver parenchyma which could drive in a near future more tailored approaches.

Therefore, even if patients with preserved liver function and PHT would not be considered as optimal candidates for LR by the current EASL/AASLD guidelines, in a single patient perspective surgery could probably still offer the best survival outcomes than any other available treatment option in selected cases. In conclusion from an analysis of the currently available literature it seems that at least a proportion of patients with HCC and clinical signs of mild PHT can be offered LR expecting good results and that when technically feasible laparoscopic LR should be considered as a viable option. Laparoscopic LR thanks to a reduction of post-operative liver failure and ascites development in comparison to standard open LR could, in selected cases challenge alternative treatments in the treatment of HCC patients with preserved liver function and clinical signs of mild PHT. A dedicated randomized controlled trial or a multicenter collection of cases would be advisable in order to investigate the role of laparoscopic LR in this clinical setting.

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Footnote

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References

1. Torre LA, Bray F, Siegel RL et al. Global Cancer Statistics, 2012. CA Cancer J Clin 2015;65:87-108.

2. Schütte K, Bornschein J, Malfertheiner P. Hepatocellularcarcinoma--epidemiological trends and risk factors. Dig Dis 2009;27:80-92.
3. Yao FY, Bass NM, Nikolai B, et al. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. Liver Transpl 2002;8:873-83.
4. Ziser A, Plevak DJ, Wiesner RH, et al. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology 1999;90:42-53.
5. Mansour A, Watson W, Shayani V, et al. Abdominal operations in patients with cirrhosis: still a major surgical challenge. Surgery 1997;122:730-5; discussion 735-6.
6. Belghiti J, Hiramatsu K, Benoist S, et al. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191:38-46.
7. Lai EC, Fan ST, Lo CM, et al. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. Ann Surg 1995;221:291-8.
8. Bruix J, Sherman M; Practice Guidelines Committee, et al. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
9. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
10. Wu CC, Cheng SB, Ho WM, et al. Liver resection for hepatocellular carcinoma in patients with cirrhosis. Br J Surg 2005;92:348-55.
11. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240:698-708; discussion 708-10.
12. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018-22.
13. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434-40.
14. Capussotti L, Ferrero A, Viganò L, et al. Portal hypertension: contraindication to liver surgery? World J Surg 2006;30:992-9.
15. Kawano Y, Sasaki A, Kai S, et al. Short- and long term outcomes after hepatic resection for hepatocellular carcinoma with concomitant esophageal varices in patient with cirrhosis. Ann Surg Oncol 2008;15:1670-6.
16. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology 2008;134:1908-16.
17. Cucchetti A, Ercolani G, Vivarelli M, et al. Is portal hypertension a contraindication to hepatic resection? Ann Surg 2009;250:922-8.
18. Choi GH, Park JY, Hwang HK, et al. Predictive factors for long-term survival in patients with clinically significant portal hypertension following resection of hepatocellular carcinoma. Liver Intern 2011;31:485-93.
19. Ruzzenente A, Valdegamberi A, Campagnaro T, et al. Hepatocellular carcinoma in cirrhotic patients with portal hypertension: is liver resection always contraindicated? World J Gastroenterol 2011;17:5083-8.
20. Boleslawski E, Petrovai G, Truant S, et al. Hepatic venous pressure gradient in the assessment of portal hypertension before liver resection in patients with cirrhosis. Br J Surg 2012;99:855-63.
21. Stremitzer S, Tamandl D, Kaczirek K, et al. Value of hepatic venous pressure gradient measurement before liver resection for hepatocellular carcinoma. Br J Surg 2011;98:1752-8.
22. Santambrogio R, Kluger MD, Costa M, et al. Hepatic resection for hepatocellular carcinoma in patients with Child- Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB (Oxford) 2013;15:78-84.
23. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. Ann Surg 2013;257:929-37.
24. Roayaie S, Jibara G, Tabrizian P, et al. The Role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-51.
25. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg 2009;250:831-41.
26. Laurent A, Cherqui D, Lesurtel M, et al. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. Arch Surg 2003;138:763-9; discussion 769.
27. Kaneko H, Takagi S, Otsuka Y, et al. Laparoscopic liver resection of hepatocellular carcinoma. Am J Surg 2005;189:190-4.

28. Shimada M, Hashizume M, Maehara S, et al. Laparoscopic hepatectomy for hepatocellular carcinoma. Surg Endosc 2001;15:541-4.
29. Lee KF, Chong CN, Wong J, et al. Long-term results of laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma: a case-matched analysis. World J Surg 2011;35:2268-74.
30. Ker CG, Chen JS, Kuo KK, et al. Liver surgery for hepatocellular carcinoma: laparoscopic versus open approach. Int J Hepatol 2011:596792.
31. Tranchart H, Di Giuro G, Lainas P, et al. Laparoscopic resection for hepatocellular carcinoma: a matched-pair comparative study. Surg Endosc 2010;24:1170-6.
32. Belli G, Limongelli P, Fantini C, et al. Laparoscopic and open treatment of hepatocellular carcinoma in patients with cirrhosis. Br J Surg 2009;96:1041-8.
33. Kim H, Suh KS, Lee KW, et al. Long-term outcome of laparoscopic versus open liver resection for hepatocellular carcinoma: a case-controlled study with propensity score matching. Surg Endosc 2014;28:950-60.
34. Cheung TT, Poon RT, Yuen WK, et al. Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. Ann Surg 2013;257:506-11.
35. Kanazawa A, Tsukamoto T, Shimizu S, et al. Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. Surg Endosc 2013;27:2592-7.
36. Aldrighetti L, Guzzetti E, Pulitanò C, et al. Case-matched analysis of totally laparoscopic versus open liver resection for HCC: short and middle term results. J Surg Oncol 2010;102:82-6.
37. Memeo R, de'Angelis N, Compagnon P, et al. Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case-control study. World J Surg 2014;38:2919-26.
38. Ai JH, Li JW, Chen J, et al. Feasibility and safety of laparoscopic liver resection for hepatocellular carcinoma with a tumor size of 5-10 cm. PLoS One 2013;8:e72328.
39. Truant S, Bouras AF, Hebbar M, et al. Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a casematched study. Surg Endosc 2011;25:3668-77.
40. Nguyen KT, Marsh JW, Tsung A, et al. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg 2011;146:348-56.
41. Hu BS, Chen K, Tan HM, et al. Comparison of laparoscopic vs open liver lobectomy (segmentectomy) for hepatocellular carcinoma. World J Gastroenterol 2011;17:4725-8.
42. Kim HH, Park EK, Seoung JS, et al. Liver resection for hepatocellular carcinoma: case-matched analysis of laparoscopic versus open resection. J Korean Surg Soc 2011;80:412-9.
43. Alemi F, Kwon E, Freise C, et al. Hepatic surgery at a VA tertiary medical center: lessons learned. Am J Surg 2010;200:591-5.
44. Sarpel U, Hefti MM, Wisnievsky JP, et al. Outcome for patients treated with laparoscopic versus open resection of hepatocellular carcinoma: case-matched analysis. Ann Surg Oncol 2009;16:1572-7.
45. Lai EC, Tang CN, Ha JP, et al. Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. Arch Surg 2009;144:143-7; discussion 148.
46. Endo Y, Ohta M, Sasaki A, et al. A comparative study of the long-term outcomes after laparoscopy- assisted and open left lateral hepatectomy for hepatocellular carcinoma. Surg Laparosc Endosc Percutan Tech 2009;19:e171-4.
47. Belli A, Fantini C, D'Agostino A, et al. Mils for HCC: the state of art. Updates Surg 2015;67:105-9.
48. Morise Z, Ciria R, Cherqui D, et al. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci 2015;22:342-52.
49. Belli G, Fantini C, Belli A, et al. Laparoscopic liver resection for hepatocellular carcinoma in cirrhosis: long-term outcomes. Dig Surg 2011;28:134-40.
50. Xiong JJ, Altaf K, Javed MA, et al. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. World J Gastroenterol 2012;18:6657-68.
51. Faitot F, Allard MA, Pittau G, et al. Impact of clinically evident portal hypertension on the course of hepatocellular carcinoma in patients listed for liver transplantation. Hepatology 2015;62:179-87.
52. Qiu J, Zheng Y, Shen J, et al. Resection versus ablation in hepatitis B virus-related hepatocellular carcinoma patients with portal hypertension: A propensity score matching study. Surgery 2015;158:1235-43.

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Laparoscopic right hepatectomy for hepatocellular carcinoma in cirrhotic patient

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Abstract: Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor worldwide and the most common primary liver cancer. Liver resection or liver transplantation is the therapeutic gold standards in patient with HCC related with or without underline liver disease. We present a video case of a 68-year-old woman admitted to our surgical and liver transplantation unit for HCC on liver segment VII. Patient has HCV cirrhosis. Patient underwent to previous right portal vein embolization. Model of end staged liver disease was 7. Body mass index (BMI) was 26.3 and ASA score was 2. Alpha-fetoprotein was 768. According with our multidisciplinary group, we suggest a laparoscopic right hepatectomy for the patient. Operation time was 343 min and blood loss estimation was 200 CC. No transfusion was required. Post-operative course was uneventful, grade 0 of Clavien-Dindo Classification. Patient was discharged in day 7. Pathology report describes a 17 mm × 15 mm HCC grade 4, pT2N0. Laparoscopic liver resection (LLR) for HCC should be performed by dedicated surgical teams in hepatobiliary and laparoscopic surgery. The use of LLR in cirrhotic patients is in many centers proposed as the first-line treatment for HCC or as bridge treatment before liver transplantation.

Keywords: Laparoscopic liver resection (LLR); hepatocellular carcinoma (HCC); cirrhosis; meld

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor worldwide and the most common primary liver cancer (1). Liver resection or liver transplantation is the therapeutic gold standards in patient with HCC related with or without underline liver disease. HCC grow on a cirrhotic liver in approximately 80% of cases (2). Liver resection in patients with cirrhosis have an increased risk of developing significant postoperative complications including ascites, gastrointestinal bleeding, encephalopathy, portal vein thrombosis and pleural effusion (3,4). Nowadays, laparoscopic liver resection (LLR) is commonly performed worldwide in patients with HCC and underlined liver disease (5). Since 2008, with the first consensus of experts in Louisville and more recently in 2015, with the second international consensus conference held in Morioka, the recommendations for LLR suggested that the best indications for laparoscopy were solitary lesions less than 5 cm, major LLR is an innovative procedure and should continue to be introduced cautiously (6,7).

Materials and methods

From 2004 to date, over 100 patients underwent a LLR for HCC. All patients were subject to preoperative general evaluation based on patient general condition and tumor biological status during our weekly multidisciplinary team (anesthesiologist, hepatologist, radiologist and surgeon) meeting. Wedge liver resection was preferred when the lesion was superficially located. Instead a segmentectomy

Figure 1 The surgical procedure of laparoscopic right hepatectomy for a hepatocellular carcinoma in patient with liver cirrhosis (10). Available online: http://www.asvide.com/articles/733

was performed when the tumor was deeply located. In our practice we performed over 20 left lateral segmentectomy in cirrhotic patients (8). We previously performed laparoscopic right hepatectomy in non-cirrhotic patients (9).

Surgical procedure

Patient was placed supine on the operative table with lower limbs apart, the surgeon between the legs. Access to the abdomen was gained by Verres needle technique pneumoperitoneum was maintained at 12 mmHg. A 10-mm port at the umbilicus housed a 30° video-camera. The other four trocars were positioned along a semicircular line with the concavity facing the right subcostal margin. Diagnostic laparoscopy was first performed and the liver was examined using laparoscopic ultrasonography (US) (Aloka Hitachi Medical Systems Europe Holding AG Zug, Switzerland) to exclude abdominal carcinosis and to confirm the extension of the HCC. Steep reverse Trendelenburg position was maintained. Central venous pressure was <5 mmHg during resection. Hepatic transection was performed with Enseal device (Ethicon Endo-Surgery Inc., Cincinnati, OH), clips, and application of Endo GIA vascular staples (Tyco Healthcare) on the portal pedicles when necessary. After section, specimen was placed in a bag and extracted with Pfannenstiel incision.

Clinical case

We present a video case of a 68-year-old woman admitted to our surgical and liver transplantation unit for HCC on liver segment VII. Patient has HCV cirrhosis. The procedure is reported on *Figure 1*. Patient underwent to previous right portal vein embolization. Model of end staged liver disease was 7. Body mass index (BMI) was 26.3 and ASA score was 2. Alpha-fetoprotein was 768. No previous abdominal surgery. According with our multidisciplinary group we suggest a laparoscopic right hepatectomy for the patient.

Operation time was 343 min and blood loss estimation was 200 CC. Pringle manoeuvre was not performed. One tubular drain was used. No transfusion was required. Post-operative course was uneventful, grade 0 of Clavien-Dindo Classification. Patient was discharged in day 7. Pathology report describes a 17 mm × 15 mm HCC grade 4, pT2N0.

Discussion

LLR is now worldwide accepted considering the excellent results shown in specialized centers (9). Liver function is considered an important indication for surgery. Most centers reserved surgery for patients with Child-Pugh class A and consider those with Child-Pugh Class B-C for transplantation (9). Nowadays, LLR is commonly performed worldwide in patients with HCC and underlined liver disease (5). The main clinical advantage of LLR is the significantly lower rate of postoperative complication considering that the abdominal wall is preserved, kinetics of the diaphragm are improved (11). The long skin incision in open surgery may induce several disadvantages for patients. Less post-operative ascites has been suggested to be as consequence of a better collateral venous drainage due to less liver mobilization in LLR. Oncological principles have been demonstrated to have no significant difference in recurrence-free or overall survival (12). A recent meta-analysis conclude that LLR for HCC is superior to open approach in terms of its perioperative results and does not compromise the oncological outcomes (13).

Conclusions

LLR for HCC should be performed by dedicated surgical teams in hepatobiliary and laparoscopic surgery. The use of LLR in cirrhotic patients is in many centers proposed as the first-line treatment for HCC or as bridge treatment before liver transplantation.

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Footnote

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References

1. Lai Q, Lerut JP. Hepatocellular cancer: how to expand safely inclusion criteria for liver transplantation. Curr Opin Organ Transplant 2014;19:229-34.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17.
3. Farges O, Malassagne B, Flejou JF, et al. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999;229:210-5.
4. Kanazawa A, Tsukamoto T, Shimizu S, et al. Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. Surg Endosc 2013;27:2592-7.
5. Ettorre GM, Levi Sandri GB. Laparoscopic approach for hepatocellular carcinoma: where is the limit? Chin J Cancer Res 2014;26:222-3.
6. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
7. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-29.
8. Levi Sandri GB, Vennarecci G, Santoro R, et al. Laparoscopic left liver lobectomy for hepatocellular carcinoma in a cirrhotic patient: a video report. Chin J Cancer Res 2014;26:735-6.
9. Ettorre GM, Laurenzi A, Lionetti R, et al. Laparoscopic liver resections in normal and cirrhotic livers: a retrospective analysis in a tertiary hepato-biliary unit. Dig Liver Dis 2014;46:353-7.
10. Levi Sandri GB, Colasanti M, Santoro R, et al. The surgical procedure of laparoscopic right hepatectomy for a hepatocellular carcinoma in patient with liver cirrhosis. Asvide 2015;2:156. Available online: http://www.asvide.com/articles/733
11. Lai EC, Tang CN, Yang GP, et al. Multimodality laparoscopic liver resection for hepatic malignancy--from conventional total laparoscopic approach to robot-assisted laparoscopic approach. Int J Surg 2011;9:324-8.
12. Gaillard M, Tranchart H, Dagher I. Laparoscopic liver resections for hepatocellular carcinoma: current role and limitations. World J Gastroenterol 2014;20:4892-9.
13. Zhou YM, Shao WY, Zhao YF, et al. Meta-analysis of laparoscopic versus open resection for hepatocellular carcinoma. Dig Dis Sci 2011;56:1937-43.

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Short and long-term outcomes of laparoscopic compared to open liver resection for colorectal liver metastases

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Background: Minimally invasive surgery (MIS) is now established as standard of care for a variety of gastrointestinal procedures for benign and malignant indications. However, due to concerns regarding superiority to open liver resection (OLR), the uptake of laparoscopic liver resection (LLR) has been slow. Data on long-term outcomes of LLR for colorectal liver metastases (CRLM) remain limited. We conducted a systematic review and meta-analysis of short and long-term outcomes of LLR compared to OLR for CRLM.

Methods: Five electronic databases were systematically searched for studies comparing LLR and OLR for CRLM and reporting on survival outcomes. Two reviewers independently selected studies and extracted data. Primary outcomes were overall survival (OS) and recurrence free survival (RFS). Secondary outcomes were operative time, estimated blood loss, post-operative major morbidity, mortality, length of stay (LOS), and resection margins.

Results: Eight non-randomized studies (NRS) were included (n=2,017 total patients). Six were matched cohort studies. LLR reduced estimated blood loss [mean difference: −108.9; 95% confidence interval (CI), −214.0 to −3.7) and major morbidity [relative risk (RR): 0.68; 95% CI, 0.56–0.83], but not mortality. No difference was observed in operative time, LOS, resection margins, R0 resections, and recurrence. Survival data could not be pooled. No studies reported inferior survival with LLR. OS varied from 36% to 60% for LLR and 37% to 65% for OLR. RFS ranged from 14% to 30% for LLR and 22% to 38% for OLR. According to the grade classification, the strength of evidence was low to very low for all outcomes. The use of parenchymal sparing resections with LLR and OLR could not be assessed.

Conclusions: Based on limited retrospective evidence, LLR offers reduced morbidity and blood loss compared to OLR for CRLM. Comparable oncologic outcomes can be achieved. Although LLR cannot be considered as standard of care for CRLM, it is beneficial for well-selected patients and lesions. Therefore, LLR should be part of the liver surgeon's armamentarium.

Keywords: Colorectal; metastases; liver; surgery; laparoscopy

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Introduction

Minimally invasive surgery (MIS) is now established as standard of care for a number of surgical procedures in both benign and malignant diseases (1-8). Advanced MIS procedures are being performed by a growing number of surgeons in various practice settings (9). Mainly owing to reduced pain, blood loss, length of hospital stay and complications, as well as faster recovery, laparoscopic offers significant benefits over laparotomy for a variety of abdominal conditions (1,2-8).

Hepatectomy remains a major and highly challenging surgery, despite the improved morbidity and mortality profiles now achieved in high volume centres. Because of the localization of the liver in the most cephalic portion of the abdomen and the complex and variable intra-hepatic anatomy, laparoscopic liver resection (LLR) is not straightforward. Some particularities of laparoscopic surgery are more disabling in LLR than other gastrointestinal MIS procedures, including loss of 3-dimensional vision, reduced depth of perception, challenging access to some cephalic areas of the liver, and limited range of motion (10). Such technical factors may explain the ongoing concerns regarding the safety, feasibility, and superiority of LLR compared to open liver resection (OLR). As a result, the uptake of LLR has been slower than in other fields (9,11).

Complete resection with hepatectomy is now well established as the standard of care for curative-intent treatment of colorectal liver metastases (CRLM). Remarkable overall survival (OS) results from 30% to 60% at 5 years can be achieved (12,13). The face of liver resection for CRLM has drastically changed over the past decades; medical perioperative care has improved, indication have broadened, techniques have transitioned towards parenchymal sparing resections, and effective perioperative multimodal oncologic therapies have been introduced (14-17). These changes have rendered the uptake of LLR even more challenging in some aspects.

The evidence supporting the use of LLR remains of low quality as currently highlighted by the second LLR Consensus Conference held in Morioka in 2014, even more so when looking specifically at the safety and efficacy of LLR in the treatment of CRLM (18). Therefore, we sought to review the short and long-term outcomes of LLR compared to OLR in the treatment of CRLM.

Methods

Search strategy

In conjunction with an information specialist, we systematically searched Medline (1966–December 2014), Embase (1974–December 2014), the Cochrane Central Register for Controlled Trials, Web Of Knowledge, and the Scopus database (1966–December 2014) to identify potential randomized controlled trials (RCT) and non-randomized studies (NRS), without language or other limitations. Two authors (KAB and JH) selected studies and extracted data independently.

Study selection

Our explicit eligibility criteria included RCT or NRS reporting the effects on short and long-term outcomes of LLR compared to OLR for CRLM. Studies including at least 10 adults (≥18 years old) undergoing liver resection for CRLM were eligible. Studies that included patients not fulfilling our inclusion criteria were excluded if we were not able to distinguish those patients from the larger population. In the event of duplicate publication, we included the most relevant and the most informative study.

Data abstraction and outcome measures

We developed and pilot tested a standardized data extraction form following the recommendations of the Cochrane Effective Practice and Organization of Care Review Group (19). Our primary outcome was recurrence-free survival (RFS) and OS. Secondary outcomes included operating time (minutes), estimated blood loss (mL), 30-day post-operative major morbidity defined as Clavien grade 3 to 5 complications (or as per the authors' definition if Clavien classification was not used), post-operative mortality (20), grade B and C post-hepatectomy liver failure (International Study Group on Liver Surgery classification) (21), R0 resection, margins (cm), and length of stay (LOS) (days).

We used the grade system to present a summary of findings and rate the overall strength of evidence (22).

Statistical analysis

We presented descriptive statistics as means and standard deviation (SD) for continuous variables, and proportions

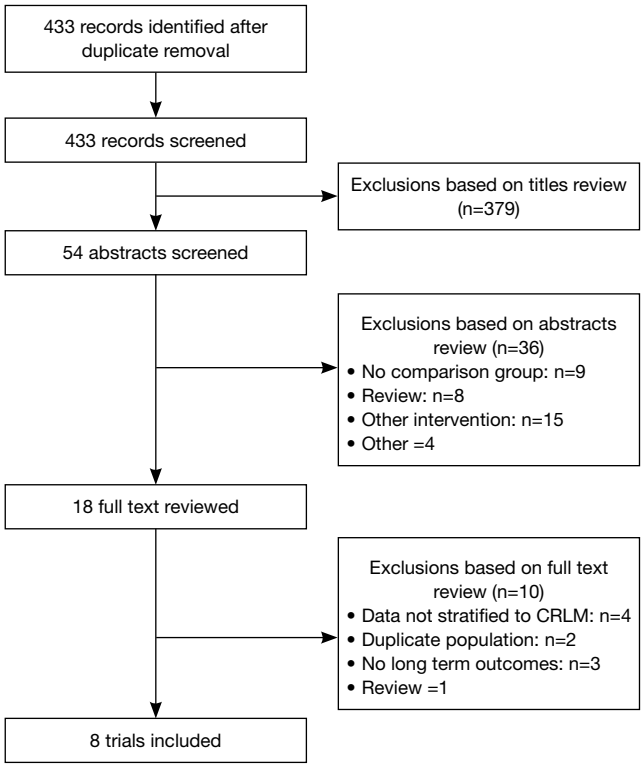

Figure 1 Flow diagram of study selection. CRLM, colorectal liver metastases.

with 95% confidence interval (CI) for dichotomous variables. When studies presented medians and range, we estimated the mean and SD with the method of Hozo (23). Meta-analysis was conducted using Review Manager (RevMan) Version 5.2.5 (The Cochrane Collaboration, Copenhagen, 2012) for each outcome with data in two or more studies. We pooled the data for each outcome using random effects models. Relative risk (RR) with 95% CI was calculated for dichotomous outcomes. We used the I^2 statistic to assess the extent of heterogeneity (24). For all tests and CIs we used a two tailed type I error rate of 5%.

Results

Systematic search

The initial electronic search identified 433 citations, from which eight NRSs enrolling a total of 2,017 patients (580 undergoing LLR) (*Figure 1*) were selected for inclusion in this review (25-32). Among studies excluded after full text review, two were for duplicate populations (33,34).

Description of included studies

All studies were published in English between 2010 and 2014. They included from 42 to 1,152 patients (*Table 1*). Six studies used matching techniques to create a comparison cohort of OLR. Criteria for matching for each study of those studies were: (I) number and size of lesions, segmental position, extent of hepatectomy, type of hepatectomy, and time period of resection (32); (II) lesions size (26); (III) tumor stage, number and size of lesions, extent of hepatectomy (undefined) (27); (IV) lesions size (30); (V) propensity score including age, gender, primary tumor localization, number, size, and bilaterality of lesions, presence of extra-hepatic disease, and pre-hepatectomy chemotherapy (25), and (VI) propensity score including age, number and size of lesions, extent of hepatectomy, synchronous colectomy, and clinical risk score (31).

In studies that did not using a matched analysis, there was a tendency towards more patients with a higher number of lesions (26,28-30) and larger lesions in the OLR group (28,29). The proportion of major liver resections varied between studies, from 5.0% to 62% for LLR, and 5.0% to 62.4% for OLR. In studies that did not match for the extent of hepatectomy, major resections were more common with LLR in one study (26), and with OLR in three studies (25,28-30).

Details of perioperative management are provided in *Table 2*. Most studies used a totally laparoscopic technique with specimen extraction through a supra-pubic (*Pfannenstiel*) incision (25-28,30,32).

Short-term post-operative outcomes

Results of the pooled analysis for short-term post-operative outcomes are presented in *Figure 2*.

No significant difference was identified between LLR and OLR in terms of blood loss, operative time, or LOS. While none of the matched studies reported a difference in LOS (25-27,30,32), the two unmatched studies outlined fewer days in hospital with LLR (28,29).

LLR was associated with a reduction in the risk of major morbidity (RR: 0.68; 95% CI, 0.56–0.83). Five out of the six matched studies did not report a significant difference in morbidity with LLR (25-27,30,32). The two unmatched studies observed a reduction (28,31). No difference was observed in post-operative mortality (RR: 0.47; 95% CI, 0.16–1.35). Four studies reporting no mortality in either LLR or OLR groups (25,28,29,31).

Table 1 Population and clinical characteristics of the included studies

Authors	Study period	Study design	Group	N	Age (years old)	Male gender [n, (%)]	Synchronous CRLM [n, (%)]	Number of lesions	Size of largest lesion (cm)
Montalti *et al.* (32)	2006–2012	MCS	LLR/OLR	57/57	61.7 [11]/63.5 [10]	37 (64.9)/34 (59.6)	31 (54.4)/28 (49.1)	NR	NR
Iwahashi *et al.* (26)	2007–2012	MCS	LLR/OLR	21/21	67.5 [11.1]/68.2 [10.4]	16 (76.2)/14 (66.7)	12 (57.1)/12 (57.1)	1.8 [1.1]/2.1 [1.2]	2.4 [0.8]/2.6 [0.8]
Cheung *et al.* (27)	2002–2011	MCS	LLR/OLR	20/40	57.5 [42–74]/64 [29–83]	13 (65.0)/29 (72.5)	NR	1 [1–2]/1 [1–2]	1.5 [0.5–4.5]/2.2 [0.5–7.0]
Guerron *et al.* (30)	2006–2012	MCS	LLR/OLR	40/40	66.2 [1.9]/62.2 [1.8]	19 (47.5)/25 (62.5)	11 (27.5)/18 (45.0)	1.3 [0.1]/1.7 [0.1]	3.3 [0.3]/3.2 [0.3]
Cannon *et al.* (31)	1995–2010	MCS	LLR/OLR	35/140	62 [10]/62 [11]	NR	3 (9.0)/13 (9.0)	1 [1.0]/1 [1.0]	4 [3.0]/5 [3.0]
Topal *et al.* (28)	2002–2008	RCS	LLR/OLR	81/193	57.6/66.0	46 (56.8)/127 (65.8)	8 (9.9)/56 (29.0)	2 [1–6]/2 [1–14]	4 [0.4–7.0]/3.2 [0.1–12.5]
Welsh *et al.* (29)	1987–2007	RCS	LLR/OLR	266/886	61.9 [10.4]/62.3 [10.1]	161 (60.5)/562 (63.4)	2 (0.7)/15 (1.7)	1 [1–10]/2 [1–20]	3.3 [1.2]/5.3 [3.6]
Castaing *et al.* (25)	1997–2007	MCS	LLR/OLR	60/60	62 [11]/62 [11]	37 (61.7)/37 (61.7)	7 (11.7)/7 (11.7)	2.2 [2.3]/2.2 [1.9]	3.3 [1.1]/4.4 [3.8]

Data reported as mean (SD) or median (range). CRLM, colorectal liver metastases; MCS, matched cohort study; LLR, laparoscopic liver resection; OLR, open liver resection; RCS, retrospective cohort study; NR, not reported.

Table 2 Perioperative and operative management characteristics of the included studies

Authors	Group	Pre-operative chemotherapy [n, (%)]	Post-operative chemotherapy [n, (%)]	Vascular clamping	Major liver resection [n, (%)]	Abdominal drain
Montalti *et al.* (32)	LLR/OLR	41 (72.0)/39 (68.0)	35 (58.0)/33 (58.0)	Selective	13 (22.8)*/13 (22.8)	Selective
Iwahashi *et al.* (26)	LLR/OLR	NR	NR	Selective	3 (14.3)/2 (9.5)	Selective, for major resections
Cheung *et al.* (27)	LLR/OLR	4 (20.0)/10 (25.0)	NR	No	1 (5.0)*/2 (5.0)	Selective
Guerron *et al.* (30)	LLR/OLR	27 (68.0)/26 (65.0)	18 (45.0)/16 (40.0)	Selective	5 (12.5)/9 (22.5)	Selective, for major resections
Cannon *et al.* (31)	LLR/OLR	31 (89.0)/117 (84.0)	NR	NR	19 (54.3)*/71 (50.7)	NR
Topal *et al.* (28)	LLR/OLR	55 (67.9)/119 (61.7)	50 (61.7)/124 (64.2)	Selective	18 (22.2)/82 (42.5)	NR
Welsh *et al.* (29)	LLR/OLR	65 (24.4)/217 (24.5)	NR	Selective	165 (62.0)/553 (62.4)	NR
Castaing *et al.* (25)	LLR/OLR	34 (56.7)/34 (56.7)	34 (57.0)/50 (83.0)	Selective	26 (43.3)/25 (41.7)	NR

*, groups matched on extent of hepatectomy. LLR, laparoscopic liver resection; OLR, open liver resection; NR, not reported.

Oncological outcomes

Pooled risk estimates for oncological outcomes are presented in *Figure 3*. LLR was not associated with any significant difference in either resection margins or proportion of R0 resections (RR: 1.05; 95% CI, 0.99–1.12). Recurrence did not differ between LLR and OLR (RR: 0.86; 95% CI, 0.66–1.12).

OS and RFS did not differ significantly in any of the included studies. Individual results are presented in *Table 3*. Five-year OS ranged from 36 to 60% for LLR, and 37–65% for OLR. Five-year RFS varied from 14% to 30% for LLR, and 22% to 38% for OLR. Median follow-up was not reported in most studies. The included studies did not provide enough information to allow for pooling of survival data (number of events and/or hazard ratios).

Strength of evidence for each pooled risk estimate is presented in *Table 4*. According to the grade system, the strength of evidence was low to very low for all considered outcomes.

Discussion

Due to benefits in terms of operative efficiency as well as post-operative pain, morbidity, and recovery, MIS has become standard of care in various gastrointestinal procedures for both benign and malignant diseases (3,6,35,36). MIS training has been formally incorporated in surgical curriculums, and more advanced procedures are being performed by larger groups of surgeons (9,37,38). Since Reich *et al.* reported the first LLR in the early 1990's, its uptake has been rather slow (39). With the advent of new technologies and laparoscopic instruments, the feasibility of LLR has improved and its adoption has recently started to increase (18,40,41). The proportion of all hepatectomies performed laparoscopically however still remains low—around 25% in single centres reports and 14% in nationwide European experiences (42,43). CRLM represent only a small portion of those LLRs. In a recent worldwide review, 50% of LLRs were performed for malignancy. Of those, 35% were CRLM. Indeed, the French experience indicates that only 7.4% of 3,044 hepatectomies performed for CRLM from 2006 to 2014 were done laparoscopically (44).

MIS offers an opportunity to reduce surgical morbidity and enhance post-operative recovery. Thus, increasing the use of LLR is important in improving outcomes for CRLM. Animal studies have revealed that laparoscopic approach results in reduced stress response to surgery as evidenced by changes in interleukin-6, tumor necrosis factor, and adhesion formation, when compared to laparotomy for liver resection (45). The results from this review confirm previous reports of lower morbidity with LLR compared to OLR for CRLM (RR: 0.68). However, this did not translate into shorter LOS in the current analysis. Most studies included in this review were matched, which may explain the difference with prior reports indicating reduced operative time and LOS (46-48). It is important to stress that the results reported here are based on pooled estimates from retrospective studies with small sample sizes, inherently susceptible to bias.

Concerns regarding the benefits of LLR for CRLM have been voiced regarding the ability to identify small lesions

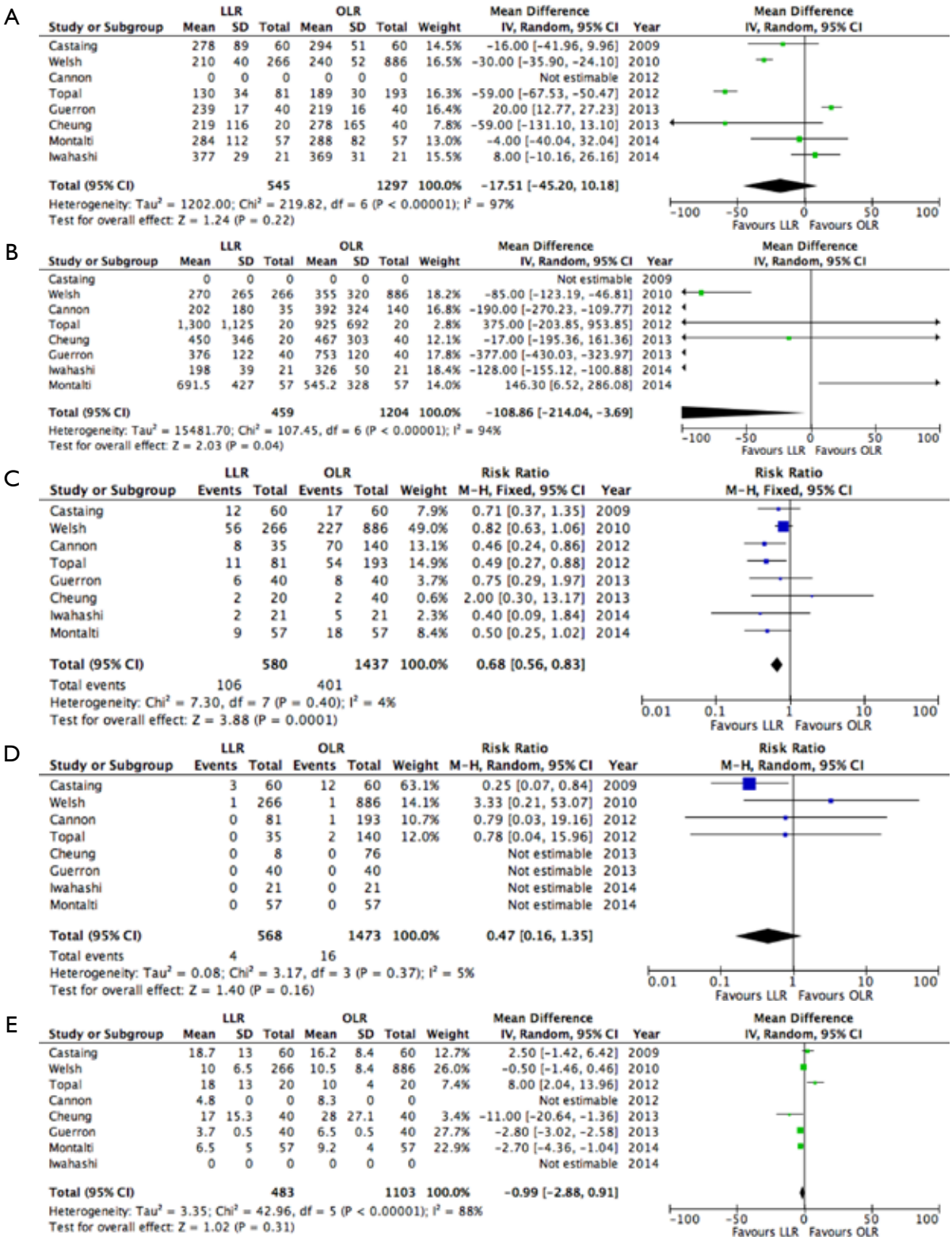

Figure 2 Forrest plots comparing short-term post-operative outcomes between LLR and OLR for colorectal liver metastases. (A) Operative time (minutes); (B) estimated blood loss (mL); (C) major morbidity; (D) mortality; (D) mortality; (E) hospital LOS (days). LLR, laparoscopic liver resection; OLR, open liver resection; CI, confidence interval; LOS, length of stay.

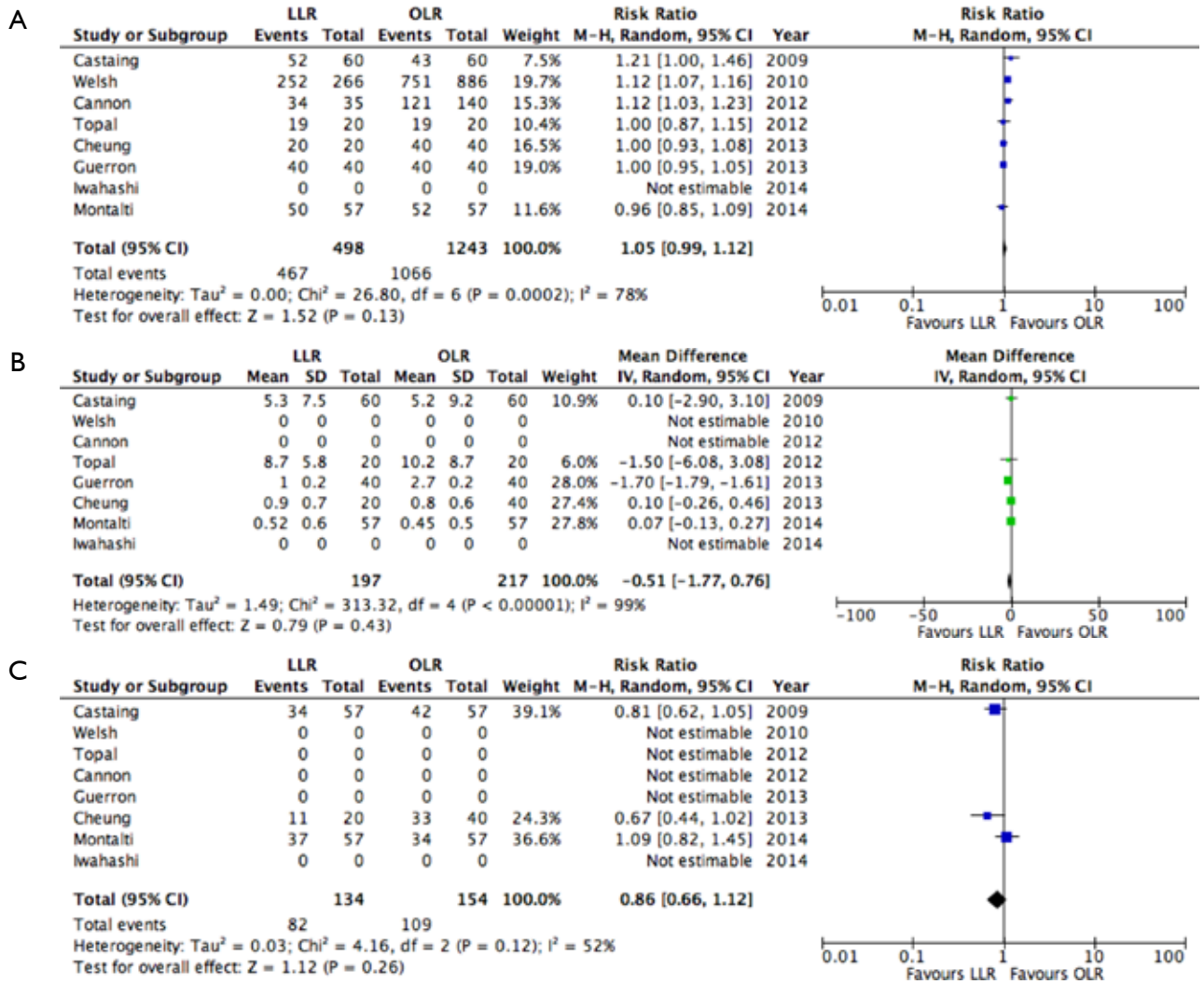

Figure 3 Forrest plot comparing oncologic outcomes between LLR and OLR for colorectal liver metastases. (A) R0 resection; (B) resection margins (cm); (C) all site recurrence. LLR, laparoscopic liver resection; OLR, open liver resection; CI, confidence interval.

Table 3 The 5-year overall and RFS for laparoscopic and open liver resection in the included studies

Authors	Median follow-up (months)		OS		RFS		Survival measure
	OLR	LLR	OLR (%)	LLR (%)	OLR (%)	LLR (%)	
Montalti *et al.* (32)	53.7	40.9	65	60	38	29	5-year
Iwahashi *et al.* (26)	NR	NR	51	42	25	14	5-year
Cheung *et al.* (27)	NR	NR	42.1	69.4	10.9	9.8	Median (months)
Guerron *et al.* (30)	16	16	81	89	30	35	2-year
Cannon *et al.* (31)	NR	NR	37	36	22	15	5-year
Topal *et al.* (28)	NR	NR	61	59	30	30	5-year
Welsh *et al.* (29)	NR	NR	32.1*	36.9*	NR	NR	5-year
Castaing *et al.* (25)	30	33	64	56	30	20	5-year

*, Cancer specific survival. RFS, recurrence free survival; OS, overall survival; LLR, laparoscopic liver resection; OLR, open liver resection; NR, not reported.

Table 4 Grade summary of findings for the effect of laparoscopic versus open liver resection for colorectal liver metastases

Outcome	Illustrative comparative risk		Effect estimate (95% CI)	Number of participants (studies)	Quality of evidence (grade)*
	LLR (%)	OLR (%)			
Operative time (minutes)	–	–	−17.5 (−45.2 to 10.2)	7	+Very low
Estimated blood loss (mL)	–	–	−108.9 (−214.0 to −3.7)	7	++Low
The 30-day major morbidity	18.2	29.5	0.68 (0.56–0.83)	8	++Low
The 30-day mortality	0.7	1.1	0.47 (0.16–1.35)	8	+Very low
LOS (days)	–	–	−0.99 (−2.88 to 0.91)	6	+Very low
Margins (cm)	–	–	−0.51 (−1.77 to 0.76)	5	+Very low
R0 resection	93.8	85.8	1.05 (0.99–1.12)	7	+Very low
Recurrence	61.2	70.8	0.86 (0.66–1.12)	5	+Very low

*, Quality rated from + (very low) to ++++ (high quality). LLR, laparoscopic liver resection; OLR, open liver resection; CI, confidence interval; LOS, length of stay.

and achieve negative margins (49). Older issues pertaining to the trophic effect of the pneumoperitoneum and port site metastases have been dismissed in assessments of colorectal cancers, including large RCT of laparoscopic colectomy (50,51). Those results can be extrapolated to CRLM. Long-term outcomes have not often been compared between LLR and OLR for CRLM. Most studies focused on technical feasibility and short-term outcomes. Therefore, we chose to consider only studies that reported on oncologic outcomes, including survival. Although data could not be pooled, none of the included studies identified inferior survival with LLR. The limited number of studies reporting on long-term outcomes after LR for CRLM, as well as their frequently small sample sizes and single-institution nature, has to be considered when interpreting the results of this review. As previously mentioned, LLR represents a challenging technique. Not many centres have adopted it. Those who have face selection biases in deciding which patients to approach laparoscopically and which ones to operate on with laparotomy. The relatively recent increase in the use of LLR for CRLM also influences the availability of long-term data to report on. Therefore, it is difficult to draw definitive conclusions as to whether LLR can achieve similar oncologic outcomes as OLR.

Being able to provide the patient with similar resection laparoscopically and open is important when looking at both short and long-term outcomes. CRLM present specific challenges for LLR; pre-hepatectomy chemotherapy alters the quality of the liver parenchyma and may render it more prone to bleeding, and parenchyma preserving procedures are paramount (14,52). The latter has been reported to significantly reduce morbidity and mortality of hepatectomy for CRLM, while providing excellent long-term outcomes with the potential for beneficial repeat resection in the face of recurrence (14,52). LLR provides better magnification of operative field than with OLR, which can help in performing a precise resection. However, other technical issues can potentially hamper the ability to save liver parenchyma. The analysis of visual and tactile stimuli necessary to properly assess the complex intra-hepatic anatomy in order to perform precise, safe, and parenchymal-sparing liver resections, is rendered even more challenging by the loss of tactile feedback, lack of 3-dimensional visualization, and difficult hand-eye coordination with laparoscopy. Therefore, concerns still exist regarding the feasibility of LLR for CRLM while meeting current oncologic resection standards. Larger pieces of liver parenchyma may have to be resected laparoscopically to treat the same lesion. This problem was highlighted in the recommendations from the recent Second Consensus on LLR held in Morioka in 2014 (18). Unfortunately, it could not be assessed in this review.

No one can deny the repeatedly reported benefits of laparoscopic surgery over laparotomy for gastrointestinal procedures (1,2-8,35). However, when looking at LLR for CRLM, one has to carefully consider patient and lesion selection to ensure that the benefits remain higher than the potential downsides of the laparoscopic technique. LLR has not yet reached the level of standard of care for CRLM resection. The appropriateness of the surgical approach has to be tailored to the patient medical condition and the disease pattern in the liver. Liver parenchyma should not be sacrificed for the sake of performing the hepatectomy laparoscopically. Selection for LLR has to be based on the

patient's ability to tolerate a potentially prolonged surgical intervention, and the number, localization, and size of lesions to be resected. Considering the long learning curve for LLR, the expertise of the surgeon also needs to be taken into consideration (11,53). Tools such as the newly described Morioka score can assist surgeons in this selection process by providing an objective appreciation of the complexity of LLR for a given patient. This scoring system is based on the size of lesions, extent of resection required, location within the liver, proximity to major vessels, and degree of fibrosis (54). However, it does not consider parenchymal sparing resections nor does it pertain specifically to CRLM.

Important limitations exist among the studies included in this review, mostly due to their small sample sizes, retrospective designs, and lack of multivariable analyses. However, this review is based on a comprehensive, systematic and highly sensitive literature search that was conducted without restriction for language or the type of publication. Including non-randomized designs allowed for a thorough review of the available literature. Thus, this review offers a systematic and objective assimilation of the available data regarding the long-term outcomes of LLR compared to OLR, as well as insight about the particularities of LLR for CRLM.

Conclusions

Based on limited retrospective evidence, LLR offers reduced morbidity and blood loss when compared to OLR in the surgical treatment of CRLM. Comparable oncologic outcomes can be achieved with LLR and OLR in terms of resection margins, R0 resection, recurrence, and long-term survival results. LLR for CRLM presents specific challenges, mainly pertaining to the feasibility of parenchymal-sparing resection. LLR cannot be considered as standard of care for CRLM at the moment. The decision to proceed with LLR over OLR rests on careful patient and lesion selection to ensure optimal risk-benefits balance. However, LLR represent a paramount tool in the liver surgeon's armamentarium. Surgeons should be proficient with LLR in order to be able to offer it to properly selected patients and provide them with the benefits of MIS when feasible.

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Footnote

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

References

1. Schlachta CM, Mamazza J, Gregoire R, et al. Could laparoscopic colon and rectal surgery become the standard of care? A review and experience with 750 procedures. Can J Surg 2003;46:432-40.
2. Smith CD, Weber CJ, Amerson JR. Laparoscopic adrenalectomy: new gold standard. World J Surg 1999;23:389-96.
3. Glasgow RE, Yee LF, Mulvihill SJ. Laparoscopic splenectomy. The emerging standard. Surg Endosc 1997;11:108-12.
4. Keus F, de Jong JA, Gooszen HG, et al. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev 2006;(4):CD006231.
5. Kuo PC, Johnson LB, Sitzmann JV. Laparoscopic donor nephrectomy with a 23-hour stay: a new standard for transplantation surgery. Ann Surg 2000;231:772-9.
6. Lujan J, Valero G, Biondo S, et al. Laparoscopic versus open surgery for rectal cancer: results of a prospective multicentre analysis of 4,970 patients. Surg Endosc 2013;27:295-302.
7. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol 2007;25:3061-8.
8. Hallet J, Labidi S, Bouchard-Fortier A, et al. Oncologic specimen from laparoscopic assisted gastrectomy for gastric adenocarcinoma is comparable to D1-open surgery: the experience of a Canadian centre. Can J Surg 2013;56:249-55.
9. Hallet J, Mailloux O, Chhiv M, et al. The integration of minimally invasive surgery in surgical practice in a Canadian setting: results from 2 consecutive province-wide practice surveys of general surgeons over a 5-year period. Can J Surg 2015;58:92-9.
10. Ishizawa T, Gumbs AA, Kokudo N, et al. Laparoscopic segmentectomy of the liver: from segment I to VIII. Ann Surg 2012;256:959-64.
11. Martin RC, Scoggins CR, McMasters KM. Laparoscopic hepatic lobectomy: advantages of a minimally invasive

approach. J Am Coll Surg 2010;210:627-34, 634-6.
12. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
13. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-25; discussion 825-7.
14. Gold JS, Are C, Kornprat P, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 2008;247:109-17.
15. de Haas RJ, Wicherts DA, Flores E, et al. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg 2008;248:626-37.
16. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236:397-406; discussion 406-7.
17. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.
18. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-29.
19. Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions. Wiley-Blackwell; 2008.
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
21. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
22. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
23. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
25. Castaing D, Vibert E, Ricca L, et al. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. Ann Surg 2009;250:849-55.
26. Iwahashi S, Shimada M, Utsunomiya T, et al. Laparoscopic hepatic resection for metastatic liver tumor of colorectal cancer: comparative analysis of short- and long-term results. Surg Endosc 2014;28:80-4.
27. Cheung TT, Poon RT, Yuen WK, et al. Outcome of laparoscopic versus open hepatectomy for colorectal liver metastases. ANZ J Surg 2013;83:847-52.
28. Topal B, Tiek J, Fieuws S, et al. Minimally invasive liver surgery for metastases from colorectal cancer: oncologic outcome and prognostic factors. Surg Endosc 2012;26:2288-98.
29. Welsh FK, Tekkis PP, John TG, et al. Open liver resection for colorectal metastases: better short- and long-term outcomes in patients potentially suitable for laparoscopic liver resection. HPB (Oxford) 2010;12:188-94.
30. Guerron AD, Aliyev S, Agcaoglu O, et al. Laparoscopic versus open resection of colorectal liver metastasis. Surg Endosc 2013;27:1138-43.
31. Cannon RM, Scoggins CR, Callender GG, et al. Laparoscopic versus open resection of hepatic colorectal metastases. Surgery 2012;152:567-73; discussion 573-4.
32. Montalti R, Berardi G, Laurent S, et al. Laparoscopic liver resection compared to open approach in patients with colorectal liver metastases improves further resectability: Oncological outcomes of a case-control matched-pairs analysis. Eur J Surg Oncol 2014;40:536-44.
33. Topal H, Tiek J, Aerts R, et al. Outcome of laparoscopic major liver resection for colorectal metastases. Surg Endosc 2012;26:2451-5.
34. Doughtie CA, Egger ME, Cannon RM, et al. Laparoscopic hepatectomy is a safe and effective approach for resecting large colorectal liver metastases. Am Surg 2013;79:566-71.
35. Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. Cochrane Database Syst Rev 2010;(10):CD001546.
36. Leung KL, Kwok SP, Lam SC, et al. Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet 2004;363:1187-92.
37. Palter VN, Grantcharov TP. Development and validation of a comprehensive curriculum to teach an advanced minimally invasive procedure: a randomized controlled trial. Ann Surg 2012;256:25-32.
38. Fowler DL, Hogle N. The impact of a full-time director

of minimally invasive surgery: clinical practice, education, and research. Surg Endosc 2000;14:444-7.
39. Orsenigo E, Baccari P, Bissolotti G, et al. Laparoscopic central pancreatectomy. Am J Surg 2006;191:549-52.
40. Gumbs AA, Gayet B, Gagner M. Laparoscopic liver resection: when to use the laparoscopic stapler device. HPB (Oxford) 2008;10:296-303.
41. Scatton O, Brustia R, Belli G, et al. What kind of energy devices should be used for laparoscopic liver resection? Recommendations from a systematic review. J Hepatobiliary Pancreat Sci 2015;22:327-34.
42. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. Ann Surg 2009;250:831-41.
43. Goumard C, Farges O, Laurent A, et al. An update on laparoscopic liver resection: The French Hepato-Bilio-Pancreatic Surgery Association statement. J Visc Surg 2015;152:107-12.
44. Allard MA, Cunha AS, Gayet B, et al. Early and Long-term Oncological Outcomes After Laparoscopic Resection for Colorectal Liver Metastases: A Propensity Score-based Analysis. Ann Surg 2015;262:794-802.
45. Burpee SE, Kurian M, Murakame Y, et al. The metabolic and immune response to laparoscopic versus open liver resection. Surg Endosc 2002;16:899-904.
46. Cai XJ, Yang J, Yu H, et al. Clinical study of laparoscopic versus open hepatectomy for malignant liver tumors. Surg Endosc 2008;22:2350-6.
47. Mizuguchi T, Kawamoto M, Meguro M, et al. Laparoscopic hepatectomy: a systematic review, meta-analysis, and power analysis. Surg Today 2011;41:39-47.
48. Simillis C, Constantinides VA, Tekkis PP, et al. Laparoscopic versus open hepatic resections for benign and malignant neoplasms--a meta-analysis. Surgery 2007;141:203-11.
49. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
50. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324-32.
51. Kuhry E, Schwenk WF, Gaupset R, et al. Long-term results of laparoscopic colorectal cancer resection. Cochrane Database Syst Rev 2008;(2):CD003432.
52. Kingham TP, Correa-Gallego C, D'Angelica MI, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. J Am Coll Surg 2015;220:471-9.
53. Dagher I, Belli G, Fantini C, et al. Laparoscopic hepatectomy for hepatocellular carcinoma: a European experience. J Am Coll Surg 2010;211:16-23.
54. Ban D, Tanabe M, Ito H, et al. A novel difficulty scoring system for laparoscopic liver resection. J Hepatobiliary Pancreat Sci 2014;21:745-53.

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Technical notes on pure laparoscopic isolated caudate lobectomy for patient with liver cancer

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Background: The advantages of laparoscopic liver resection become more obvious as evidence on its long-term outcome has emerged. Compared to open resection, there is no difference in term of overall survival. Many reports showed that the hospital stay was shorter and blood loss was less when laparoscopic hepatectomy was used. However, laparoscopic approach for caudate lobe resection remains a challenging procedure. The close proximity to inferior vena cava (IVC) and hepatic vein make this procedure extra difficult. This paper will demonstrate the use of pure laparoscopic approach for a patient with caudate lobe liver metastasis. Haemostasis by intracorporal suturing is safely performed when bleeding is encountered from the IVC.

Method: The patient was a 54-year-old lady who had carcinoma of the rectum with laparoscopic anterior resection performed. She was found to have a 2 cm lesion in the left caudate lobe of the liver on follow-up. Her platelet count was only 120×10^{9}/L. Pure laparoscopic resection of the caudate lobe was performed as shown in the video.

Results: The operation last for 180 minutes. Blood loss was 220 mL and no blood transfusion was required. She resumed diet on the next day and was discharged 3 days after the operation. Histopathological examination showed 2 cm colorectal liver metastasis with a clear margin. Contrast CT scan performed 1 year after the operation showed no recurrence of the disease.

Conclusions: Laparoscopic approach for caudate lobe resection is a feasible option. It can be performed to patients in center by surgeons with experience in both hepatobiliary and laparoscopic skills.

Keywords: Laparoscopic liver resection; hepatectomy; laparoscopic approach

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Introduction

The role of laparoscopic liver resection has been gaining more popularity and supports (1-3). It has been shown that with the same stage of disease, laparoscopic liver resection provides the same oncological clearance and survival benefit over open hepatectomy. In most of the literatures, laparoscopic liver resection demonstrated a shorter hospital stay, smaller incisions of wound, shorter operation times and most importantly less blood loss. Patients with hepatocellular carcinoma (HCC) and liver cirrhosis are no longer contraindication for pure laparoscopic liver resection (1,4-6). The number of major hepatectomy performed for liver cancer has also been increasing. Comparing to minor liver resection, the expertise requirement is much higher in major liver resection and thus the second international consensus meeting of laparoscopic liver resection stated that major hepatectomy can be performed by expert centers but more evidence is needed to support its role as a standard treatment for liver cancer (7). Surgeons who had experience in open hepatectomy for complicated cases have to acquire a new set of skills in order to perform safe surgery in laparoscopic approach.

A difficulty score of laparoscopic hepatectomy is thus

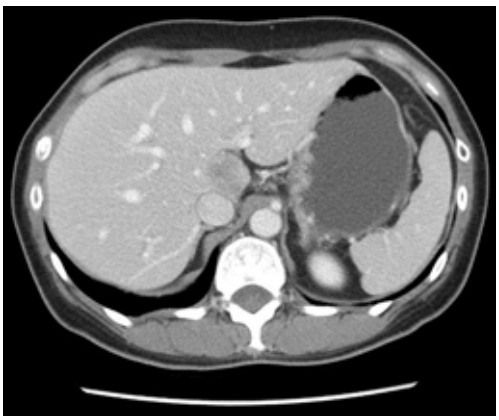

Figure 1 Contrast CT scan showed a 2 cm liver metastasis in the caudate lobe of the liver.

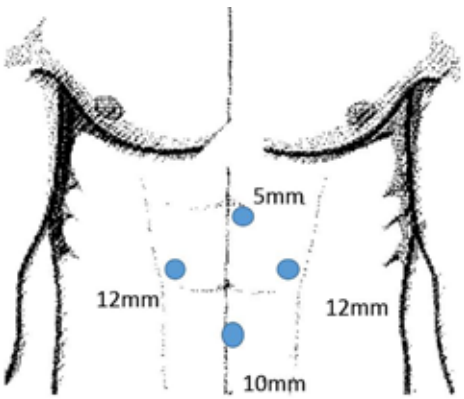

Figure 2 Details of the ports placement. Two 12 mm ports and one 5 mm ports was introduced as working ports. 10 cm space was allowed between each port to avoid instrument interference.

needed which will guide the surgeons to performed laparoscopic liver resection according to their laparoscopic experience (8). Laparoscopic caudate lobectomy has been considered as one of the most difficult procedures in laparoscopic liver resection.

Surgical technique

The patient was a 54-year-old lady who had carcinoma of the rectum with laparoscopic anterior resection performed. Adjuvant chemotherapy was given to her for 6 cycles. She was regularly followed up in the hospital with contrast CT scan of the abdomen performed every 6 months (*Figure 1*). A 2 cm lesion was found in the left caudate lobe of the liver 1 year after the colectomy. PET only revealed the caudate lobe lesion. There was no extrahepatic metastasis. The haemoglobin level was 11 g/dL and her platelet count was only 120×10^9/L.

Pure laparoscopic resection of the caudate lobe was proposed.

The patient was put on supine position with both leg spread opened (French position). The surgeon was standing in between the legs and one assistant was standing on patient's left side. The 30 degree laparoscope was placed in subumbilical region. Two 12 mm ports and one 5 mm ports was introduced as working ports. 10 cm space was allowed between each port to avoid instrument interference (*Figure 2*). Pneumoperitoneum was created at 12 mmHg. Intraoperative ultrasound was performed to localized the lesion, confirmed the extension of the tumour and excluded the presence of additional nodule. The lesion was found only in the caudate lobe with close proximity to the inferior vena cava (IVC). The left lateral section of the liver was lift up by retractor through a 5 mm port. The peritoneal reflection was opened and the IVC was exposed (*Figure 3A*). A replaced left hepatic artery was identified during mobilization of the liver. The Spiegel's lobe of caudate was mobilized and separated from the IVC by CUSA (*Figure 3B*). The short hepatic vessel was controlled with metal clips. Liver parenchymal transection was performed using the CUSA. The caudate pedicle was controlled by clips (*Figure 3C*). The IVC was fully exposed after the transection of the caudate lobe (*Figure 3D*). Bleeding from parenchymal transection was controlled with clips and diathermy. Bleeding from a branch of short hepatic and IVC was encountered. The bleeding site was controlled by grasping forceps and intracorporal suture was performed. The caudate lobectomy was completed by using the CUSA running anterior to the IVC surface. The specimen was put into a bag and delivered via enlargement of the subumbilical wound.

Pringle maneuver was not required and no drain was place after completion of caudate lobectomy. The procedure was recorded in multimedia format (*Figure 4*).

Results

The operation last for 180 minutes. Blood loss was 220 mL and no blood transfusion was required. She resumed diet on the next day and was discharged 3 days after the operation. Histopathological examination showed 2 cm colorectal liver metastasis with a clear margin. Contrast CT scan performed 1 year after the operation showed no recurrence of the

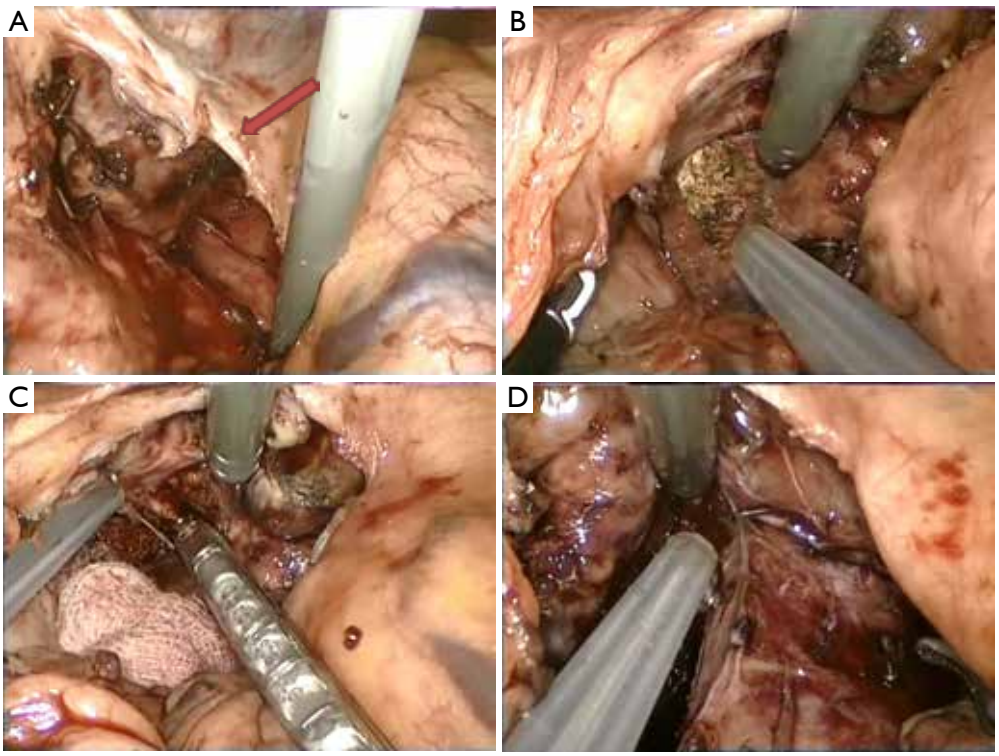

Figure 3 Technical aspect for pure laparoscopic caudate lobectomy. (A) The left lateral section of the liver was lifted up and the caudate lobe was exposed. A replaced left hepatic artery was identified (arrowed); (B) caudate lobe liver transection was performed using CUSA. The right lateral margin was mapped by intraoperative USG; (C) after parenchymal transection with CUSA the caudate pedicle was exposed. The caudate pedicle was controlled with clips; (D) at the end of the caudate lobectomy, the whole length of the IVC was fully exposed. CUSA was used to facilitate the dissection along the IVC.

Figure 4 Pure laparoscopic resection of caudate lobe liver metastasis (9). Available online: http://www.asvide.com/articles/1015

disease (*Figure 5*).

Discussion

Isolated caudate lobectomy has been considered as one of the most technically demanding surgery for liver surgeons even in open approaches. The caudate lobe lied posterior to the confluence of the left and middle hepatic veins as they entered the IVC. Any injury to these vital vessels will lead to massive bleeding (10,11).

Different approaches to isolated caudate lobectomy were reported. They were the posterior approach with or without total hepatic vascular exclusion described by Yanaga *et al.* (12); the left lateral approach described by Colonna *et al.* (13) and the anterior approach described by Yamamoto *et al.* (14) and modified anterior approach described by Cheung *et al.* (15).

The technical demand for caudate lobectomy in pure laparoscopic approach will be high as the anatomy of caudate lobe remains deep seated in the liver. The most reasonable way to resect the caudate lobe through pure laparoscopy is by left lateral approach. Big tumour mainly located in the right caudate process will not be a suitable candidate for left lateral approach. A right posterior approach or in association with formal right hepatectomy is required.

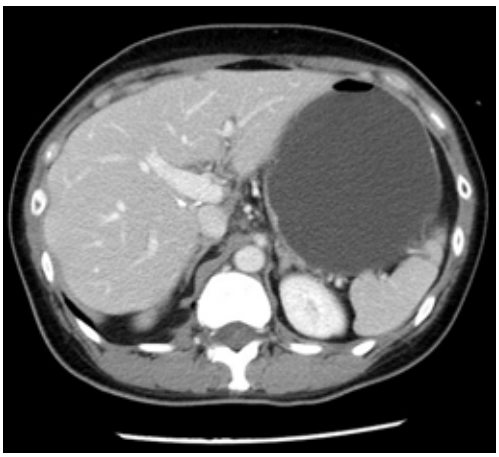

Figure 5 Contrast CT scan of the abdomen was performed 1 year after the caudate lobectomy showed complete resection and no recurrence of tumour.

In pure laparoscopic approach, the surgeon has the benefit of looking at the caudate lobe from below. With today's high definition display unit and with future 4k display unit, the anatomic structure including the small vessel branches can be visualized clearly with magnifications. The left lateral approach with a viewing angle from inferior end allowed minimal mobilization of the left lobe of the liver. The use of CUSA and modern energy devices which incorporated haemostasis and sealing ability enable effective and safer parenchymal transection.

The blood loss in this operation was only 220 mL. As a general principle in hepatectomy, the central venous pressure should be kept at below 5 cm water. The presence of pneumoperitoneum at 12 mmHg gave a very favorable negative gradient to prevent venous oozing during parenchymal transection. Pringle maneuver was not required during the operation. Little bleeding would be encountered as long as the parenchymal transection was at the anatomical boundaries of the caudate lobe.

The patient had a very small wound and most important of all, the lobectomy reviewed a clear margin. Minimal adhesion will be expected even if the patient required another surgery in future (16).

Conclusions

Pure laparoscopic lobectomy through a left lateral approach can be a safe treatment option for patients with caudate lobe tumour by surgeons with experience in laparoscopic surgery and complicated liver surgery.

Acknowledgements

None.

Footnote

Conflicts of Interest: The video of this paper has been presented in the Morioka 2nd International Consensus Conference on Laparoscopic Liver Resection and won the best video award.

Ethical Statement: The study was approved by institutional ethic board and written informed consent was obtained from all patients.

References

1. Han HS, Shehta A, Ahn S, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma: Case-matched study with propensity score matching. J Hepatol 2015;63:643-50.
2. Cheung TT, Poon RT, Yuen WK, et al. Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. Ann Surg 2013;257:506-11.
3. Wakabayashi G. Laparoscopic liver resection: how far can we go? J Hepatobiliary Pancreat Surg 2009;16:403-4.
4. Cheung TT, Poon RT, Lo CM. Reply to Letter: "Long-term Survival Analysis of Pure Laparoscopic Versus Open Hepatectomy for Hepatocellular Carcinoma in Patients With Cirrhosis: A Single-center Experience". Ann Surg 2015;262:e20-1.
5. Cheung TT, Poon RT, Yuen WK, et al. Outcome of laparoscopic versus open hepatectomy for colorectal liver metastases. ANZ J Surg 2013;83:847-52.
6. Kim KH, Jung DH, Park KM, et al. Comparison of open and laparoscopic live donor left lateral sectionectomy. Br J Surg 2011;98:1302-8.
7. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-29.
8. Ban D, Tanabe M, Ito H, et al. A novel difficulty scoring system for laparoscopic liver resection. J Hepatobiliary Pancreat Sci 2014;21:745-53.
9. Cheung TT. Pure laparoscopic resection of caudate lobe liver metastasis. Asvide 2016;3:255. Available online: http://www.asvide.com/articles/1015

10. Liu P, Qiu BA, Bai G, et al. Choice of approach for hepatectomy for hepatocellular carcinoma located in the caudate lobe: isolated or combined lobectomy? World J Gastroenterol 2012;18:3904-9.
11. Kosuge T, Yamamoto J, Takayama T, et al. An isolated, complete resection of the caudate lobe, including the paracaval portion, for hepatocellular carcinoma. Arch Surg 1994;129:280-4.
12. Yanaga K, Matsumata T, Hayashi H, et al. Isolated hepatic caudate lobectomy. Surgery 1994;115:757-61.
13. Colonna JO 2nd, Shaked A, Gelabert HA, et al. Resection of the caudate lobe through "bloody gultch". Surg Gynecol Obstet 1993;176:401-2.
14. Yamamoto J, Kosuge T, Shimada K, et al. Anterior transhepatic approach for isolated resection of the caudate lobe of the liver. World J Surg 1999;23:97-101.
15. Cheung TT, Yuen WK, Poon RT, et al. Improved anterior hepatic transection for isolated hepatocellular carcinoma in the caudate. Hepatobiliary Pancreat Dis Int 2014;13:219-22.
16. Cheung TT, Ng KK, Poon RT, et al. A case of laparoscopic hepatectomy for recurrent hepatocellular carcinoma. World J Gastroenterol 2010;16:526-30.

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Preoperative portal vein embolization in liver cancer: indications, techniques and outcomes

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Abstract: Postoperative liver failure is a severe complication of major hepatectomies, in particular in patients with a chronic underlying liver disease. Portal vein embolization (PVE) is an approach that is gaining increasing acceptance in the preoperative treatment of selected patients prior to major hepatic resection. Induction of selective hypertrophy of the non-diseased portion of the liver with PVE in patients with either primary or secondary hepatobiliary, malignancy with small estimated future liver remnants (FLR) may result in fewer complications and shorter hospital stays following resection. Additionally, PVE performed in patients initially considered unsuitable for resection due to lack of sufficient remaining normal parenchyma may add to the pool of candidates for surgical treatment. A thorough knowledge of hepatic segmentation and portal venous anatomy is essential before performing PVE. In addition, the indications and contraindications for PVE, the methods for assessing hepatic lobar hypertrophy, the means of determining optimal timing of resection, and the possible complications of PVE need to be fully understood before undertaking the procedure. Technique may vary among operators, but cyanoacrylate glue seems to be the best embolic agent with the highest expected rate of liver regeneration for PVE. The procedure is usually indicated when the remnant liver accounts for less than 25-40% of the total liver volume. Compensatory hypertrophy of the non-embolized segments is maximal during the first 2 weeks and persists, although to a lesser extent during approximately 6 weeks. Liver resection is performed 2 to 6 weeks after embolization. The goal of this article is to discuss the rationale, indications, techniques and outcomes of PVE before major hepatectomy.

Keywords: Portal vein embolization (PVE); liver anatomy; liver cancer; cyanoacrylate; surgery

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Introduction

Complete resection of hepatic tumors remains the first choice for curative treatment of primary and secondary liver malignancies, giving the patient the only chance of long-term survival. In up to 45% of primary and secondary liver tumors, extended liver resection is necessary to achieve clear resection margins (1). The reason for unresectability is that often the remnant liver is of insufficient volume to support postoperative liver function, which itself is still the principal cause of postoperative death after major hepatectomy. The mortality rate after major liver resection ranges from 3.2% to 7% in patients with non-injured liver parenchyma and increases up to 32% in patients with cirrhosis (1-3). It has been demonstrated that liver failure is directly related to the size of remnant functional liver volume, and various procedures have been developed to induce liver regeneration. Preoperative embolization of the portal vein (PV) branches feeding the hepatic segments to

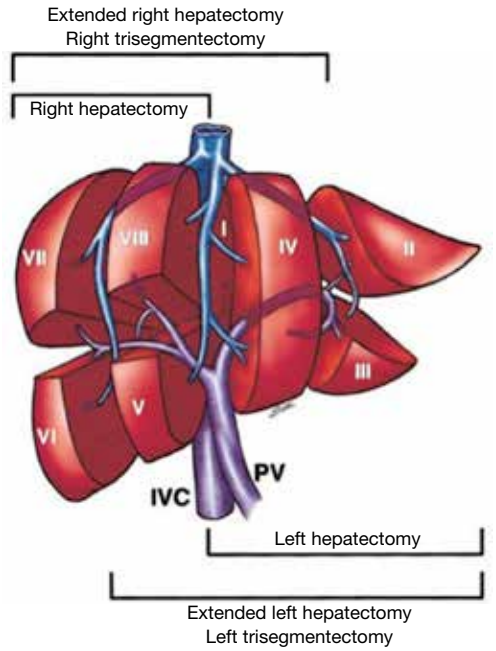

Figure 1 Schematic illustrates Couinaud segmental liver anatomy and the normal portal venous structures. The possible hepatic resection procedures are also shown. IVC, inferior vena cava; PV, portal vein.

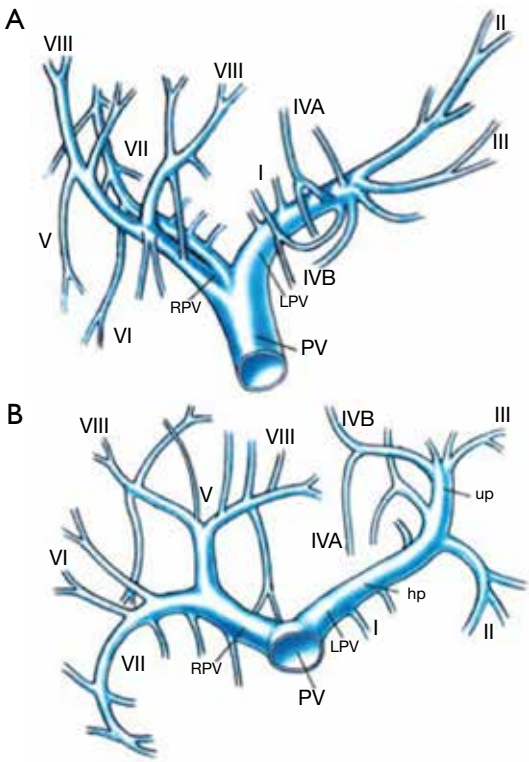

Figure 2 (A,B) Schematics illustrate the normal portal vein (PV) branches from anterior (A) and inferior (B) perspectives. hp, horizontal part; LPV, left portal vein; RPV, right portal vein; up, umbilical (vertical) part.

be resected reduced the risk of postoperative liver failure after major liver resection and increased the number of resectable patients (2-5). In this article, we discuss and illustrate normal PV anatomy and variants, indications and contraindications for portal vein embolization (PVE), technical considerations and periprocedural issues related to percutaneous transhepatic PVE, and potential complications of the procedure.

Anatomy

A comprehensive knowledge of functional liver anatomy is imperative for performing PVE. The most widely used classification system was proposed in 1957 by Couinaud (6). The liver is divided into two hemilivers (left and right, separated by the main portal fissure) and eight segments. Hepatic segmentation is based on the distribution of the portal pedicles and the location of the hepatic veins.

Normal PV anatomy

The PV is formed in the retroperitoneum by the confluence of the superior mesenteric vein and the splenic vein behind the neck of the pancreas and courses behind the duodenal bulb. The main PV and the right and left portal veins (LPVs) are in the hilar fissure. The portal bifurcation may be extrahepatic (48% of cases), intrahepatic (26%), or located right at the entrance of the liver (26%) (7,8). *Figures 1* and *2* illustrate the most common portal venous anatomy. On the right, there are usually two sectoral portal branches (anterior and posterior); on the left, there are two parts to the (main) LPV: the extrahepatic portion [the horizontal part (hp)] and the intrahepatic portion (the umbilical vertical part). In general, the sectoral branch divides into several segmental portal branches, which in turn supply the various segments. One segmental branch usually supplies segments II, VI, and VII and, more rarely, segment III. Segments IV, V, and VIII are commonly supplied by more than one segmental branch. Segmental veins then divide into subsegmental branches, which further divide into small veins leading to the portal venule of the liver acinus (9).

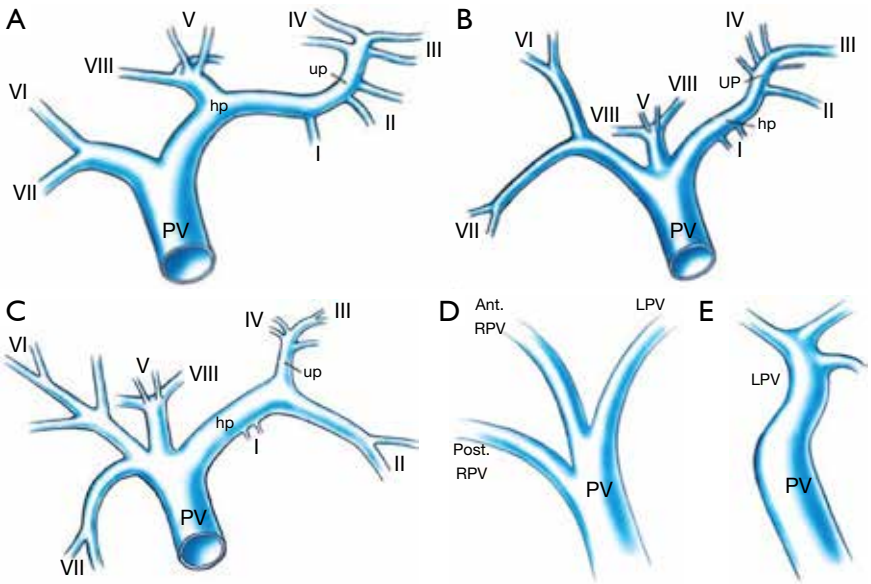

Figure 3 Schematics illustrate selected variants of the portal venous system. (A) Bifurcation of the right posterior sectoral branch from the left main portal branch, with the right anterior sectoral branch arising from the left main portal branch; (B) portal trifurcation; (C) portal quadrifurcation; (D) bifurcation of the right portal vein (RPV) into anterior (Ant.) and posterior (Post.) branches, which supply segments V/VIII and VI/VII, respectively; (E) complete absence of the RPV. All hepatic segments are supplied by the LPV. hp, horizontal part; LPV, left portal vein; PV, portal vein; up, umbilical (vertical) part.

PV variants

Anatomic variants of the PV are uncommon (10-15% of cases) (*Figure 3*) (10). However, when present, they are important to recognize because they may have profound implications for whether PVE or subsequent resection can be performed successfully. In a small portion (11%) of the population, the PV divides into one left and two right portal branches. This variant, known as portal trifurcation, is present if three branches stem from the main portal trunk: the posterior branch, the anterior branch, and the left main branch (*Figure 3B*). In addition, the right anterior segment PV may branch from the left main PV (4% of cases), or the left main PV may branch from the right anterior PV. Alternatively, the right posterior branch may stem from the main portal trunk, with the anterior branch forming a bifurcation with the LPV (5% of cases). Quadrifurcation of the PV can also occur, consisting of a branch for segment VII, a branch for segment VI, an anterior branch, and a left main portal branch (LPV) (*Figure 3C*). In exceptional cases, a branch for subsegment IVb or an additional branch for segments VI, VII, or even VIII may stem from the portal bifurcation. Only very rarely (1% of cases) are bifurcation of the PV completely absent [no right portal vein (RPV)] (*Figure 3E*) (11). When this occurs, the solitary PV in the hilum passes through the entire liver, either from right to left or from left to right. Failure to recognize this variation in the setting of hilar portal ligation leads to hepatic failure and death. Resection or liver transplantation may require PV resection and reconstruction, which greatly increases the complexity of these procedures (11). Additional variations can occur in both the right and left portal systems. It is extremely important to be aware of portal anomalies because failure to do so can lead to non-target embolization with potential risk to the future liver remnants (FLR).

Indications

At present, four factors are important to consider when deciding whether to perform PVE. First, the ratio of FLR to total estimated liver volume (TELV) should be calculated. Second, cases need to be categorized into those with and those without underlying liver disease because this factor will determine how much FLR is needed to reduce postoperative morbidity and mortality. The minimum absolute liver volume necessary to support postresection hepatic function has not been clearly defined. However, a

FLR/TELV ratio of at least 25% is recommended in patients with otherwise normal livers, with a ratio of at least 40% in patients in whom the liver is considered compromised (from chronic liver disease or high-dose chemotherapy) (12-17). When FLR/TELV ratios are below these levels, PVE may be performed in an attempt to increase FLR volume. Third, the presence of systemic disease such as diabetes mellitus may limit hepatic hypertrophy. Insulin is a comitogenic factor with HGF that often leads to slower rates of regeneration (18). Fourth, planning for the type and extent of the anticipated surgical procedure (right hepatectomy and pancreaticoduodenectomy) is important because more functional hepatic reserve may be required to reduce postoperative morbidity.

Contraindications

Patients with metastatic diseases such as distant metastases or periportal lymphadenopathy cannot undergo resection and therefore are not candidates for PVE. Patients with bilobar multiple metastases were not considered as the candidates for PVE before (9), but recent studies confirm that some of these patients can benefit from PVE in combination with two-stage hepatectomy (19). Other relative contraindications for PVE include an uncorrectable coagulopathy, tumor invasion of the PV, tumor precluding safe transhepatic access, biliary dilatation (in cases of biliary tree obstruction, drainage is recommended), portal hypertension, and renal failure that requires dialysis. PVE in cases of tumor invasion of the PV may not be warranted because there may be no significant benefit from the procedure (5).

Techniques

Pre-embolization work-up

Prior to PVE, a complete patient history is taken and a thorough physical examination performed. Laboratory studies including complete blood cell count, prothrombin time, liver function tests, and blood urea nitrogen/creatinine levels are essential prior to PVE. If patient has an elevated total bilirubin (>3.0 mg/dL), percutaneous or endoscopic biliary drainage is beneficial. CT or MRI scanning is a fundamental radiological investigation prior to PVE, for it documents the extent of disease (extrahepatic disease or involvement of the planned FLR), FLR size, and portal venous anatomy (5,9).

Patients should be informed that this procedure is not an antitumoral treatment but a treatment made to increase safety or to enable a surgical procedure. Minor complications are encountered in 20% to 25% of cases and are mainly associated with slight fever and abdominal discomfort and pain. Major complications are infrequent and mainly include infection and subcapsular hematoma, hemobilia, and PV thrombosis (<2% of cases). Mortality due to PVE has not been reported (19,20).

PVE technique

Although general anesthetic may be requested, the procedure is most often performed with local anesthetic (1% lidocaine hydrochloride) and intravenously administered sedatives that allow the patient to remain conscious. Access to the portal system should be done under ultrasound guidance to puncture a peripheral branch (21). Access can be obtained by way of controlateral approach (puncture of the left portal branch and embolization of the right portal branches) or ipsilateral approach (puncture of the right portal branch to embolize right portal branches). The advantage of the controlateral approach is easier catheterization, but there is a risk of damage to the FLR. Five-French materials (catheter or introductory sheath) are usually recommended. The catheter should be placed at the splenomesenteric confluence to perform a portography to visualize portal anatomy, including its variations, and to localize segment IV branches. Measurement of portal pressure is not routinely performed in patients with normal liver. In cirrhotic patients, measuring the portal and central venous pressures is useful to determine whether the patient has a portosystemic gradient >12 mmHg in which case the patient is at major risk of perisurgical complications (20,22,23). These patients are not eligible for PVE. The aim of embolization is complete obstruction of the targeted branches and redistribution of flow to the FLR branches only. Final portography is mandatory to verify this objective. A final pressure measurement should be obtained at the end of the procedure in patients with chronic liver disease to document portal pressure increase, which is usually approximately 3 mmHg. Embolization of segment IV branches is recommended in patients with tumors who are undergoing extended right hepatectomy. However, if embolization of that segment causes risk of reflux into the portal branch of the FRL, such embolization must not be performed because any major reflux into FRL portal branches might preclude surgery.

Table 1 Influence of embolic agent on the hypertrophy response

Embolic agent	Authors	No. of patients	Increase FRL (%)
Gelatin sponge	Fujii *et al*. (24)	30	17.8
	Kusaka *et al*. (25)	18	21.2
	Kakizawa *et al*. (26)	14	23.8
	Nanashima *et al*. (27)	30	29.4
PVA + coils/plugs	Covey *et al*. (28)	100	24.3
	van den Esschert JW *et al*. (29)	10	26.1
	Libicher *et al*. (30)	10	26.4
N-butyl cyanoacrylate	De Baere *et al*. (31)	107	57.8
	Giraudo *et al*. (32)	146	41.7
	Elias *et al*. (33)	68	59.1
	Broering *et al*. (1)	17	69.4
Fibrin glue	Nagino *et al*. (34)	105	27.4
	Liem *et al*. (35)	15	31.4

PVA, polyvinyl alcohol.

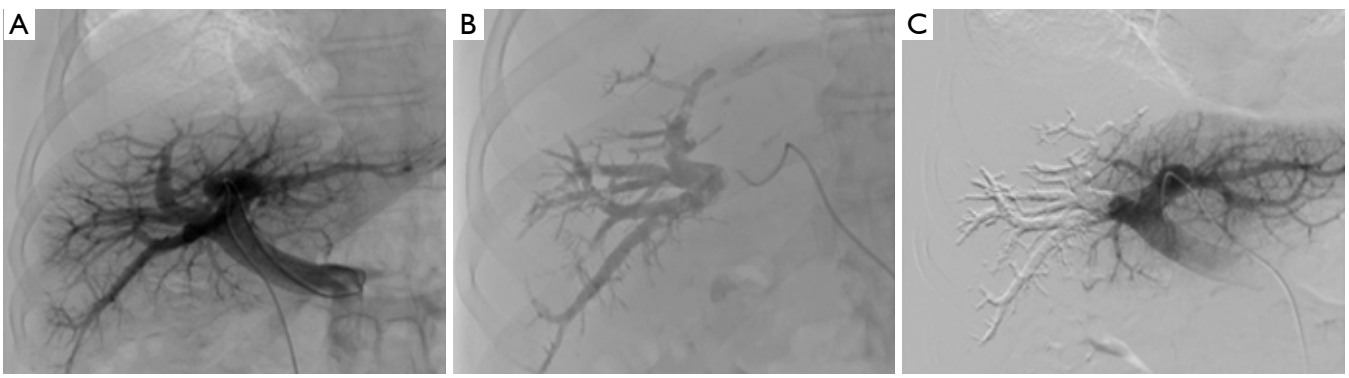

Figure 4 Right PVE. (A) Portal venogram with a 5-Fr standard catheter placed through a 5-Fr vascular sheath by left-side contralateral approach demonstrates normal subsegmental portal branches; (B) X-ray control after embolization of the right portal vein (RPV) and its branches with a cyanoacrylate glue (Glubran®2)/Lipiodol mixture in a 1:8 ratio shows radiopaque distribution of embolization material; (C) final portogram reveals that the left portal branches and segment IV veins continue to have blood flow. PVE, portal vein embolization.

Choice of embolic agent

Various embolic materials have been used. Some products are not recommended due to reported recanalization or lower induced hypertrophy (*Table 1*). Gelfoam is associated with a high rate of PV recanalization and seems less efficient than other products (21,24-27). Nonspherical polyvinyl alcohol (PVA) particles have been used but are less efficient than spherical particles (36). Direct intraportal alcohol injection has been described. Although efficient, it is hard to control and has been associated with significant morbidity (liver necrosis, PV thrombosis) (14).

Recommended products (36-38) include the following. Mixture of n-butyl-cyanoacrylate and iodized oil has been described extensively as showing good results and low morbidity. Usually a mixture of one part n-butyl 2-cyanoacrylate (NBCA) (Histoacryl®, B/Braun, Germany; or Glubran®2, GEM, Italy) to one or two parts Lipiodol (Guerbet, France) is used. Injections of small aliquots in between abundant flushing with nonionic liquid, such as dextran or glucose 5%, is the most commonly reported technique (31-33). In our practice, we used a higher dilution

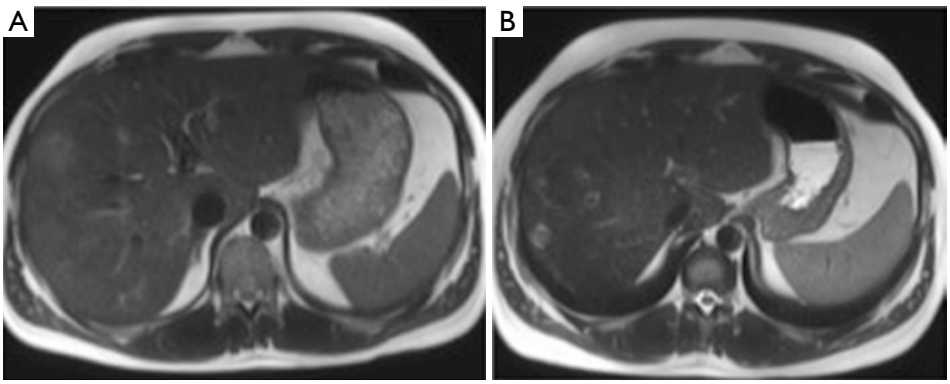

Figure 5 Left hepatic lobar hypertrophy in a 40-year-old man with multiple metastases of the right hepatic lobe. (A,B) MRI scans obtained prior to (A) and following (B) PVE of the right portal vein (RPV) show the FLR (segments I, II, III, IV). The FLR/TELV ratio was 16.0% before PVE and 27% after PVE, representing an increase of 11%. The patient subsequently underwent successful right hepatectomy. PVE, portal vein embolization; FLR, future liver remnants; TELV, total estimated liver volume.

mixture (1:8 ratio) to obtain a very distal embolization (39). Glue allows for fast procedure in comparison with other embolic agents (*Figure 4*). Spherical microparticles are associated with coil embolization, which is mostly described in North American reports, and have been reported to be superior to nonspherical PVA (28-30). It seems as efficient as NBCA, although it has never been compared in randomized trials. Most teams start with 300- to 500-µm particles and finish with 700- to 900-µm particles (20). Coils are used at the end of the procedure to allow for complete occlusion of the proximal trunk. It is advisable to avoid all too proximal occlusions and rather leave 1 cm unembolized segment of the right portal branch to facilitate surgical ligation at the time of liver resection. Association of fibrin glue with iodized oil has mostly been described in Japan and has the drawback of requiring special catheters that are only available in Asia (34,35). Amplatzer vascular plugs can be used instead of coils for occlusion of the proximal trunk or before glue embolization by ipsilateral approach to avoid reflux in the controlateral branches (30).

Post-procedural monitoring

Evaluation for signs of postembolization syndrome or liver insufficiency includes review of patient symptoms, clinical signs, and laboratory data (such as elevated white blood cell count, increasing transaminase levels, or prothrombin time). Patients are discharged when they are clinically stable and without complaints, usually the next day. Repeat CT is performed after 2-4 weeks to assess FLR hypertrophy and disease spread. If liver regeneration occurs and there is no spread of disease that would contraindicate the procedure, resection is performed. Otherwise, follow-up CT is performed at monthly intervals. Because the minimum safe FLR volume that would contraindicate resection has not yet been determined, we still perform resection in all patients who demonstrate regeneration (40). Although studies in animals show that most regeneration occurs within the first 2 weeks, this has not yet been proved in humans. Selective hepatic lobar hypertrophy is illustrated in *Figure 5*.

Outcomes

Technical success

The technical success rate should be close to 100%. Few cases of failures or repeated procedures have been reported in the literature (9,40). The resection rate should be approximately 85%. This rate may decrease to 70% in the case of cirrhotic patients. Reasons for non-resection are tumor progression, peritoneal metastases, or unsuspected metastases discovered at laparotomy. Absence of hypertrophy is rare, <10% in metastatic liver, but it can reach 20% in cirrhotic patients (19,20).

Hypertrophy response

CT, sometimes MRI, with volumetric is the cornerstone for planning surgical resection (19). There are different methods of calculating liver volumes, making comparison of results obtained at different institutions difficult. The

Table 2 Potential complications after PVE

Type of complications	Percentage (%)
Minor complications	
Fever	36.9
Elevation of transaminase	34.8
Abdominal discomfort/pain	22.9
Nausea and vomiting	2
Ileus	1.2
Major complications	
Portal thrombosis	0.8
Embolization of nontarget vessels	0.6
Liver hematoma	0.4
Infection/abscess	0.4
Intra-abdominal bile leakage	0.3

PVE, portal vein embolization.

growth of the FRL as a result of PVE can be calculated or expressed in two ways.

The difference in FRL volume before and after embolization in relation to the FRL volume before embolization (percentage volume increase):

FRL volume increase (%) = FRLpost-PVE (%) – FRLpre-PVE/FRLpre-PVE (%) × 100%

The difference between the percentage FRL before and after embolization [in literature referred to degree of hypertrophy (DH)]:

DH (%) = FRLpost-PVE (%) – FRLpre-PVE (%)

In patients with normal liver and liver metastases, the increase of the FLR ratio is between 8% and 25%, and regeneration is always observed after PVE. In cirrhotic patients, PVE fails to induce left-lobe hypertrophy in 20% of cases. Increased rate of FLR ratio in this population is slightly lower, between 6% and 20%.

Recent studies have demonstrated that hypertrophy is inversely proportional to the FRL ratio before PVE, meaning that the smaller FRL before PVE will have the larger hypertrophy (19,20). Consequently there is no lower limit for the FRL ratio to perform PVE.

Complications

PVE is considerably less toxic than arterial embolization, so side effects are minimal. Signs and symptoms of postembolization syndrome, such as nausea and vomiting, are rare. Fever and pain are infrequent. Changes in liver function following PVE are usually minor and transient (50% of patients have no appreciable change) (*Table 2*). When transaminase levels rise, they usually peak at a level less than three times baseline 1-3 days after embolization and return to baseline in 7-10 days, regardless of the embolic materials used. Slight changes in total bilirubin value and white blood cell count may be seen. Synthetic function (prothrombin time) is almost never affected. PV thrombosis is extremely rare. Of course, it is essential to avoid the reflux of embolizing material into the portal venous branches of the remnant liver (13,21,40).

Unresolved issues regarding PVE

The purpose of PVE is to increase the hepatic functional reserve of FLR as well as its volume (41). However, there are four potential issues facing PVE: (I) PVE stimulates the growth of hepatic tumor (2,42,43); (II) PVE may fail to increase the volume of FLR in some patients, especially those with fibrotic or cirrhotic liver (3); (III) is PVE safe in patients with high-grade varices? The mechanisms of fast tumor growth after PVE are still poorly understood. Kokudo *et al.* (43) assessed the proliferative activity of intrahepatic metastases in the embolized liver after PVE in 18 patients with colorectal metastases and found a significantly increased tumor Ki-67 labeling index in the metastases group with PVE compared to hepatic metastases without PVE. It was postulated that the tumor growth after PVE might be controlled by three factors: malignant potential of the tumors, changes in cytokines or growth factors induced by PVE and changes in blood supply after PVE. Animal models of PV branch ligation demonstrated that HGF-mRNA markedly increased in the non-ligated growing lobe, but was only slightly elevated in the ligated shrinking lobe. Increased tissue levels of HGF might increase the level in plasma, thus stimulating the growth of hepatic tumors. Barbaro *et al.* (42) noted a significant increase in hepatic tumor volume from colorectal carcinoma after PVE, while hepatic tumor volume from carcinoid tumor was unchanged. Another factor potentially stimulating tumor growth after PVE is increased hepatic arterial blood flow in embolized liver after PVE, for supply of intrahepatic metastases depends solely on arterial blood supply (44). But these cannot explain why PVE increased hepatic tumor volume from colorectal carcinoma, while did not stimulate the growth of carcinoid tumor. Butyrate

is known to stimulate proliferation of normal crypt cells, whereas it induces apoptosis and has antiangiogenic effects on colon cancer cells (45). Therefore, the lack of butyrate from PV blood may contribute to the increase in hepatic metastasis volume of colorectal carcinoma and, meanwhile, the enrichment of butyrate in FLR may help prevent tumor recurrence in patients treated with two-stage strategy. Hepatic arterial blood flow in embolized liver is increased after PVE and the supply of intrahepatic metastases depends solely on arterial blood supply, so PVE combined with transcatheter arterial embolization (TAE) may help prevent tumor growth and at the same time accelerate the hypertrophy of FLR. Pioneering reports from Inaba *et al*., and Sugawara *et al*., have confirmed that PVE in combination with TAE is safe, effective, and hence recommendable. PV pressure rises about 4 cm H_2O after PVE (46), however, there is no report of PVE-related acute variceal hemorrhage. Liver transplantation is an excellent alternative to liver resection in treating the cirrhotic patient with small oligonodular hepatocellular carcinoma (HCC), but for large HCCs, partial liver resection remains the best therapeutic option for cure because neither liver transplantation nor percutaneous treatments are indicated. So PVE has become an important tool to induce hypertrophy of the FLR before major liver resection in cirrhotic patients (4); In PVE performed prior to an extended right hepatectomy, increasing attention has been given to embolization of segment IV. This embolization is performed for two reasons: (I) all tumor-bearing liver is embolized because accelerated tumor growth has been reported with incomplete embolization (47), and (II) segment IV embolization may contribute to better hypertrophy of segments I, II, and III before extended right hepatectomy (48). In addition, it is important to avoid reflux of the embolic material into the veins that will supply the FLR because bilateral or main PV occlusion remains a risk.

Conclusions

Preoperative PVE is an effective method to increase FRL volume with a high technical and clinical success rate. The complication rate is low, but local tumor progression after PVE is an imminent cause of unresectability. Pre-existing liver damage due to cirrhosis seems to have a negative effect on the hypertrophy response. Chemotherapy however does not seem to have any influence on the hypertrophy response, except for platin agents. The use of n-butyl cyanoacrylate may result in a greater hypertrophy response compared with the other embolization materials used.

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Footnote

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

References

1. Broering DC, Hillert C, Krupski G, Fischer L, Mueller L, Achilles EG, Schulte am Esch J, Rogiers X. Portal vein embolization vs. portal vein ligation for induction of hypertrophy of the future liver remnant. J Gastrointest Surg 2002;6:905-13; discussion 913.
2. Hemming AW, Reed AI, Howard RJ, Fujita S, Hochwald SN, Caridi JG, Hawkins IF, Vauthey JN. Preoperative portal vein embolization for extended hepatectomy. Ann Surg 2003;237:686-91; discussion 691-3.
3. Farges O, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V, Denys A, Sauvanet A. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237:208-17.
4. Jaeck D, Bachellier P, Nakano H, Oussoultzoglou E, Weber JC, Wolf P, Greget M. One or two-stage hepatectomy combined with portal vein embolization for initially nonresectable colorectal liver metastases. Am J Surg 2003;185:221-9.
5. Liu H, Fu Y. Portal vein embolization before major hepatectomy. World J Gastroenterol 2005;11:2051-4.
6. Couinaud C. Le foie: études anatomiques et chirurgicales. Paris, France: Masson, 1957;75.
7. Schultz SR, LaBerge JM, Gordon RL, Warren RS. Anatomy of the portal vein bifurcation: intra- versus extrahepatic location--implications for transjugular intrahepatic portosystemic shunts. J Vasc Interv Radiol 1994;5:457-9.
8. Yamane T, Mori K, Sakamoto K, Ikei S, Akagi M. Intrahepatic ramification of the portal vein in the right and caudate lobes of the liver. Acta Anat (Basel) 1988;133:162-72.
9. Madoff DC, Hicks ME, Vauthey JN, Charnsangavej C, Morello FA Jr, Ahrar K, Wallace MJ, Gupta S. Transhepatic portal vein embolization: anatomy, indications, and technical considerations. Radiographics

2002;22:1063-76.
10. Atri M, Bret PM, Fraser-Hill MA. Intrahepatic portal venous variations: prevalence with US. Radiology 1992;184:157-8.
11. Hardy KJ, Jones RM. Failure of the portal vein to bifurcate. Surgery 1997;121:226-8.
12. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, Hicks M, Alsfasser G, Lauwers G, Hawkins IF, Caridi J. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512-9.
13. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. Br J Surg 2001;88:165-75.
14. Shimamura T, Nakajima Y, Une Y, Namieno T, Ogasawara K, Yamashita K, Haneda T, Nakanishi K, Kimura J, Matsushita M, Sato N, Uchino J. Efficacy and safety of preoperative percutaneous transhepatic portal embolization with absolute ethanol: a clinical study. Surgery 1997;121:135-41.
15. Lee KC, Kinoshita H, Hirohashi K, Kubo S, Iwasa R. Extension of surgical indications for hepatocellular carcinoma by portal vein embolization. World J Surg 1993;17:109-15.
16. Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, Harihara Y, Takayama T. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology 1997;26:1176-81.
17. Azoulay D, Castaing D, Krissat J, Smail A, Hargreaves GM, Lemoine A, Emile JF, Bismuth H. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. Ann Surg 2000;232:665-72.
18. Nagino M, Nimura Y, Kamiya J, Kondo S, Uesaka K, Kin Y, Hayakawa N, Yamamoto H. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 1995;21:434-9.
19. van Lienden KP, van den Esschert JW, de Graaf W, Bipat S, Lameris JS, van Gulik TM, van Delden OM. Portal vein embolization before liver resection: a systematic review. Cardiovasc Intervent Radiol 2013;36:25-34.
20. Denys A, Bize P, Demartines N, Deschamps F, De Baere T; Cardiovascular and Interventional Radiological Society of Europe. Quality improvement for portal vein embolization. Cardiovasc Intervent Radiol 2010;33:452-6.
21. de Baere T, Roche A, Elias D, Lasser P, Lagrange C, Bousson V. Preoperative portal vein embolization for extension of hepatectomy indications. Hepatology 1996;24:1386-91.
22. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, Visa J, Bru C, Rodés J. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018-22.
23. Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999;229:210-5.
24. Fujii Y, Shimada H, Endo I, Kamiyama M, Kamimukai N, Tanaka K, Kunisaki C, Sekido H, Togo S, Nagashima Y. Changes in clinicopathological findings after portal vein embolization. Hepatogastroenterology 2000;47:1560-3.
25. Kusaka K, Imamura H, Tomiya T, Makuuchi M. Factors affecting liver regeneration after right portal vein embolization. Hepatogastroenterology 2004;51:532-5.
26. Kakizawa H, Toyota N, Arihiro K, Naito A, Fujimura Y, Hieda M, Hirai N, Tachikake T, Matsuura N, Murakami Y, Itamoto T, Ito K. Preoperative portal vein embolization with a mixture of gelatin sponge and iodized oil: efficacy and safety. Acta Radiol 2006;47:1022-8.
27. Nanashima A, Sumida Y, Abo T, Nonaka T, Takeshita H, Hidaka S, Sawai T, Yasutake T, Sakamoto I, Nagayasu T. Clinical significance of portal vein embolization before right hepatectomy. Hepatogastroenterology 2009;56:773-7.
28. Covey AM, Brown KT, Jarnagin WR, Brody LA, Schwartz L, Tuorto S, Sofocleous CT, D'Angelica M, Getrajdman GI, DeMatteo R, Kemeny NE, Fong Y. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 2008;247:451-5.
29. van den Esschert JW, de Graaf W, van Lienden KP, Busch OR, Heger M, van Delden OM, Gouma DJ, Bennink RJ, Laméris JS, van Gulik TM. Volumetric and functional recovery of the remnant liver after major liver resection with prior portal vein embolization: recovery after PVE and liver resection. J Gastrointest Surg 2009;13:1464-9.
30. Libicher M, Herbrik M, Stippel D, Poggenborg J, Bovenschulte H, Schwabe H. Portal vein embolization using the amplatzer vascular plug II: preliminary results. Rofo 2010;182:501-6.
31. de Baere T, Teriitehau C, Deschamps F, Catherine L, Rao P, Hakime A, Auperin A, Goere D, Elias D, Hechelhammer L. Predictive factors for hypertrophy

of the future remnant liver after selective portal vein embolization. Ann Surg Oncol 2010;17:2081-9.
32. Giraudo G, Greget M, Oussoultzoglou E, Rosso E, Bachellier P, Jaeck D. Preoperative contralateral portal vein embolization before major hepatic resection is a safe and efficient procedure: a large single institution experience. Surgery 2008;143:476-82.
33. Elias D, Ouellet JF, De Baère T, Lasser P, Roche A. Preoperative selective portal vein embolization before hepatectomy for liver metastases: long-term results and impact on survival. Surgery 2002;131:294-9.
34. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg 2006;243:364-72.
35. Liem MS, Liu CL, Tso WK, Lo CM, Fan ST, Wong J. Portal vein embolisation prior to extended right-sided hepatic resection. Hong Kong Med J 2005;11:366-72.
36. Madoff DC, Abdalla EK, Gupta S, Wu TT, Morris JS, Denys A, Wallace MJ, Morello FA Jr, Ahrar K, Murthy R, Lunagomez S, Hicks ME, Vauthey JN. Transhepatic ipsilateral right portal vein embolization extended to segment IV: improving hypertrophy and resection outcomes with spherical particles and coils. J Vasc Interv Radiol 2005;16:215-25.
37. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N, Jiao LR. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49-57.
38. de Baere T, Denys A, Paradis V. Comparison of four embolic materials for portal vein embolization: experimental study in pigs. Eur Radiol 2009;19:1435-42.
39. Loffroy R, Guiu B, Cercueil JP, Krausé D. Endovascular therapeutic embolisation: an overview of occluding agents and their effects on embolised tissues. Curr Vasc Pharmacol 2009;7:250-63.
40. Madoff DC, Hicks ME, Abdalla EK, Morris JS, Vauthey JN. Portal vein embolization with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy: safety and effectiveness--study in 26 patients. Radiology 2003;227:251-60.
41. Kubo S, Shiomi S, Tanaka H, Shuto T, Takemura S, Mikami S, Uenishi T, Nishino Y, Hirohashi K, Kawamura E, Kinoshita H. Evaluation of the effect of portal vein embolization on liver function by (99m)tc-galactosyl human serum albumin scintigraphy. J Surg Res 2002;107:113-8.
42. Barbaro B, Di Stasi C, Nuzzo G, Vellone M, Giuliante F, Marano P. Preoperative right portal vein embolization in patients with metastatic liver disease. Metastatic liver volumes after RPVE. Acta Radiol 2003;44:98-102.
43. Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, Ohta K, Yamaguchi T, Matsubara T, Takahashi T, Nakajima T, Muto T, Ikari T, Yanagisawa A, Kato Y. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. Hepatology 2001;34:267-72.
44. Kito Y, Nagino M, Nimura Y. Doppler sonography of hepatic arterial blood flow velocity after percutaneous transhepatic portal vein embolization. AJR Am J Roentgenol 2001;176:909-12.
45. Zgouras D, Wächtershäuser A, Frings D, Stein J. Butyrate impairs intestinal tumor cell-induced angiogenesis by inhibiting HIF-1alpha nuclear translocation. Biochem Biophys Res Commun 2003;300:832-8.
46. Ko GY, Sung KB, Yoon HK, Kim JH, Weon YC, Song HY. Preoperative portal vein embolization with a new liquid embolic agent. Radiology 2003;227:407-13.
47. Elias D, De Baere T, Roche A, Mducreux, Leclere J, Lasser P. During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. Br J Surg 1999;86:784-8.
48. Nagino M, Nimura Y, Kamiya J, Kondo S, Uesaka K, Kin Y, Kutsuna Y, Hayakawa N, Yamamoto H. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. Surgery 1995;117:677-81.

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Bridging and downstaging therapy in patients suffering from hepatocellular carcinoma waiting on the list of liver transplantation

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Abstract: Hepatocellular carcinoma (HCC) is a common primary malignancy worldwide especially in the patients with the background of chronic liver disease. Liver transplantation (LT) is the only curative treatment effective for both malignancy as well as the cirrhosis and portal hypertension. Unfortunately, living donor is not always possible and the deceased graft is scarce. Neoadjuvant therapies, therefore, have been developed as a downstaging treatment to try to downstage the tumor within the transplant criteria, or as a bridging therapy to control the tumor growth in patients while waiting in the transplant list. This paper reviewed the common modalities used as bridging and downstaging therapies for patients suffering from HCC before undergoing LT.

Keywords: Liver transplant (LT); downstaging; radiofrequency ablation (RFA); high intensity focuses ultrasound (HIFU)

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the most common primary liver malignancy worldwide (1,2). Most cases of HCC in Asia are hepatitis B related, which is prevalent in the region (3). It is the third most common cancer causing death in Hong Kong (4). However, the prognosis of majority of HCC patients remained poor due to low resectability rate of 20% (5,6).

Transplant criteria

Liver transplantation (LT) remains the best curative surgical treatment option for patients with HCC and cirrhosis. It removes the tumorous liver as well as corrects the underlying disease liver, and a 5-year post-transplant survival rate of >70% is expected (7-10). The established Milan criteria (11) and the UCSF [University of California, San Francisco] criteria (12) had been well validated and were used as the guideline to list the patients for LT, especially deceased donor LT. Unfortunately, its applicability of LT is limited by the shortage of liver graft supply (13).

Patients, who suffered from HCC with or without poor liver function, who were out of the transplant criteria, remained the most difficult group to be treated. Disease could be downstaged or controlled by various anticancer therapies, which might bring them chance of undergoing a curative treatment such as LT. Local ablative therapies, chemoembolization and/or targeted therapy were used. Some of the tumors showed response to the therapies, however the optimal type of therapy that should be used

and the upper limit of tumor size that should be downstaged were still not clear. A disease-free period of at least three months was recommended after the disease was downstaged (14-17); unfortunately, the optimal waiting time to offer LT remained unclear.

The interval between HCC diagnosis and LT is an important prognostic factor, as drop out rate from the waiting list as a result of tumor progression increases in a time-dependent manner (18). This is particular the case because of the scarcity supply of the liver grafts, hence patients on the LT waiting list have to suffer from a long period of waiting time, result in disease progression and drop out from the waiting list (19-21). A predicted 12% probability of 6-month drop out for patients in whom the tumor is left untreated during the waiting period (19,22).

In view of this, bonus Model for End-Stage Liver Disease (MELD) score are granted for patients for stage 2 HCC (single HCC between 2 and 5 cm or up to three HCCs with none larger than 3 cm). Initial MELD score of 22 points and additional MELD points every 3 months if their tumors remained at stage 2 was given in the United States. In Hong Kong, patients with HCC that remained at stage 2 six months after their tumors had been confirmed as stage 2 HCCs by imaging were assigned an arbitrary MELD score of 18 points. Two MELD points were added every three months. The policy of a 6-month waiting period has benefited HCC patients in the deceased donor LT waiting list who practically have no chance of undergoing living donor LT (23).

Despite the bonus points, the drop out rate was still substantial (24). Increase tumor burden during a long period of waiting time might also adversely affect post-LT survival rate (25). Bridging therapy focused on treating patients within the criteria while they were on the waiting list, in order to avoid tumor progression to more advanced stage and therefore drop out from the waiting list. Bridging therapy was estimated to decrease drop out rate for HCC meeting the Milan criteria to 0–10%. To minimize the number of drop out from the waiting list and reduce the potential risk of recurrent tumor after LT, intervention strategies such as transarterial chemoembolization (TACE) and image guided ablative therapies have been offered to the patients. Effective bridging therapy during the waiting period would help to slow down the disease progression, and therefore, allow them to undergo deceased donor LT. Tumor recurrence rate after LT was found to increase from 12% for patients remaining within Milan criteria, either spontaneously or following bridging therapy, to 45% for those who had a tumor progression beyond the Milan criteria (11,26). Therefore, neoadjuvant therapy to control tumor growth and vascular invasion of the HCC and thereby avoidance of drop out during waiting time is of paramount importance. TACE has been used widely and is the most common bridging therapy.

This review focuses on various bridging and downstaging modalities in the treatment of HCC, in preparing patients for LT.

Diagnostic criteria for hepatocellular carcinoma (HCC) and pre-liver transplantation (LT) work up

The diagnostic criteria for HCC in our center were as follows: (I) typical abnormality with arterial enhancement and contrast washout in the portal venous phase in 3—phases contrast enhanced computed tomography (CT) or magnetic resonance imaging and/or (II) an elevated serum Alpha fetoprotein (AFP) level of greater than 400 ng/mL. Needle tumor biopsy was generally avoided in resectable cases to avoid the risk of needle tract seeding of tumor cells. The diagnosis of HCC was confirmed histologically in the resected or transplanted specimen. Major vascular invasion was defined as tumor thrombosis inside the major branch of the portal vein or hepatic vein macroscopically. In our centre, dual—tracer positron emission tomography (PET) with [^{11}C] acetate and [^{18}F] fludeoxyglucose (FDG) scan, or CT thorax and bone scan, were also used as part of the LT work up. Dual—tracer PET scan with the additional use of [^{11}C] could further improve the sensitivity and specificity in diagnosis of HCC and detection of metastasis to 96.8% and 91.7% respectively (27). Furthermore, PET scan had been used to predict the HCC with poor differentiation as well as presence of microvascular invasion especially by the [^{18}F] tracer (28).

Liver resection

Liver resection can be used as a form of primary treatment for HCC or as a bridging or down staging for LT. Liver resection can potentially control tumor growth with clear resection margin; in addition, it allows assessment of the tumor biology, such as tumor differentiation, presence of microvascular invasion, or capsular effraction, and provides hints for those patients who should be evaluate for earlier LT if possible (29).

Simple liver resection can only be performed in selected patients. Single exophytic or superficial tumor such as subcapsular neoplasms, or tumors in the left lobe are better

tumors to be performed in bridging or downstaging setting. Liver resection can allow salvage LT to be performed as the only curative measure if the tumors are still within the criteria after a period of wait and see. Reports suggested that the post–operative course, complications, and the 3- and 5-year survival rates did not differ significantly between cirrhotic HCC patients undergoing primary LT or secondary LT after the initial liver resection (30), especially those tumors initially submitted to liver resection with the Milan criteria (31,32), or the UCSF criteria (33). In our centre, approximately 80% of patients were still eligible for salvage LT at the time of tumor recurrence (34). However liver resection had risk of surgical complications, and it could only be performed in well-compensated patients without severe portal hypertension. Poor liver function, which was reflected by the high Child-Pugh grading, high indocyanine green retention rate at 15 minutes, i.e., >14% in major resection and 22% in minor liver resection (35), as well as thrombocytopenia were shown to be independent predictor of morality in patients with HCC and cirrhosis (14,36), and therefore, contraindicated for liver resection. Furthermore, the operated abdomen can make the subsequent LT technically more difficult and demanding, with a higher risk of post-operative complications (37).

Transarterial chemoembolization (TACE)

TACE has been proven to improve survival and control symptom (38). It has the advantage of instillation of the chemotherapeutic agent directly into the liver tumor, which was carried by the lipiodol, as well as ischemic necrosis induced by arterial embolization. It has been used for unresectable HCC in patients who are awaiting LT as well as those who are not transplant candidates opted for palliative care (39,40). Adequate tumor necrosis was achieved in the explant liver in the range of 27–57% in patients within Milan criteria (41,42). The use of TACE did not only to affect the features of tumor lesions, but also to impact recurrence rate of HCC after LT (41).

Various reports had suggested some of patients could be bridged as well as downstaged, which resulted in favorable long-term outcome (43-46). Unfortunately, not all patients responded to TACE. AFP level >100 ng/mL and high 3-year calculated survival probability might predict a good response to downstaging therapy after TACE (17). The aim is to achieve 100% necrosis of the tumors, but less than 30% of the cases could achieve complete pathological responds in the histological evaluation (41,45,47,48), hence the reported necrosis rate in the survival benefit after downstaging by TACE remained questionable (41,45,46,49). There was also report suggesting partial necrosis was a risk factor for tumor recurrence after LT (50). A recent study had shown that the significant of to achieve complete or nearly complete pathological response as bridging therapy improved long term survival after LT as it decreased the active tumor load (51). Moreover, a multicenter study suggested that preoperative loco-regional therapy decreased the risk of tumor recurrence in patients with pathologic T2 and T3 HCC (52). In addition, larger degree of tumor necrosis, i.e., >60%, of the largest tumor in the explant resulted in significant better survival than those with less degree of tumor necrosis (15). Afterall, sustained response to TACE would be a better selection criterion for LT than the initial assessment of tumor size or number (53). Majno et al. found a significantly prolonged recurrence-free 5-year survival of 71% in patients successfully downstaged with TACE compared to 29% where TACE did not lead to tumor reduction (41). Decaens *et al.* used TACE as the bridging therapy in a mean waiting time of 4.2 months which resulted >80% of tumor necrosis in the explants without significant difference in the long term survival (46). While another study didn't find significant difference in terms of the recurrent rate, however it attributed the possibility difference in the pathologic characteristic in which TACE group might have larger tumor without presence of the capsules (54). TACE given before LT was found useful for those patients with tumors >3 cm. Despite the controversy, TACE remained one of the commonest bridging and downstaging modalities. However it had to be balanced with the large tumors that were generally considered poor candidates for LT. The low incidence of recurrence for the tumor being downstaged within Milan criteria was similar to the patients with smaller tumors to start with, and therefore should not be excluded from LT (41).

Afterall, TACE is not applicable to every patient with cirrhosis. Patients who suffered from ascites and main portal vein thrombosis resulted from cirrhosis, poor liver function at risk of liver failure, poor renal function at risk of contrast nephropathy, difficult arterial anatomy and difficult cannulation are contraindication from TACE (38,55). These patients are at risk of tumor progression without any intervention. Therefore other forms of bridging therapy must be attempted and developed. Side effects range from post-embolization syndrome, tumor necrosis and rarely liver failure. The judicious use of the TACE would certainly help as a bridging and downstaging modality to LT.

Doxorubicin eluting bead (DEB) transarterial chemoembolization (TACE)

DEB aimed to bind, deliver and elute doxorubicin directly to the tumorous tissue in a sustained fashion (56-58). There are three substantial pharmacokinetic advantages associated with DEB: a continuous elution of the drug for prolonged period of time, a higher concentration locally into the tumor and a lower systematic exposure to the drug in comparison to TACE (56).

Despite reports suggested that there was no significant difference in terms of the safety profile, tumor response, tumor recurrence and overall survival rate for DEB as compared to TACE in non-transplant patients (57,59), DEB was shown to have lower tumor recurrence rate after LT and was identified as an independent predictor of recurrence-free survival in the multivariate analysis (60). Further study should be carried out to confirm the superiority of this technique.

Radiofrequency ablation (RFA)

RFA made use of the radiofrequency (RF) electrode tip, generating alternating electrical current (300–1,000 kHz), inducing temperature of 60–100 ℃. Irreversible damage was resulted by the coagulation necrosis. RF electrode tip could generate an ablative zone of 3–5 cm in diameter (61). An ablative margin of 0.5–1 cm of the peritumoral tissue was necessary as if a clear resection margin achieved during the resection of the HCC, and it should be able to be visualized by the ultrasound for both open and percutaneous procedures. The use of central bile duct cooling during RFA of periductal HCC was effective in preventing thermal injury of bile duct (62). However, the presence of the 'heat-sink effect' may affect the complete ablation of the tumor near the major vessels, and therefore increase the chance of local recurrence after RFA (63,64).

The use of RFA was proven to be safe and effective treatment modality for patients with advanced cirrhosis and non-resectable HCC (65). Majority of the lesions were shown to have high tumor necrotic rate (66), and especially for those HCC less than 3 cm in size (67-69). The drop out rate from the transplant list had decreased after treatment with RFA (67,68). Unfortunately, the remarkable necrotic effect was less than 50% when used in larger tumors (67-69). In fact, tumor size larger than 3 cm was found to be the risk factors for persistent HCC after the treatment (68,69). In addition, the procedure may be associated with a higher rate of satellite nodules occurrence (66). There are some limitations associated with the use of RFA. RFA could not be used in large tumor, preferred less than 5 cm (70), and its greatest effect as bridging therapy was found in patients with tumors 3 cm or smaller who were listed less than 1 year for transplant (71). Whereas higher rate of recurrence exceeding the Milan criteria was found in patients, especially for patient who had a larger tumor size (>2 cm) and/or a higher AFP level (>100 ng/mL) at their initial presentation and early recurrence after initial RFA (72).

Complications of RFA can be classified into collateral thermal damage, direct mechanical injury or other uncommon reported complications, such as haemobilia (73), liver failure (74), cardiac tamponade (75), liver abscess in the presence of bilioenteric anastomosis (76). Tumor seeding could be a potential problem, although rare ~0.3–0.5% (76,77), especially in the setting of bridging therapy, which may render potential LT impossible.

Microwave ablation (MWA)

MWA made use of the electromagnetic energy, creating an electromagnetic field that allowed rapid and homogenous heating of the tissue and resulted in heat-based thermal cytotoxicity from frictional heating from the rapid oscillation of water molecules (78). It also converted kinetic energy into heat through ionic polarization, therefore coagulation necrosis. Similar to RFA, the lesion should be able to be visualized by the ultrasound for proper localization. It created a predictable and reproducible area of tissue necrosis, and it could ablate the tumor capsule as well as surrounding extracapsular invasion. For larger tumors, multiple needle electrode insertions might be needed for complete tumor ablation (79). MVA appeared to be less susceptible to heat sink effects than RFA (80), which might be more effective near the hepatic veins and IVC (81). In general, studies had demonstrated similar complete ablation rate with RFA (82-85), data also showed similar survival rates after RFA and MVA for curative treatment for HCC (82,83,86). While MWA was shown to be a safe procedure use as a bridge for LT, it also allowed complete tumor necrosis (87). Unfortunately, there was higher rate of local tumor recurrence, which was attributed to the potential tumor seeding by the use of larger application (5 mm in diameter) (88). Complications are similar to those RFA, including bile duct stenosis and haemorrhage, with a potential risk of tumor seeding due to

large probe is used (89).

Irreversible electroporation (IRE)

IRE was a non-thermal ablative therapy that used high-voltage, low electrical current to irreversibly increase the permeability of target cells, disrupt cellular homeostasis, and induce apoptosis (90). It also induced complete cell death up to the margin of large vessels bypassing the heat sink effect seen such as in the RFA (91). Up-to-date, there is not much data regarding the use of IRE as bridging therapy, however complete necrosis was achieved in treatment of the tumor <3 cm by IRE (92). There is a potential role of using IRE in management patients waiting for LT.

Transarterial radioembolization (TARE)

Radioembolization involved the transarterial infusion of microspheres containing Y90 loaded microspheres, iodine-131-iodized poppy seed oil, or similar agents into the hepatic artery by transarterial techniques (93). The highly concentrated radioactive substance would be administrated to the tumor, while keeping the level of toxicity affecting the functional liver parenchyma at the minimal and preserving the blood supply (94,95). It was also safe for use in patients with portal vein thrombosis (96).

Candidates with good functional status and relatively adequate liver reserve with relatively normal liver function, low tumor burden without extrahepatic metastasis would be the ideal candidate for radioembolization (97). Reports found a trend towards shorter times to tumor response and longer times to tumor progression were apparent with TARE when compared with TACE (98,99), suggesting a potential advantage as a bridging therapy in patients waiting for LT.

Results of transarterial radioembolization (TARE)

There are limited papers describing downstaging of HCC by means of TARE (96,98,100,101). Downstaging of the tumor had been observed in the rate of around 37% without significant difference as compare to TACE, while the recurrence rate is 26% (102).

However, not all patients could undergo TARE. Pre-treatment mesenteric angiogram and 99Tc macroaggregated albumin scans were required to assess the anatomy and the presence of vascular shunting. This helped to minimize the risk of radiation pneumonitis due to the shunting. (98,99,103)In case of vascular shunting more than >20%, it could be embolized before therapy began. It appeared to be a safe treatment modality. The side effect is usually mild and limited to fatigue and constitutional symptoms (104,105). Nonetheless significant side effects due to non-targeted radiation resulted in cholecystitis, gastrointestinal ulcers, and pneumonitis were reported (43,97,103,106-109).

High intensity focused ultrasound (HIFU)

HIFU was an extracorporeal ablative modality making use of multiple ultrasound (USG) beams. It induced heat generation, produced mechanical effect and radiation forces, aiming at a temperature of 60 ℃ or higher, in order to cause coagulation necrosis and cell death. It allowed minimal thermal damage to tissue located between the transducer and the focal point (110). Clinical results for HIFU ablation of the tumor from China produced some encouraging findings in terms of significant tumor shrinkage and prolonged survival of patients (111-114).

HIFU had been shown to achieve favorable radiological responses for patients suffered from unresectable HCC and Child-Pugh C cirrhosis (115,116). Satisfactory tumor necrosis was also observed according to histological examinations of excised livers in a few transplant recipients (116,117).

HIFU had been shown to be an effective ablative modality in which similar tumor necrosis was achieved in in the explant liver as compared to the TACE. It had the advantage to be offered to the patients who are contraindicated for TACE, i.e., ascites, Child-Pugh C cirrhosis, portal vein thrombosis. It had also proven to improve the percentage of patients receiving bridging therapy in the transplant waiting list (118). In addition the number of drop out rate decreased (119). Nonetheless, whether this converted any survival benefit after the LT remained an area for further research.

Unfortunately, not every HCC could be treated by HIFU. It had to be visualized and localized by the ultrasound before HIFU could be carried out. It was a safe and totally extracorporeal procedure with minimal risk. Minor complications such as skin and subcutaneous tissue injuries occurred in most patients (116), however, more severe complications were reported such as bile duct injury. The patient should be fit to undergo general anesthesia, so to allow momentarily holding of breathing for more precise ablation.

Stereotactic body radiotherapy (SBRT)

SBRT involved the precision delivery of a highly focused dose of radiation to the target tumor over a short number of treatments. With the advancement of the imaging methods for localizing HCC, precise treatment planning facilitated the delivery of targeted radiation with minimal treatment of uninvolved tissue (120). Lesions near the bowels were not ideal for SBRT since there was risk of gastrointestinal perforation and bleeding, however it had the advantage to treat the lesions adjacent to the central biliary system that were not amenable to surgery or ablation (121).

SBRT had been used as one of the bridging therapies and it was found to be effective, safe with low toxicity profile (122-124). The dosage given ranged from 40 to 51 Gy. Complete necrosis in some of the lesions could be achieved at around 27%. Most of the tumors could be decreased in size or remained stable without dropped off (123).

Radiation induced liver toxicity

Radiation induced liver disease (RILD) had been defined as a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes occurring from 2 weeks to 4 months after radiotherapy. The probability of RILD rose up to 50% for a mean dose of 43 Gy given (125). In some severe cases, RILD might result in liver failure and mortality. Hence, careful administration of the radiation and precise planning of the radiotherapy would minimize the complications.

Sorafenib

Sorafenib was an oral multi-kinase inhibitor, which had been shown to have significant efficacy in prolonging the time-to-progression and was the standard treatment for patients with advanced HCC (126,127). Study on the use of sorafenib as bridging or downstaging therapy before LT was limited. A study on this issue, however, was given in patient median times to LT shorter than six months, suggested its cost-effectiveness while comparing to those without any therapy for T2-HCC patients waiting for LT (128). Combination of TACE and sorafenib might be a potential therapeutic approach for both bridging and downstaging HCC before LT. TACE allowed embolization of the tumor feeding vessel with focal chemotherapeutic effect, whereas sorafenib inhibited angiogenesis and retarded the tumor progression. There were clinical trials and studies working on the combination of the sorafenib with other modalities before LT (129).

Combination of modalities

Bridging loco-regional therapies should be sued whenever possible to prevent drop out and to minimize HCC recurrence after LT, particularly when the expected time to LT is longer than six months. TACE had been mostly studied as both bridging and downstaging protocols, especially for multifocal tumors (130). Combinations of various loco-regional modalities seemed to be more effectively downstage the patients than TACE alone (15,131). Given the effects of various modalities, tumor necrotic rate would potentially be increased, however whether this would convert to survival benefit would require confirmation from further studies. The role of the combinations of therapies in the bridging or downstaging setting is still to be determined.

Conclusions

Different modalities had been use as bridging therapies for LT so to decrease the number of drop out rate. At the same time, effective downstaging therapies allowed more patients to be put into transplant waiting list as long as the diseases are remained stable and within the criteria. Combine different modalities could be effective in achieve these goals. However, identification of tumors that would respond to the therapies, and therefore allowed better selection of the patients to be transplanted would benefit a more long term outcome.

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Footnote

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References

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-17.
2. Kim do Y, Han KH. Epidemiology and surveillance of hepatocellular carcinoma. Liver Cancer 2012;1:2-14.
3. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide

burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
4. Hong Kong Cancer Registry [Internet]. 2012. Available online: www3.ha.org.hk › cancereg
5. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. Annals of surgery 1999;229:322-30.
6. Fong Y, Sun RL, Jarnagin W, et al. An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg 1999;229:790-9; discussion 9-800.
7. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
8. Lee KK, Kim DG, Moon IS, et al. Liver transplantation versus liver resection for the treatment of hepatocellular carcinoma. J Surg Oncol 2010;101:47-53.
9. Ito T, Takada Y, Ueda M, et al. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. Liver Transpl 2007;13:1637-44.
10. Tamura S, Sugawara Y, Kokudo N. Living donor liver transplantation for hepatocellular carcinoma: the Japanese experience. Oncology 2011;81 Suppl 1:111-5.
11. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
12. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-403.
13. Lo CM, Fan ST, Liu CL, et al. The role and limitation of living donor liver transplantation for hepatocellular carcinoma. Liver Transpl 2004;10:440-7.
14. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
15. Yao FY, Hirose R, LaBerge JM, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. Liver Transpl 2005;11:1505-14.
16. Ravaioli M, Grazi GL, Piscaglia F, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant 2008;8:2547-57.
17. Bova V, Miraglia R, Maruzzelli L, et al. Predictive factors of downstaging of hepatocellular carcinoma beyond the Milan criteria treated with intra-arterial therapies. Cardiovasc Intervent Radiol 2013;36:433-9.
18. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl 2002;8:765-74.
19. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434-40.
20. Yao FY, Bass NM, Nikolai B, et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. Liver Transpl 2003;9:684-92.
21. Yamashiki N, Gaynor JJ, Kato T, et al. Competing risks analysis of predictors of delisting owing to tumor progression in liver transplant candidates with hepatocellular carcinoma. Am J Transplant 2004;4:774-81.
22. Washburn K, Edwards E, Harper A, et al. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. Am J Transplant 2010;10:1643-8.
23. Chan SC, Sharr WW, Chok KS, et al. Wait and transplant for stage 2 hepatocellular carcinoma with deceased-donor liver grafts. Transplantation 2013;96:995-9.
24. Llovet JM, Mas X, Aponte JJ, et al. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. Gut 2002;50:123-8.
25. Yao FY, Bass NM, Nikolai B, et al. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. Liver Transpl 2002;8:873-83.
26. Otto G, Schuchmann M, Hoppe-Lotichius M, et al. How to decide about liver transplantation in patients with hepatocellular carcinoma: size and number of lesions or response to TACE? J Hepatol 2013;59:279-84.
27. Cheung TT, Ho CL, Lo CM, et al. 11C-acetate and 18F-FDG PET/CT for clinical staging and selection of patients with hepatocellular carcinoma for liver transplantation on the basis of Milan criteria: surgeon's perspective. J Nucl Med 2013;54:192-200.
28. Cheung TT, Chan SC, Ho CL, et al. Can positron emission tomography with the dual tracers [11 C]acetate and [18 F]fludeoxyglucose predict microvascular invasion in hepatocellular carcinoma? Liver Transpl 2011;17:1218-25.
29. Sala M, Fuster J, Llovet JM, et al. High pathological risk

of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transpl 2004;10:1294-300.
30. Belghiti J, Cortes A, Abdalla EK, et al. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003;238:885-92; discussion 892-3.
31. Del Gaudio M, Ercolani G, Ravaioli M, et al. Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of Bologna experience. Am J Transplant 2008;8:1177-85.
32. Facciuto ME, Koneru B, Rocca JP, et al. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol 2008;15:1383-91.
33. Liu F, Wei Y, Wang W, et al. Salvage liver transplantation for recurrent hepatocellular carcinoma within UCSF criteria after liver resection. PloS One 2012;7:e48932.
34. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-82.
35. Fan ST. Liver functional reserve estimation: state of the art and relevance for local treatments: the Eastern perspective. J Hepatobiliary Pancreat Sci 2010;17:380-4.
36. Bleibel W, Caldwell SH, Curry MP, et al. Peripheral platelet count correlates with liver atrophy and predicts long-term mortality on the liver transplant waiting list. Transpl Int 2013;26:435-42.
37. Earl TM, Chapman WC. Hepatocellular carcinoma: resection versus transplantation. Semin Liver Dis 2013;33:282-92.
38. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
39. Blum HE. Hepatocellular carcinoma: therapy and prevention. World J Gastroenterol 2005;11:7391-400.
40. Bruix J, Sherman M, Practice Guidelines Committee AAftSoLD. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
41. Majno PE, Adam R, Bismuth H, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997;226:688-701; discussion 701-3.
42. Golfieri R, Cappelli A, Cucchetti A, et al. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) hepatocellular carcinomas. Hepatology 2011;53:1580-9.
43. Harnois DM, Steers J, Andrews JC, et al. Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. Liver Transpl Surg 1999;5:192-9.
44. Hayashi PH, Ludkowski M, Forman LM, et al. Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation. Am J Transplant 2004;4:782-7.
45. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. Liver Transpl 2003;9:557-63.
46. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, et al. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. Liver Transpl 2005;11:767-75.
47. Oldhafer KJ, Chavan A, Fruhauf NR, et al. Arterial chemoembolization before liver transplantation in patients with hepatocellular carcinoma: marked tumor necrosis, but no survival benefit? J Hepatol 1998;29:953-9.
48. Spreafico C, Marchiano A, Regalia E, et al. Chemoembolization of hepatocellular carcinoma in patients who undergo liver transplantation. Radiology 1994;192:687-90.
49. Roayaie S, Frischer JS, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. Ann Surg 2002;235:533-9.
50. Ravaioli M, Grazi GL, Ercolani G, et al. Partial necrosis on hepatocellular carcinoma nodules facilitates tumor recurrence after liver transplantation. Transplantation 2004;78:1780-6.
51. Allard MA, Sebagh M, Ruiz A, et al. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome after liver resection or transplantation? J Hepatol 2015;63:83-92.
52. Yao FY, Kinkhabwala M, LaBerge JM, et al. The impact of pre-operative loco-regional therapy on outcome after liver transplantation for hepatocellular carcinoma. Am J Transplant 2005;5:795-804.
53. Otto G, Herber S, Heise M, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. Liver

Transpl 2006;12:1260-7.
54. Pérez Saborido B, Meneu JC, Moreno E, et al. Is transarterial chemoembolization necessary before liver transplantation for hepatocellular carcinoma? Am J Surg 2005;190:383-7.
55. Maleux G, van Malenstein H, Vandecaveye V, et al. Transcatheter chemoembolization of unresectable hepatocellular carcinoma: current knowledge and future directions. Dig Dis 2009;27:157-63.
56. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46:474-81.
57. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010;33:41-52.
58. Lewis AL, Taylor RR, Hall B, et al. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006;17:1335-43.
59. Sacco R, Bargellini I, Bertini M, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol 2011;22:1545-52.
60. Nicolini D, Svegliati-Baroni G, Candelari R, et al. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. World J Gastroenterol 2013;19:5622-32.
61. Rhim H, Goldberg SN, Dodd GD 3rd, et al. Essential techniques for successful radio-frequency thermal ablation of malignant hepatic tumors. Radiographics 2001;21 Spec No:S17-35; discussion S36-9.
62. Lam VW, Ng KK, Chok KS, et al. Safety and efficacy of radiofrequency ablation for periductal hepatocellular carcinoma with intraductal cooling of the central bile duct. J Am Coll Surg 2008;207:e1-5.
63. Machi J, Uchida S, Sumida K, et al. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. J Gastrointest Surg 2001;5:477-89.
64. Lu DS, Raman SS, Limanond P, et al. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. J Vasc Interv Radiol 2003;14:1267-74.
65. Fontana RJ, Hamidullah H, Nghiem H, et al. Percutaneous radiofrequency thermal ablation of hepatocellular carcinoma: a safe and effective bridge to liver transplantation. Liver Transpl 2002;8:1165-74.
66. Brillet PY, Paradis V, Brancatelli G, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma before liver transplantation: a prospective study with histopathologic comparison. AJR Am J Roentgenol 2006;186:S296-305.
67. Lu DS, Yu NC, Raman SS, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. Hepatology 2005;41:1130-7.
68. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg 2004;240:900-9.
69. Pompili M, Mirante VG, Rondinara G, et al. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. Liver Transpl 2005;11:1117-26.
70. Cucchetti A, Cescon M, Bigonzi E, et al. Priority of candidates with hepatocellular carcinoma awaiting liver transplantation can be reduced after successful bridge therapy. Liver Transpl 2011;17:1344-54.
71. Belghiti J, Carr BI, Greig PD, et al. Treatment before liver transplantation for HCC. Ann Surg Oncol 2008;15:993-1000.
72. Tsuchiya K, Asahina Y, Tamaki N, et al. Risk factors for exceeding the Milan criteria after successful radiofrequency ablation in patients with early-stage hepatocellular carcinoma. Liver Transpl 2014;20:291-7.
73. Rhim H, Lim HK, Kim YS, et al. Hemobilia after radiofrequency ablation of hepatocellular carcinoma. Abdom Imaging 2007;32:719-24.
74. Bertot LC, Sato M, Tateishi R, et al. Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol 2011;21:2584-96.
75. Loh KB, Bux SI, Abdullah BJ, et al. Hemorrhagic cardiac tamponade: rare complication of radiofrequency ablation of hepatocellular carcinoma. Korean J Radiol 2012;13:643-7.
76. de Baère T, Risse O, Kuoch V, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. AJR Am J Roentgenol 2003;181:695-700.
77. Mulier S, Mulier P, Ni Y, et al. Complications of radiofrequency coagulation of liver tumours. Br J Surg 2002;89:1206-22.

78. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics 2005;25 Suppl 1:S69-83.
79. Ishikawa M, Ikeyama S, Sasaki K, et al. Intraoperative microwave coagulation therapy for large hepatic tumors. J Hepatobiliary Pancreat Surg 2000;7:587-91.
80. Yu NC, Raman SS, Kim YJ, et al. Microwave liver ablation: influence of hepatic vein size on heat-sink effect in a porcine model. J Vasc Interv Radiol 2008;19:1087-92.
81. Lubner MG, Brace CL, Hinshaw JL, et al. Microwave tumor ablation: mechanism of action, clinical results, and devices. J Vasc Interv Radiol 2010;21:S192-203.
82. Dong B, Liang P, Yu X, et al. Percutaneous sonographically guided microwave coagulation therapy for hepatocellular carcinoma: results in 234 patients. AJR Am J Roentgenol 2003;180:1547-55.
83. Liang P, Dong B, Yu X, et al. Prognostic factors for survival in patients with hepatocellular carcinoma after percutaneous microwave ablation. Radiology 2005;235:299-307.
84. Lu MD, Chen JW, Xie XY, et al. Hepatocellular carcinoma: US-guided percutaneous microwave coagulation therapy. Radiology 2001;221:167-72.
85. Shibata T, Iimuro Y, Yamamoto Y, et al. Small hepatocellular carcinoma: comparison of radio-frequency ablation and percutaneous microwave coagulation therapy. Radiology 2002;223:331-7.
86. Lu MD, Xu HX, Xie XY, et al. Percutaneous microwave and radiofrequency ablation for hepatocellular carcinoma: a retrospective comparative study. J Gastroenterol 2005;40:1054-60.
87. Zanus G, Boetto R, Gringeri E, et al. Microwave thermal ablation for hepatocarcinoma: six liver transplantation cases. Transplant Proc 2011;43:1091-4.
88. Lee KF, Hui JW, Cheung YS, et al. Surgical ablation of hepatocellular carcinoma with 2.45-GHz microwave: a critical appraisal of treatment outcomes. Hong Kong Med J 2012;18:85-91.
89. Liang P, Yu J, Lu MD, et al. Practice guidelines for ultrasound-guided percutaneous microwave ablation for hepatic malignancy. World J Gastroenterol 2013;19:5430-8.
90. Davalos RV, Mir IL, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng 2005;33:223-31.
91. Charpentier KP, Wolf F, Noble L, et al. Irreversible electroporation of the liver and liver hilum in swine. HPB (Oxford) 2011;13:168-73.
92. Cheng RG, Bhattacharya R, Yeh MM, et al. Irreversible Electroporation Can Effectively Ablate Hepatocellular Carcinoma to Complete Pathologic Necrosis. J Vasc Interv Radiol 2015;26:1184-8.
93. Lencioni R, Crocetti L, De Simone P, et al. Loco-regional interventional treatment of hepatocellular carcinoma: techniques, outcomes, and future prospects. Transpl Int 2010;23:698-703.
94. Sato K, Lewandowski RJ, Bui JT, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. Cardiovasc Intervent Radiol 2006;29:522-9.
95. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol 2006;17:1251-78.
96. Iñarrairaegui M, Pardo F, Bilbao JI, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol 2012;38:594-601.
97. Sangro B, Salem R, Kennedy A, et al. Radioembolization for hepatocellular carcinoma: a review of the evidence and treatment recommendations. Am J Clin Oncol 2011;34:422-31.
98. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9:1920-8.
99. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140:497-507.e2.
100. Tohme S, Sukato D, Chen HW, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. J Vasc Interv Radiol 2013;24:1632-8.
101. Pracht M, Edeline J, Lenoir L, et al. Lobar hepatocellular carcinoma with ipsilateral portal vein tumor thrombosis treated with yttrium-90 glass microsphere radioembolization: preliminary results. Int J Hepatol 2013;2013:827649.
102. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl 2015;21:1142-52.
103. Salem R, Lewandowski RJ, Mulcahy MF, et al.

Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138:52-64.
104. Salem R, Thurston KG. Radioembolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. J Vasc Interv Radiol 2006;17:1425-39.
105. Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. J Vasc Interv Radiol 2009;20:1121-30; quiz 31.
106. Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology 2010;52:1741-9.
107. Chan AO, Yuen MF, Hui CK, et al. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. Cancer 2002;94:1747-52.
108. Naymagon S, Warner RR, Patel K, t al. Gastroduodenal ulceration associated with radioembolization for the treatment of hepatic tumors: an institutional experience and review of the literature. Dig Dis Sci 2010;55:2450-8.
109. Carretero C, Munoz-Navas M, Betes M, et al. Gastroduodenal injury after radioembolization of hepatic tumors. Am J Gastroenterol 2007;102:1216-20.
110. Dubinsky TJ, Cuevas C, Dighe MK, et al. High-intensity focused ultrasound: current potential and oncologic applications. AJR Am J Roentgenol 2008;190:191-9.
111. Wu F, Wang ZB, Chen WZ, et al. Advanced hepatocellular carcinoma: treatment with high-intensity focused ultrasound ablation combined with transcatheter arterial embolization. Radiology 2005;235:659-67.
112. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of patients with large hepatocellular carcinoma. Ann Surg Oncol 2004;11:1061-9.
113. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal high intensity focused ultrasound ablation in the treatment of 1038 patients with solid carcinomas in China: an overview. Ultrason Sonochem 2004;11:149-54.
114. Wu F, Wang ZB, Chen WZ, et al. Extracorporeal focused ultrasound surgery for treatment of human solid carcinomas: early Chinese clinical experience. Ultrasound Med Biol 2004;30:245-60.
115. Ng KK, Poon RT, Chan SC, et al. High-intensity focused ultrasound for hepatocellular carcinoma: a single-center experience. Ann Surg 2011;253:981-7.
116. Cheung TT, Chu FS, Jenkins CR, et al. Tolerance of high-intensity focused ultrasound ablation in patients with hepatocellular carcinoma. World J Surg 2012;36:2420-7.
117. Cheung TT, Chok KS, Lo RC, et al. High-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients awaiting liver transplantation. Hepatobiliary Pancreat Dis Int 2012;11:542-4.
118. Chok KS, Cheung TT, Lo RC, et al. Pilot study of high-intensity focused ultrasound ablation as a bridging therapy for hepatocellular carcinoma patients wait-listed for liver transplantation. Liver Transpl 2014;20:912-21.
119. Cheung TT, Fan ST, Chan SC, et al. High-intensity focused ultrasound ablation: an effective bridging therapy for hepatocellular carcinoma patients. World J Gastroenterol 2013;19:3083-9.
120. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26:657-64.
121. Eriguchi T, Takeda A, Sanuki N, et al. Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. Int J Radiat Oncol Biol Phys 2013;85:1006-11.
122. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e447-53.
123. Katz AW, Chawla S, Qu Z, et al. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. Int J Radiat Oncol Biol Phys 2012;83:895-900.
124. O'Connor JK, Trotter J, Davis GL, et al. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl 2012;18:949-54.
125. Dawson LA, Normolle D, Balter JM, et al. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002;53:810-21.
126. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
127. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
128. Vitale A, Volk ML, Pastorelli D, et al. Use of sorafenib

in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety. Hepatology 2010;51:165-73.
129. Hoffmann K, Glimm H, Radeleff B, et al. Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation - HeiLivCa [ISRCTN24081794]. BMC Cancer 2008;8:349.
130. Bhoori S, Sposito C, Germini A, et al. The challenges of liver transplantation for hepatocellular carcinoma on cirrhosis. Transpl Int 2010;23:712-22.
131. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013;31:426-32.

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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-dimentional 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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References

1. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines:

management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
2. Bosch FX, Ribes J. Epidemiology of liver cancer in Europe. Can J Gastroenterol 2000;14:621-30.
3. de Graaf W, van Lienden KP, Dinant S, et al. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. J Gastrointest Surg 2010;14:369-78.
4. Cieslak KP, Runge JH, Heger M, et al. New Perspectives in the Assessment of Future Remnant Liver. Dig Surg 2014;31:255-68.
5. Garcea G, Ong SL, Maddern GJ. Predicting liver failure following major hepatectomy. Dig Liver Dis 2009;41:798-806.
6. Kokudo N, Vera DR, Makuuchi M. Clinical application of TcGSA. Nucl Med Biol 2003;30:845-9.
7. Kwon AH, Ha-Kawa SK, Uetsuji S, et al. Use of technetium 99m diethylenetriamine-pentaacetic acid-galactosyl-human serum albumin liver scintigraphy in the evaluation of preoperative and postoperative hepatic functional reserve for hepatectomy. Surgery 1995;117:429-34.
8. Beppu T, Hayashi H, Okabe H, et al. Liver functional volumetry for portal vein embolization using a newly developed 99mTc-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system. J Gastroenterol 2011;46:938-43.
9. Iimuro Y, Kashiwagi T, Yamanaka J, et al. Preoperative estimation of asialoglycoprotein receptor expression in the remnant liver from CT/99mTc-GSA SPECT fusion images correlates well with postoperative liver function parameters. J Hepatobiliary Pancreat Sci 2010;17:673-81.
10. Satoh K, Yamamoto Y, Nishiyama Y, et al. 99mTc-GSA liver dynamic SPECT for the preoperative assessment of hepatectomy. Ann Nucl Med 2003;17:61-7.
11. de Graaf W, van Lienden KP, van Gulik TM, et al. (99m)Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. J Nucl Med 2010;51:229-36.
12. de Graaf W, van Lienden KP, van den Esschert JW, et al. Increase in future remnant liver function after preoperative portal vein embolization. Br J Surg 2011;98:825-34.
13. Du S, Mao Y, Tong J, et al. A novel liver function evaluation system using radiopharmacokinetic modeling of technetium-99m-DTPA-galactosyl human serum albumin. Nucl Med Commun 2013;34:893-9.
14. Mao Y, Du S, Ba J, et al. Using Dynamic 99mT c-GSA SPECT/CT Fusion Images for Hepatectomy Planning and Postoperative Liver Failure Prediction. Ann Surg Oncol 2015;22:1301-7.

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Individualized multidisciplinary treatment options for hepatocellular carcinoma in the department of liver surgery: experiences in Xiangya Hospital of Central South University

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Abstract: Hepatocellular carcinoma (HCC) is a highly heterogeneous disease. Genomic and morphological heterogeneity has been well identified in HCC. The overall survival (OS) of HCC patients after hepatic resection (HR) is heterogeneous. The histology-based definition of the morphological heterogeneity of HCC has been modified and refined to treat patients with targeted therapies, but this still cannot solve all the problems. In addition, recent advances in genomic medicine have enhanced the understanding of genetic and epigenetic events occurring in HCC, raising the possibility of personalizing targeted agents in accordance with the genetic make-up of the tumors. In this review article, we aim to give a summary of the recent the development of individualized multidisciplinary treatment for HCC.

Keywords: Hepatocellular carcinoma (HCC); tumor heterogeneous; multidisciplinary treatment

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and also the second most frequent cause of cancer-related death worldwide. Each year more than 50% of new HCC cases and deaths occur in China (466,000 and 422,000, respectively) (1,2). To date, a variety of treatments including surgical resection, radiofrequency ablation, transcatheter arterial chemoembolization (TACE), molecular targeted therapy (sorafenib), and radiotherapy have been developed for HCC. Nevertheless, surgical resection remains the treatment of choice for HCC (3,4). Unfortunately, the overall survival (OS) rate of HCC patients has not been substantially improved over the past two decades (5), which may be mainly explained by the fact that HCC is an extremely invasive and metastatic cancer. Thus, prevention of metastasis and recurrence has become a key strategy in improving the postoperative OS of HCC. How to improve the efficacy of HCC treatment is a common challenge for all countries across the world. HCC is a heterogeneous tumor, with its etiologies being remarkably different globally (for instance, it is mainly caused by hepatitis C virus infection and alcoholic liver disease in Western countries), which may lead to even more complicated prognosis and treatment options (5,6). Currently, multidisciplinary team (MDT) for tumors has become a popular mode for the clinical treatment of tumors both as home and abroad, and the establishment of MDT may help to achieve the optimal individualized treatment of HCC.

MDT establishes individualized treatment protocol for HCC patients

An MDT typically is a group of professionals from two or more disciplines (usually more than two) to provide diagnosis and treatment advices on the disease of a specific

organ or on a systemic disease via regular meetings. Based on the experiences in MDT establishment and combined therapies in China and abroad (especially, surgery is the optimal treatment for HCC (7-10), we established an MDT in the Department of Liver Cancer Surgery: with a surgeon as the leader, professionals from different departments including departments of tumor chemotherapy, radiotherapy, interventional radiology, sonography, radiology, pathology, and infectious diseases are invited to provide the optimal treatment protocol for patients with advanced HCC via case discussions and regular meetings, followed by the implementation of the protocol by all the relevant departments separately or jointly. The MDT members gather on a quarterly basis to discuss and analyze the collected complex cases to form preliminary recommendations for diagnosis and treatment; then, the primary care physician will be responsible for contact the relevant departments to coordinate and arrange the subsequent treatment for the patients. In addition, the MDT members are arranged to attend seminars and workshops in relevant departments quarterly to learn the cutting-edge technologies and recent advances in therapeutic methods. The in-depth exchanges and close cooperation among multiple disciplines have enabled a full integration of HCC diagnosis and treatment theories, technologies, and experiences. Based on the currently available technologies and treatments, the MDT can provide individualized treatment for each patient, thus ensuring each HCC patient can get the optimal individualized diagnosis and treatment protocol and high-quality medical services.

Introduction of the concept of precise hepatectomy

Along with the advances in liver surgical techniques, the obstacles in HCC resection have been broken down one by one, and various hepatic segmentectomy can be smoothly performed. At present, with the developments in the liver surgery techniques, there is no more “forbidden zone” for traditional surgery and laparoscopic liver resection. Surgery-based multidisciplinary treatment remains the mainstream treatment for HCC (11). Anatomical resection is particularly important for liver tumors. Precision hepatectomy is the ultimate goal of liver surgery. Evaluation of liver reserve function combined with computer-aided comprehensive measurement of liver volume can provide reliable information for determining the safe and permissible limits of hepatectomy (12). Before a liver surgery, assessment for tolerance should be performed firstly, along with assessment of hepatic reserve function (ICG clearance test). By using the three-dimensional (3D) imaging technology, the doctors should have a thorough understanding of the anatomical variations of liver; meanwhile, the residual liver volume and the resected normal liver volume should be calculated by using the 3D simulation module of this software, so as to evaluate the safety of surgical resection. Finally, an appropriate surgical plan is developed (13). During the operation, the satellite lesions in liver parenchyma can be detected by ultrasound, and any injury to the major hepatic duct structures should be avoided. After the measurements, anatomical hepatectomy should be performed with an adequate distance from the outermost edge of the tumor to achieve radical resection. In addition, after localization of the lesion with intraoperative ultrasound, regional vascular occlusion at hepatic hila can reduce the time of normal hepatic ischemia during surgery and control intraoperative bleeding; thus, it can maximize the preservation of liver function and promote postoperative recovery.

Comprehensive application of hepatectomy and its role in rapid rehabilitation following liver resection

According to the concept of modern precision surgery, a liver resection not only requires satisfactory effectiveness but also needs to control intraoperative bleeding and ensure the stabilization of liver function during and after operation. Thus, a right hepatic portal occlusion procedure should be selected for each operation. For hemi-hepatectomy, the first and the second hepatic hilum should be selected, if possible for selective hepatic vascular occlusion. The third hepatic hilum can also be dissected to reduce intraoperative hepatic venous bleeding. Some short hepatic veins can be ligated. Or, prophylactic banding of the superior and inferior vena cava may be performed. Alternatively, by using the liver hanging maneuver, the doctor can lift the liver before or near the inferior vena cava, so as to reduce hepatic vein hemorrhage. Compared with the Pringle maneuver, selective hepatic vascular occlusion can remarkably alleviate the hepatic ischemia-reperfusion injury and thus is particularly valuable for patients with liver dysfunction and small residual functional liver volume after liver resection (9). During hepatic lobectomy or hepatectomy, hepatic inflow occlusion following the dissection of Glissonean pedicle can be performed under the guidance of intraoperative ultrasound. By doing so, we

can both effectively control the intraoperative bleeding and ensure the perfusion of healthy liver, thus maximizing the preservation of liver function. Resection approaches include clamping and snip-electrocoagulation, in combination with high-intensity focused ultrasound (HIFU), bipolar electrocoagulation, and cavitational ultrasonic surgical aspiration (CUSA). After the surgery, the patients should be monitored regularly to assess for liver function and general condition, so as to determine the postoperative recovery. Timely and appropriate postoperative treatment can decrease perioperative mortality, reduce postoperative complications, promote rapid recovery of patients, and shorten hospital stay. Early withdrawal of drainage tube, nasal catheter, and urinary catheter can help the patients to get out of bed as soon as possible, reduce the risk of deep vein thrombosis of lower limbs, promote the recovery of gastrointestinal function, and thus allow rapid resumption of oral feeding. Appropriate postoperative analgesia can reduce the pain during recovery and thus promote adequate rest and maintain sufficient energy. In summary, the integration of precision liver surgery with perioperative Enhanced Recovery After Surgery (ERAS) can both ensure the effectiveness of surgical treatment of liver cancer and promote the rapid and safe recovery after operation. Thus, attention must be paid to its role in liver resection.

Surgical treatment of HCC with portal vein tumor thrombus (PVTT)

PVTT is a common lesion associated with advanced HCC. Patients with HCC with PVTT often have various unfavorable features such as early intrahepatic dissemination of tumors, early treatment failure, and deterioration of liver function, and the treatment outcomes are often far from satisfactory (14). Some authors have classified PVTT into three types: type A (tumor thrombi involving the main portal vein trunk); type B (tumor thrombi involving right/left portal vein); and type C (tumor thrombi involving segmental branches of portal vein or above). After the combined treatment with HR and TACE, the OS of patients with type B/C PVTT was 57%, which was significantly higher than that (13%) of TACE alone group. In patients with type A PVTT, however, the response rate showed no significant difference between the combination group and TACE alone group (8). In a previous study, HCC with PVTT was regarded as a surgical contraindication, and only conservative treatment was given; however, the efficacy of systemic chemotherapy was poor, with an average survival time of only 3.9 months; furthermore, regional chemotherapy also only yielded an average survival time of 9.2 months (15). For HCC patients with PVTT, hepatic resection (HR) is the only possible way to completely remove the tumor from the liver parenchyma and portal vein, and can reduce the burden of the tumor and the risk of intrahepatic metastases; also, it can lower portal vein pressure, reduce complications caused by portal hypertension, and improve liver function; finally, after the tumor is removed, it provides opportunities and conditions for further multidisciplinary treatment (16). With the development of surgical techniques, the safety of surgical operations has constantly being improved, and the superiority of surgical treatment over conservative treatment has increasingly been recognized. However, the effectiveness of surgical treatment alone in treating HCC with PVTT is not satisfactory. Although PVTT is no longer a surgical contraindication and it is safe and feasible to perform HR, there is no significant improvement in the outcomes. Thus, the surgical treatment should be carefully selected and tailored. The advances in MDT treatment and precision medicine will further improve the holistic treatment of HCC.

Highly selective application of two-stage hepatectomy

Based on the deeper understanding of liver anatomy, Schkitt firstly reported the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) (17). ALPPS is based on the following principle: the regeneration of the liver requires the portal vein blood flow that is rich in liver regeneration factors; selective transection of the portal vein at one side can adjust/change hepatic inflow and promote the regeneration of future liver remnant (FLR). Thus, some HCC patients who were traditionally regarded as inoperable now have a chance of surgical treatment and may avoid postoperative liver failure. The concept of ALPPS has been widely recognized. The ALPPS procedure is considered to be a revolutionary breakthrough in surgical strategy or liver technology (18). It is suitable not only for radical resection of metastatic liver cancer but also for HCC and cholangiocarcinoma. At the first step of the operation, the left and right livers need to be split *in situ*; for patients with preexisting chronic liver disease, it can easily cause complications such as abnormal liver function, liver failure, or severe infections. As a result, the perioperative morbidity and mortality rates can be high in patients who have

undergone ALPPS, and the perioperative deaths are mainly caused by postoperative bile leakage and infections (19). Therefore, different surgical instruments should be used in a standard and reasonable manner during dissection, hepatectomy, hemostasis, and management of bile leakage, so as to give full play to the advantages of these instruments. The superficial hepatic tissue is cut open by conventional electric knife, and the hepatic parenchyma is dissected by the alternate application of HIFU and electrocoagulation. Blood vessels and bile ducts should be ligated by using silk sutures of the corresponding thickness according to the lumen diameters. Hemostasis can be achieved by ligation with vascular sutures or electrocoagulation. Notably, once a bile duct is transected, it should be immediately ligated with vascular sutures to avoid postoperative bile leakage. ALPPS is a challenging procedure. The operator must be well trained and, particularly, have skills and experiences in living-donor liver transplantation (LDLT). This operation is suitable for primary hospitals. ALPPS is considered to be one of the most innovative techniques in hepatobiliary surgery in recent years and has become an important part of multidisciplinary treatment for advanced liver cancer. However, as a palliative treatment, its evidence level is still low from the perspective of evidence-based medicine. Its role in treating malignancies needs to be further validated in prospective randomized controlled trials with large sample sizes. Therefore, the development of this procedure has been accompanied by controversies.

Liver transplantation still plays a key role in liver cancer surgery

Liver transplantation has been one of the most effective ways for treating end-stage liver diseases. At present, liver transplantation has been performed nationwide. While shortage of donor organs is a worldwide problem, LDLT has become a mature technique in centers with rich experiences in liver transplantation (20). In 2007, the first case of LDLT in Hunan Province was successfully carried out in our center; since then, we have performed LDLT in more than ten patients. On February 10, 2007, we successfully performed the first case of LDLT using a sibling donor in China. In addition to informed consent, whether it is safe to harvest sufficient grafts and whether there is a risk of transmission of infection from donor to recipient should be carefully evaluated. Also, the donor must understand the whole process of LDLT and overcome any possible psychological effect. Generally, the age limit for LDLT is 18–60 years. In Western countries, liver donors must have a compatible blood type with the recipient. In Asian countries, however, due to the scarcity of donor organs, ABO-incompatible adult LDLT has achieved acceptable outcomes (21). For the safety of the donor, it is necessary to ensure that the donors have a remnant liver volume of no less than 30–35% of the estimated total liver volume, so as to avoid liver dysfunction, residual liver failure, and death; for the safety of the recipient, the graft-to-body weight ratio (GRBWR) shall be no less than 0.8%, so as to avoid small-for-size syndrome (SFSS) and early graft failure after surgery (22). However, low GRBWR may also be acceptable in patients with good performance status and mild portal hypertension.

For HCC patients undergoing liver transplantation, the recipients are typically selected based on the Hangzhou Criteria. Shortage of liver grafts for transplantation is a global problem, and the waiting time is often too long for many patients. Under such circumstance, downstaging of HCC may be performed before transplantation; that is, a series of treatment approaches are used to reduce the tumor burden, lower the stage, and thus ensure that the disease is well controlled within the transplant criteria. The downstaging therapy is mainly feasible for HCC patients who do not meet the current HCC transplantation criteria but have no large vascular (portal vein or inferior vena cava) invasion or distant metastasis (23,24). The methods of downstaging include surgery, local ablation, and TACE. The efficacy of the downstaging treatment can be evaluated by contrast-enhanced CT and MRI in combination with AFP measurement, and the assessment indicators include tumor size/number and AFP level. In addition, the combination of a variety of treatment methods can achieve better downstaging efficacy (25,26). Furthermore, for HCC patients with hepatitis B, antiviral treatment should be as initiated as early as possible before liver transplantation, hepatitis B immune globulin should be given during anhepatic phase, and the postoperative use of anti-HBV drugs can also prevent hepatitis B recurrence after transplantation. Immunosuppressive therapy and other appropriate therapies should be applied after liver transplantation to prevent tumor recurrence.

Alternative treatments for HCC

In addition to surgical treatment, many other treatments including radiotherapy, chemotherapy, ablation therapy (including radiofrequency, microwave, and cryoablation),

interventional therapy, and molecularly targeted therapy have also been widely used for HCC in different stages. The ablation is done via three approaches: percutaneous, laparoscopic, and open, and the treatment methods include chemical ablation (including intratumoral injection of anhydrous alcohol, acetic acid, etc.) and physical ablation (mainly includes radiofrequency ablation, microwave solidification, and cryoablation). In principle, ablation therapy is feasible for patients meeting the following criteria: Child-Pugh class A or B; without blood vessel, bile duct, and/or adjacent organ involvement; without distant metastasis; mass sized ≤5 cm (27). The patient's general condition and the tumor's biological behaviors should be thoroughly evaluated before ablation; imaging assessment should be fully performed, and appropriate imaging guidance pathway should be selected. Meanwhile, the whole treatment process should be monitored to ensure the safety and effectiveness of the ablation.

Liver biopsy may be performed before ablation, if necessary. Surgical patients routinely fast postoperatively, with their vital signs closely monitored for 4 hours. Patients should be bedridden for at least 6 hours, during which they should undergo examinations including routine blood tests and hepatic/renal function tests to avoid any infection. A second contrast-enhanced CT/MRI scans or contrast-enhanced liver ultrasound should be performed one month after ablation therapy to evaluate the ablation effectiveness. A second ablation treatment or other therapies may be applied for patients with residual tumor.

As a first-line non-radical treatment, TACE is the preferred and most effective treatment for inoperable advanced HCC (28). The main indications of TACE include: unresectable advanced HCC; after failed surgical treatment or for prevention of tumor recurrence; downstaging before tumor resection; and small liver cancer that is not suitable for surgery or the patient is unwilling to receive a surgery. After TACE treatment, if the tumor is unfeasible for surgical resection or if a combination with local ablation therapy is not feasible, a combination with sorafenib (a targeted therapy drug) may be considered to prolong TTP and OS (29,30). TACE is an effective treatment for patients with resectable HCC since it can remarkably improve the quality of life. Radiochemotherapy can also play an important role in the treatment of residual tumor and recurrence of HCC after surgery. In particular, radiotherapy can be applied for local recurrence on abdominal wall and in retroperitoneal and hilar areas. Survival benefit can also be obtained after radiotherapy combined with hepatic arterial chemotherapy in patients with advanced HCC (31). In addition, patients with hepatitis-associated HCC should complete antiviral treatment for a full treatment course. Strict and effective control of viral replication can reduce the incidence of liver cancer.

Pay attention to the results of histopathological examinations

At present, the improvement of HCC treatment is mainly due to the advances in diagnostic techniques. In particular, the development of imaging technology enables the early detection and radical treatment of some HCC cases. In MDT, the role of the department of pathology cannot be neglected. A detailed pathology report can help clinicians to judge the disease process and predict the prognosis, guide the clinicians to establish individualized subsequent treatment protocols, and thus provide the optimal health care service to each patient. At present, the pathology report in our hospital include the following items: number of tumor, tumor size, tumor type and differentiation, any satellite lesion, any capsular invasion, any microvascular invasion (MVI) (32,33), any tumor thrombus visible to the naked eyes, resection margin, liver tissues adjacent to the tumor, and immunohistochemical findings. After reading the pathology report, the clinicians can attend a second MDT meeting to decide the subsequent treatment protocol (including the need for interventional therapy, chemotherapy, radiotherapy, targeted therapy, etc.). MDT provides a chance for specialists from different departments to share their views and opinions to decide which approach can be used as the first-line treatment and whether a single treatment or a combination of multiple treatments should be applied in the subsequent management (34). In addition, the MDT model helps to establish a consultation and case discussion system, which can help the MDT members to expand their professional knowledge and accumulate valuable clinical experiences.

Conclusions

In summary, the role of MDT in the treatment of liver cancer has increasingly become important and has become an important part of the hospital health care system. The MDT model can ensure each HCC patient to get the optimal individualized diagnosis and treatment protocol and high-quality medical services. The exchanges and

discussions among specialists from different departments can help the MDT members to follow the HCC-related evidence-based guidelines and literature and thus help the clinicians to establish and optimize the standardized and individualized treatment protocols for HCC patients.

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Footnote

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: a cancer journal for clinicians 2015;65:5-29.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China,2015. CA Cancer J Clin 2016;66:115-32.
3. Roayaie S, Jibara G, Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-51.
4. El-Serag HB. Hepatocellular Carcinoma. N Engl J Med 2011;365:1118-27.
5. Nault JC, Villanueva A. Intratumor molecular and phenotypic diversity in hepatocellular carcinoma. Clin Cancer Res 2015;21:1786-8.
6. Friemel J, Rechsteiner M, Frick L, et al. Intratumor heterogeneity in hepatocellular carcinoma. Clin Cancer Res 2015;21:1951-61.
7. Maluccio M, Covey A. Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. CA Cancer J Clin 2012;62:394-9.
8. Barone C, Koeberle D, Metselaar H, et al. Multidisciplinary approach for HCC patients: hepatology for the oncologists. Ann Oncol 2013;24 Suppl 2:ii15-23.
9. Gish RG, Lencioni R, Di Bisceglie AM, et al. Role of the multidisciplinary team in the diagnosis and treatment of hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 2012;6:173-85.
10. Marrero JA. Multidisciplinary management of hepatocellular carcinoma:where are we today? Semin Liver Dis 2013;33 Suppl 1:S3-10.
11. Ulahannan SV, Duffy AG, McNeel TS, et al. Earlier presentation and application of curative treatments in hepatocellular carcinoma. Hepatology 2014;60:1637 -44.
12. Yoon JH, Choi JI, Jeong YY, et al. Pre-treatment estimation of future remnant liver function using gadoxetic acid MRI in patients with HCC. J Hepatol 2016;65:1155-62.
13. Fang CH, Tao HS, Yang J, et al. Impact of three-dimensional reconstruction technique in the operation planning of centrally located hepatocellular carcinoma. J Am Coll Surg 2015;220:28-37.
14. Chen JS, Wang Q, Chen XL, et al. Clinicopathologic characteristics and surgical outcomes of hepatocellular carcinoma with portal vein tumor thrombosis. J Surg Res 2012;175:243-50.
15. Wang HL, Cucchetti A, Zhong JH, et al. Should hepatic resection be recommended to patients with hepatocellular carcinoma and portal vein invasion? J Hepatol 2016;65:1057-8.
16. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
17. Clavien PA, Lillemoe KD. Associating liver partition and portal vein ligation for staged hepatectomy. Ann Surg 2016;263:835-6.
18. Schlegel A, Lesurtel M, Melloul E, et al. ALPPS: from human to mice highlighting accelerated and novel mechanisms of liver regeneration. Ann Surg 2014;260:839-46.
19. Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? Ann Surg 2012;256:e9.
20. Gordon EJ, Rodde J, Skaro A, et al. Informed consent for live liver donors:A qualitative, prospective study.J Hepatol 2015; 63:838-47.
21. Trotter JF, Everhart JE. Outcomes among living liver donors. Gastroenterology 2012;142:207-10.
22. Clavien PA, Lesurtel M, Bossuyt PM, et al. OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma:an international consensus conference report.Lancet Oncol 2012;13:e11-22.
23. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology 2004;127:S277-82.
24. Rummler S, Bauschke A, Baerthel E, et al. ABO-Incompatible Living Donor Liver Transplantation in Focus of Antibody Rebound. Transfus Med Hemother 2017; 44:46-51.
25. Bhangui P, Vibert E, Majno P, et al. Intention-to-treat analysis of liver transplantation for hepatocellular

carcinoma: living versus deceased donor transplantation. Hepatology 2011;53:1570-9.
26. Goldberg DS, French B, Abt PL, et al. Superior survival using living donors and donor-recipient matching using a novel living donor risk index. Hepatology 2014;60:1717-26.
27. Wang W, Zhao Y, Bai W, et al. Response assessment for HCC patients treated with repeated TACE: The optimal time-point is still an open issue. J Hepatol 2015;63: 1530-1.
28. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. J Hepatol 2016;64:1090-8.
29. Yau T, Tang VY, Yao TJ, et al. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014;146:1691-700.e3.
30. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol 2015;62:1187-95.
31. Barry A, Knox JJ, Wei AC, et al. Can stereotactic body radiotherapy effectively treat hepatocellular carcinoma? J Clin Oncol 2016;34:404-8.
32. Roayaie S, Blume IN, Thung SN, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology 2009;137:850-5.
33. Banerjee S, Wang DS, Kim HJ, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. Hepatology 2015;62:792-800.
34. Siddique O, Yoo ER, Perumpail RB, et al. The importance of a multidisciplinary approach to hepatocellular carcinoma. J Multidiscip Healthc 2017;10:95-100.

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Perioperative chemotherapy and hepatic resection for resectable colorectal liver metastases

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Abstract: The role of perioperative chemotherapy in the management of initially resectable colorectal liver metastases (CRLM) is still unclear. The EPOC trial [the European Organization for Research and Treatment of Cancer (EORTC) 40983] is an important study that declares perioperative chemotherapy as the standard of care for patients with resectable CRLM, and the strategy is widely accepted in western countries. Compared with surgery alone, perioperative FOLFOX therapy significantly increased progression-free survival (PFS) in eligible patients or those with resected CRLM. Overall survival (OS) data from the EPOC trial were recently published in *The Lancet Oncology*, 2013. Here, we discussed the findings and recommendations from the EORTC 40983 trial.

Keywords: Colorectal liver metastases (CRLM); perioperative chemotherapy; the European Organization for Research and Treatment of Cancer (EORTC) trial (40983)

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The high rate of recurrence in patients with colorectal liver metastases (CRLM) after curative resection remains an unsettled problem (1-3). The most probable explanation for these recurrences is the persistence of microscopic residual disease after surgery. To reduce postoperative recurrences, combining chemotherapy with resection for CRLM is of major interest.

EORTC 40983 (EPOC) trial and new EPOC trial

The European Organization for Research and Treatment of Cancer (EORTC) intergroup trial 40983 (EPOC) clearly demonstrated that perioperative FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) therapy (six cycles before surgery and six cycles after) significantly increased progression-free survival (PFS) compared with surgery alone in eligible patients or those with resected liver-only CRLM (4). The trial was registered with ClinicalTrials.gov, number NCT00006479. The absolute increase in the rate of PFS at 3 years was 7.3% (from 28.1% to 35.4%, HR 0.79; P=0.058) in randomized patients; 8.1% (from 28.1% to 36.2%, HR 0.77; P=0.041) in eligible patients; and 9.2% (from 33.2% to 42.4%, HR 0.73; P=0.025) in patients who underwent hepatic resection. Thereafter, perioperative chemotherapy became the standard of care for patients with resectable CRLM, especially in western countries (5).

The overall survival (OS) data from the EPOC trial were published in *The Lancet Oncology* in 2013 (1). After a median follow-up of 8.5 years, OS in all randomly assigned patients did not differ significantly between groups (HR 0.88, P=0.34) or among eligible patients (HR 0.87, P=0.30). In intention-to-treat analysis, median overall survival (MST) was 61.3 and 54.3 months in the perioperative chemotherapy and surgery alone groups, respectively. In all randomized patients, the absolute difference between groups in the proportion of patients with 5-year OS was 3.4%; in all eligible patients it was 4.1%. However, a greater proportion of eligible patients were alive at 5 years (50/182) in the perioperative chemotherapy group than in the surgery alone group (42/182). Two reasons can be posited

to explain the lack of any significant advantage in OS. First, this trial was designed to detect a PFS benefit; therefore, any findings regarding OS constituted a secondary endpoint. Second, the positive long-term outcome in the surgery-only group (MST 73.3 months) proved that demonstrating a treatment benefit for perioperative chemotherapy was more difficult. The 4.1% absolute survival benefit at 5 years in the eligible population was similar to other positive adjuvant trials in stage II or III primary colorectal cancer (1). The MOSAIC trial (6) actually reported a 4.2% OS benefit at 6 years of follow-up. The sample size of 364 (Remark 4) was insufficient to detect a significant difference in OS compared with a relatively large sample size of 1,347 patients with stage II or III colon cancer. In the future, such large numbers of patients will be impossible to enroll in clinical trials entailing resectable CRLM (1).

A new EPOC trial (ISRCTN22944367) was registered to assess whether the combination treatment of cytotoxic chemotherapy with targeted agents could improve the outcome (7). However, the addition of cetuximab to FOLFOX and surgery for patients with resectable CRLM in KRAS exon 2 wild-type resulted in significantly shorter PFS compared with the FOLFOX and surgery group (14.1 *vs*. 20.5 months, HR 1.48; P=0.030).

Perioperative chemotherapy for resectable CRLM in the future

The advantages of preoperative chemotherapy for resectable CRLM include the ability to check chemo-responsiveness before hepatectomy, elimination of micrometastasis, and tumor shrinkage for R0 resection (1,5,8); the disadvantages include unresectable tumor progression, hepatic toxicity that increases morbidity/mortality, and missing tumors by complete radiological response (Remark 5) (1,5,8,9). Although certain tumors became unresectable in some patients with initially resectable CRLM, half of the progression occurred outside the liver. Thus, these patients would have received unnecessary hepatic resection (4). Considering that recurrences are frequently observed in approximately 75% of patients with CRLM, even after curative hepatic resection (3,10), further evaluation of perioperative chemotherapy is definitely required.

The EPOC study demonstrated no significant difference by the addition of perioperative chemotherapy to FOLFOX4 compared with surgery alone in OS for patients with CRLM. Previous clinical trials in a CRLM adjuvant setting were judged using disease-free survival (DFS) or PFS as the primary endpoint; the improvement of which cannot be seen as tantamount to a long-term survival benefit. Future progress in this area will probably have to rely on surrogate endpoints for OS. Oba and Hasegawa *et al*. (11) proposed a new composite endpoint, time to surgical failure (TSF), as a surrogate marker for OS after the resection of CRLM. Their research clearly demonstrated that the first recurrence after an initial hepatic resection does not reflect surgical failure or noncurability; if a surgical approach cannot be selected, any survival time beyond the recurrence is prolonged by appropriate chemotherapy. In contrast, re-resections for recurrences in the remnant liver have been accepted as providing a survival benefit (2,12). As shown by the high repeat resection rate (>40%) for patients with recurrence in the EORTC 40983 trial, the first recurrence-related event does not reflect long-term OS (4). Recently, we reported the predictive value for OS using the half-life of carcinoembryonic antigen (CEA) after induction chemotherapy for CRLM (13). After only three courses of chemotherapy (6 weeks) with oxaliplatin, when the patients in this study were divided into two groups according to the median value of 20 days, significant differences were detected not only in OS but also in the pathological response. The half-life of CEA is easily measured and can contribute to proper decision making, avoiding ineffective treatment.

After assessing long-term OS in the EPOC trial, adequate patient selection should be performed at the time of enrollment. Jones *et al*. (14) reported that patients with liver-only CRLM should be managed in three separate groups as follows: group one, those with easily resectable disease who should be offered immediate surgery followed by adjuvant therapy if considered appropriate; group two, those with borderline resectable or high recurrence risk CRLM who could be offered appropriate systemic neoadjuvant chemotherapy prior to planned liver surgery; and group three, those with unresectable but liver-only CRLM who should be offered the most effective systemic therapy with the primary purpose of achieving maximal disease response with the intention of conversion to curative hepatic resection. An exploratory retrospective analysis (EORTC study 40983) involving perioperative FOLFOX was conducted to identify possibly predictive baseline factors that could prolong PFS (15). Perioperative FOLFOX seems to benefit in particular patients with resectable CRLM with elevated CEA (>5 ng/mL) when PS is unaffected, regardless of the number of liver metastases (1 *vs*. 2-4). Adam *et al*. demonstrated that preoperative chemotherapy does not seem to benefit the outcome of

patients with solitary metachronous CRLM (16).

We recently demonstrated a nomogram developed by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (HBPS) that predicted the DFS of CRLM patients treated with hepatic resection (3). A total of 727 patients with liver-only CRLM resected without chemotherapy were enrolled. This nomogram can easily calculate the median and yearly DFS rates from only six preoperative variables: synchronous metastases, 3 points; primary lymph node positive, 3 points; two to four tumors, 4 points and ≥5, 9 points; largest tumor diameter >5 cm, 2 points; extrahepatic metastasis at hepatectomy, 4 points; and preoperative carbohydrate antigen 19-9 level >100, 4 points. Estimated median DFS time was calculated as follows: >8.4 years for patients with 0 points, 1.9 years for 5 points, 1.0 year for 10 points; rates were lower than 0.6 years for patients with more than 10 points. The HBPS nomogram is a very useful tool for determining the likelihood of early recurrence and the necessity for perioperative chemotherapy. Patients with over 10 points may be good candidates for perioperative chemotherapy because their DFS is shorter than 1 year.

In Japan, the randomized phase II and III trial "JCOG0603" has been conducted to compare "hepatectomy alone" with "hepatectomy followed by adjuvant 12 courses of FOLFOX" as treatment in patients with curatively resected CRLM to improve survival with intensive chemotherapy (17). Subsequently, "EXPERT trial" is ongoing to evaluate the efficacy and the safety of surgery and perioperative chemotherapy for resectable liver-only and KRAS exon 2 wild-type CRLM patients. This randomized phase III trial compare "surgery plus perioperative 12 courses of FOLFOX plus cetuximab" and "surgery followed by mFOLFOX6 as adjuvant chemotherapy".

In conclusion, perioperative chemotherapy combined with hepatic resection should be tested because the recurrences occurred frequently even in curatively resected CRLM patients. Prospective clinical trials with adequate restriction of enrolled patients and surrogate markers for OS are strongly recommended to determine the optimal protocol.

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References

1. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.
2. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440-8.
3. Beppu T, Sakamoto Y, Hasegawa K, et al. A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci 2012;19:72-84.
4. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.
5. Adam R, De Gramont A, Figueras J, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist 2012;17:1225-39.
6. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109-16.
7. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol 2014;15:601-11.
8. Benoist S, Nordlinger B. The role of preoperative chemotherapy in patients with resectable colorectal liver metastases. Ann Surg Oncol 2009;16:2385-90.
9. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-72.
10. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer 1996;77:1254-62.
11. Oba M, Hasegawa K, Matsuyama Y, et al. Discrepancy between recurrence-free survival and overall survival in patients with resectable colorectal liver metastases: a

potential surrogate endpoint for time to surgical failure. Ann Surg Oncol 2014;21:1817-24.
12. Wicherts DA, de Haas RJ, Salloum C, et al. Repeat hepatectomy for recurrent colorectal metastases. Br J Surg 2013;100:808-18.
13. Nagai Y, Beppu T, Sakamoto Y, et al. Carcinoembryonic antigen half-life is an early predictor of therapeutic effects in induction chemotherapy for liver metastases from colorectal cancer. Anticancer Res 2014;34:5529-35.
14. Jones RP, Malik HZ, Fenwick SW, et al. Perioperative chemotherapy for resectable colorectal liver metastases: where now? Eur J Surg Oncol 2013;39:807-11.
15. Sorbye H, Mauer M, Gruenberger T, et al. Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). Ann Surg 2012;255:534-9.
16. Adam R, Bhangui P, Poston G, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? Ann Surg 2010;252:774-87.
17. Kanemitsu Y, Kato T, Shimizu Y, et al. A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone as treatment for liver metastasis from colorectal cancer: Japan Clinical Oncology Group Study JCOG0603. Jpn J Clin Oncol 2009;39:406-9.

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Perioperative chemotherapy for resectable colorectal hepatic metastases—What does the EORTC 40983 trial update mean?

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Abstract: The liver is the most common site of colorectal cancer metastasis. Although successful resection leads to durable overall survival (OS), local and distant recurrence is common. As a result, multidisciplinary strategies have been developed to decrease recurrence rates as well as increase the number of candidates for resection. A recent update to the European Organisation for Research and Treatment of Cancer (EORTC) Intergroup trial 40983 has been published comparing perioperative chemotherapy to surgery alone. This randomized trial initially demonstrated a benefit in progression free survival (PFS) with the administration of perioperative FOLFOX chemotherapy, albeit with an increased rate of complications. Although this led many investigators and clinicians to adopt the perioperative approach, the recent update failed to report any advantage in OS and therefore results in further controversy as to the role of perioperative systemic chemotherapy in the treatment of resectable colorectal hepatic metastases.

Keywords: Chemotherapy; colorectal neoplasms; liver neoplasms; neoplasm metastases

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Colorectal cancer (CRC) is the third most common cancer in the world with 1.4 million new cases in 2012 (1). Nearly 50% of patients present with or develop hepatic metastases during their lifetime. If complete surgical resection of these metastases can be performed, 5-year overall survival (OS) rates can be as high as 50%—an impressive achievement for a metastatic gastrointestinal malignancy (2,3). Unfortunately, only 15-20% of patients are initial candidates for resection and even after resection, recurrence rates are significant, both in the remaining liver as well as elsewhere (4).

This prompted interest in the use of adjuvant systemic chemotherapy to reduce these recurrence rates (similar to that used in stage 3 disease). In the 1990s, two prospective randomized trials attempted to address the role of adjuvant chemotherapy in the treatment of resected hepatic metastasis from CRC. In both studies, resected patients were randomized to 5-fluororacil/Leucovorin (5-FU/LV) for 6 months *vs*. observation. Unfortunately, both studies were plagued by poor accrual and were therefore closed. Subsequent pooled results from these studies demonstrated a small but statistically significant benefit to adjuvant 5-FU/LV after resection in regards to progression free survival (PFS) (HR: 1.39, 95% CI: 1.04-1.85, P=0.026) and OS (HR: 1.39, 95% CI: 1.00-1.93, P=0.046) (5). Since these results were pooled and failed to study more modern systemic agents such as oxaliplatin, irinotecan, and targeted therapies, the role of adjuvant chemotherapy after successful hepatic resection of metastatic CRC remained unclear.

In the early 2000s, Ychou *et al*. compared adjuvant 5-FU/LV to FOLFIRI (5-FU/LV and irinotecan) after complete resection of liver metastases from CRC. Patients in this study were randomized to receive 12 cycles of either regimen and there was no significant difference in disease free or overall survival (6). In addition, toxicity with the FOLFIRI regimen was significantly higher and therefore it has not been used in the adjuvant setting. Since this trial did not include a surgery-only arm, the specific question of whether there is role for adjuvant chemotherapy after resection of hepatic metastases from CRC was not addressed.

In the mid to late 2000s, interest in neoadjuvant strategies for potentially resectable hepatic metastases from CRC also emerged. The goals for neoadjuvant (and perioperative) systemic therapy included: (I) to convert patients from unresectable to resectable disease (7,8); and (II) to identify the best candidates for a curative treatment (9). In a recent issue of *Lancet Oncology*, the European Organisation for Research and Treatment of Cancer (EORTC) published their long-term results of the prospective randomized intergroup 40983 trial (EPOC) investigating the use of perioperative FOLFOX4 (folinic acid, fluorouracil, oxaliplatin) in patients with resectable colorectal hepatic metastases. This trial enrolled 364 patients with resectable hepatic metastases and primary tumor, if not already removed, who were randomized to 6 cycles of FOLFOX4 every 14 days before and after liver resection *vs.* liver resection alone. Importantly, the trial's primary endpoint was PFS; the trial was designed to detect a 40% increase in median PFS in all patients randomly assigned to perioperative chemotherapy with 80% power at a two-sided 5% significance level, requiring 278 events (10). After 6.5 years, only 235 events had occurred, but due to pressure from the medical community, an interim analysis was reported in 2008.

Of the patients who were deemed eligible to undergo resection, 3-year PFS was significantly better with the use of perioperative FOLFOX compared to surgery alone [36.2% *vs.* 28.1%, (HR: 0.77, 95% CI: 0.60-1.00, P=0.041)]. Of the patients who actually underwent resection, 3-year PFS was also significantly better in the chemotherapy group compared to surgery alone [42.4% *vs.* 33.2%, (HR: 0.73, 95% CI: 0.55-0.97, P=0.025)]. A total of 79% patients in the chemotherapy group completed all 6 preoperative cycles but less than half of those who received preoperative therapy received all 6 planned postoperative cycles. Interestingly, 87% patients in the chemotherapy group went onto operation and complete resection was achieved in 83% patients. Four percent (4%) patients were deemed unresectable at the time of surgery secondary to more advanced disease (seven patients) and liver injury (one patient). In the surgery alone group, 93% of patients underwent attempted resection and complete resection was achieved in 84% patients. Ten percent (10%) patients were deemed unresectable at the time of surgery and all were due to advanced disease.

Despite a significant improvement in PFS, there was an increased incidence of post-operative complications in those who received perioperative chemotherapy (25% *vs.* 16%), although mortality was similar in both groups at 1%. Notably, OS was not reported in the interim analysis.

Results of this trial as well as data regarding conversion of patients with initially unresectable disease to resectable disease resulted in some of the medical and surgical oncology community to utilize neoadjuvant therapy in patients with potentially resectable colorectal liver metastases (11). Nevertheless, this strategy has gained more acceptance in patients with initially unresectable disease rather than upfront resectable, perhaps due to the concern for increased complications with the use of preoperative chemotherapy as well as lack of OS benefit.

In the recently published article, the authors report their long-term secondary outcome results of OS. With a median follow up of 8.5 years, 107 (59%) patients in the perioperative chemotherapy group had died *vs.* 114 (63%) patients in the surgery group (HR: 0.88, 95% CI: 0.68-1.14, P=0.34). In all randomized patients, median OS in the perioperative chemotherapy group was 61.3 *vs.* 54.3 months in the surgery alone group (P=0.34). In patients eligible to undergo resection, median OS was 63.7 months in the perioperative chemotherapy group *vs.* 55.0 months in the surgery alone group (P=0.30). In patients that underwent resection, median OS was 77.5 *vs.* 73.3 months (P=0.35) (12). The authors also reported long term PFS results. In all randomly assigned patients, median PFS was 20.0 months in the perioperative chemotherapy group *vs.* 12.5 months in the surgery alone group (P=0.068). In patients eligible for resection, median PFS was 20.9 months in the perioperative chemotherapy group *vs.* 12.5 months in the surgery alone group (P=0.035).

There are several important findings to note from this recent update. Although it may be somewhat surprising that perioperative chemotherapy did not show an OS benefit, there are several potential explanations for this. First and perhaps most importantly, as the authors discuss, the original study was not designed nor powered to detect differences in OS. In addition, the OS in the surgery alone group was 54 months and an impressive 73 months in those that underwent resection. Although perioperative chemotherapy resulted in an absolute difference in survival of 4-8 months depending on the comparison group (equal or better than other randomized adjuvant trials) this trial was not nearly large enough to detect that difference from a statistical standpoint. Second, as the authors also discuss, more patients in the surgery group with disease progression received chemotherapy as treatment when compared to the patients in the perioperative chemotherapy group

who progressed. This confounding variable could clearly affect OS (but not PFS) making it difficult to demonstrate a benefit to perioperative chemotherapy. Also, any further therapies after the initial treatment were not recorded and therefore not reported in this study—yet another confounding variable. Third, since OS would include all causes of death, any increased number of non cancer-related deaths in the perioperative chemotherapy group likely diminished any OS benefit in that group. Finally, Nordlinger *et al*. cite the higher than expected PFS in the surgery group as a potential confounder as it made the "demonstration of treatment benefit for perioperative chemotherapy… more difficult" (12).

Several other important points are also worth mentioning. In the EORTC trial, less than half of the patients in the perioperative chemotherapy group actually completed their adjuvant doses of chemotherapy. Presumably some of this may have been due to complications after surgery and general deconditioning of patients after resection. It is possible that the lack of OS benefit was due to inadequate duration of therapy. To that end, it is also unclear what role the neoadjuvant portion *vs*. the adjuvant portion plays in the benefit of prolonged PFS. Certainly for colon cancers, adjuvant therapy for stage 3 and high risk stage 2 provides a survival benefit (13) while in rectal cancer, neoadjuvant therapy has shown a benefit in PFS (14). Since the current trial did not include an adjuvant only arm, this question still remains. Furthermore, although fewer patients may be able to receive adjuvant therapy following hepatic resection, the increase in complication rates and presumed hepatic toxicity may be avoided if resection was to be performed first. What role these factors play, if any, would only be answered in a randomized trial comparing perioperative therapy to adjuvant therapy.

In conclusion the EORTC Intergroup trial 40983 is the first prospective randomized trial comparing perioperative chemotherapy to surgery alone for the treatment of resectable hepatic metastases from colon cancer. While it demonstrates a significant improvement in PFS, this most recent update did not demonstrate any significant benefit in OS. Systemic chemotherapy, with or without targeted therapy, be it before and or after hepatic resection most likely provides a benefit in patients with resected colorectal hepatic metastases. Unfortunately, several questions remain unanswered and therefore widespread use of this strategy may still be hindered. These include what specific agents to use as well as how and when to administer it.

Moving forward, randomized trials that can definitely show a benefit for the use of adjuvant systemic therapy using modern chemotherapy and targeted therapy combinations should be undertaken. Assuming there is a benefit compared to resection alone, additional studies comparing the role of neoadjuvant or perioperative therapy *vs*. adjuvant only should be undertaken in hopes of defining the best strategy for patients with colorectal hepatic metastases. Special attention must be given to properly define "resectable" disease and to exclude and/or stratify those that are not upfront resectable when studying neoadjuvant strategies. In addition, defining the proper endpoint will be crucial. As is the case with the current study, it is very difficult to draw conclusions from analyses of secondary endpoints since the trials are not often designed or powered to detect a difference. Although both PFS and OS are acceptable primary endpoints (15), both have their advantages and disadvantages that must be kept in mind when these future trials are designed.

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References

1. International Agency for Research on Cancer and Cancer Research UK. World Cancer Factsheet. Cancer Research UK, London, 2014. [Internet]. Available online: http://scholar.google.com/scholar?q=related:bjmLmuEA4jsJ:scholar.google.com/&hl=en&num=20&as_sdt=0,5
2. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.
3. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3677-83.
4. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440-8.
5. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol 2008;26:4906-11.
6. Ychou M, Hohenberger W, Thezenas S, et al. A

randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol 2009;20:1964-70.
7. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939-45.
8. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.
9. Gruenberger B, Scheithauer W, Punzengruber R, et al. Importance of response to neoadjuvant chemotherapy in potentially curable colorectal cancer liver metastases. BMC Cancer 2008;8:120.
10. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.
11. Nordlinger B, Van Cutsem E, Rougier P, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer 2007;43:2037-45.
12. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.
13. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
14. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
15. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030-3.

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Intraoperative margin re-resection for colorectal cancer liver metastases

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Abstract: One of the basic tenets of surgical oncology is the achievement of margin-negative resection. The importance of surgical margins in hepatic resection for colorectal cancer liver metastases (CRCLM) is reflected in the abundance of literature written about this topic. However, the definition of the ideal surgical margin has evolved in parallel with advances in systemic chemotherapy, biologic therapy and surgical technology. A better understanding of the biology of liver metastasis is of critical importance in the context of surgical strategy for CRCLM. The value of intraoperative margin re-resection to achieve R0 status for CRCLM is addressed, taking into consideration current understandings of cancer biology.

Keywords: Colorectal cancer liver metastasis; intraoperative margins; colorectal cancer; margin re-resection; liver metastasis

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Background

Over 143,000 individuals are estimated to be diagnosed with colorectal cancer (CRC) in the United States in 2012, with nearly 52,000 secondary deaths (1). CRC represents the most common gastrointestinal malignancy globally, and it is believed that of the 1.2 million people afflicted each year, 609,000 will die (2). The liver represents the most common site of initial clinical metastasis and approximately 60% patients develop colorectal cancer liver metastasis (CRCLM) during their primary or recurrent presentation (3). Approximately 20% of these patients will be eligible for hepatic resection with curative intent and with careful selection 5-year overall survival rates up to 25-58% can be reached (4-10). Advances in surgical technique, surgical series defining favorable clinical characteristics, and modern systemic chemotherapies have all contributed to these favorable outcomes. Despite these encouraging numbers, caution should be exercised in interpretation of the data because the benefits of resection are not based on prospectively randomized data but rather on retrospective series showing survival benefits compared to historical controls.

Over the last quarter century, the question of appropriate surgical margins in CRCLM has come to the forefront of debate. Surgical opinion regarding margin management in CRCLM has evolved but has been hindered somewhat by the lack supporting level 1 data. During the 1980s and 1990s, it was claimed that at least a 1-cm margin was required for hepatectomy to minimize disease recurrence and optimize survival (11-15). This led to a substantial period during which a requirement for resectability was the ability to achieve a 1-cm margin. However, this argument was weakened by the retrospective nature of the supporting data, which included studies that were underpowered, had suboptimal patient stratification, and lacked multivariate analysis. Near the turn of the last century, reports that questioned the necessity of 1-cm as the minimal resection margin began to appear. Surgeons from North America, Europe, and elsewhere reported large institutional series showing that outcomes in recurrence and survival depended more closely on the achievement of microscopically negative margins rather than a 1-cm negative margin (16-21). More recently, several groups have begun to question whether negative margins are in fact absolutely necessary in

surgical resections (22-25). These most recent studies have shown that positive microscopic margins may still result in equivalent overall survival and recurrence as patients with negative margins. Given this changing notion of the appropriate surgical margin, the question of whether intraoperative margin re-resection is of benefit in CRCLM becomes even more interesting.

Surgical margins

In 1986 Ekberg and colleagues from Sweden presented their data regarding outcomes after surgical resection for CRCLM (11). In this now-classic retrospective series of 72 patients, they concluded that it is "essential to obtain a margin of resection that is 10 mm or more" because this clinical variable was associated with a favorable overall survival. During this time period, the experience of several other groups was similar and thus the "standard of care" for liver resections in CRCLM was to consider patients for curative resection only if 1-cm margins could be achieved (11-15).

This viewpoint began to change around the turn of the century. The largest retrospective series to question the 1-cm margin paradigm was by Pawlik and colleagues (16). This international, multi-institutional retrospective series comprised of 557 patients stratified margin status by positive margins and negative margins of either 1-4 mm, 5-9 mm and >10 mm. All patients with negative margins had similar overall recurrence rates, but patients with positive margins had a significantly poorer median overall survival (5-year overall survival of 17.1% *vs.* 63.6%, P=0.01) and were more likely to have surgical margin recurrence (38.6% *vs.* 51.1%, P=0.04). Furthermore, patients with positive recurrence margins tended to have more metastatic lesions and a higher preoperative CEA level. This study concluded that subcentimeter, negative surgical margins were sufficient for liver resections. Equally important, it also suggested that a different tumor biology driving metastasis, rather than surgical technique, accounted for a positive margin. Several investigators have also shown that subcentimeter negative margins of resection provide similar clinical outcomes as patients undergoing hepatectomy with greater than 1-cm margins (17-21).

The belief that even microscopically negative margins are absolutely necessary for CRCLM has recently been challenged. De Haas and colleagues reviewed 436 patients undergoing hepatectomy for CRCLM with either an R1 or R0 margin of resection on patients operated between 1990-2006 (22). They showed that patients undergoing R0 and R1 resections had no significant difference in 5-year overall survival (61% *vs.* 57%, P=0.27) and median disease-free survival (P=0.12). Although patients with R1 resections had higher numbers of intrahepatic recurrences, when the investigators looked specifically at surgical margin recurrence, they found both groups to have equivalent surgical margin recurrence. Predictors of poor overall survival were not microscopically positive margins, but rather tumors greater than 3 cm and bilobar distribution. These data also strongly suggest that there are inherent biological differences in tumor behavior in patients undergoing R0 and R1 resections. Interestingly, this difference in tumor biology among positive and negative margins is similar to the conclusions implied in the study by Pawlik *et al.*, which notably drew different conclusions about surgical margins. It is plausible to conceive that when liver resections are performed by experienced hepatopancreatobiliary surgeons, differences in tumor biology rather than surgical technique are responsible for differences in margin status.

It is not a coincidence that evolution of surgical opinion regarding margins has paralleled advances in systemic chemotherapy and biologic therapy in CRC. We have seen substantially improved outcomes in metastatic CRC as more modern systemic therapies have been introduced. In 1993 when systemic chemotherapy with fluorouracil-based therapy was first shown by the Scheithauer and colleagues to improve the overall survival compared to palliative care, therapeutic options were limited (26). This landmark trial reported prolonged median overall survival to 11 months, but it was not until much later that oxaliplatin- and irinotecan-containing regimens were shown in prospective trials to prolong median overall survival to 19 months. Most recently the introduction of biologic agents (i.e., bevacizumab, cetuximab) has further increased median survival data to 24 months (27,28). Not only has survival improved in widely metastatic CRC, but also groups of patients with CRCLM that were initially deemed unresectable have become resectable after systemic chemotherapy, such as demonstrated in a French retrospective series of 701 patients (29). Interestingly, a Dutch group reported a series of 264 patients undergoing hepatectomy for CRCLM and found no differences in clinical outcome in patients receiving neoadjuvant chemotherapy between those with R0 and R1 resections (25). However in patients that did not receive upfront chemotherapy, R1 resection was associated with a worse clinical outcome. Thus, significant advances in systemic therapies have

become part of the multidisciplinary care of CRC patients and will continue to influence the outcome of liver surgery.

As ideas about the importance of margin status have evolved, so too has the role of intraoperative margin re-resection to achieve R0 status during hepatectomy for CRCLM. Unfortunately, the issue of margin re-resection is even less well informed by the surgical literature. When surgeons are confronted with positive intraoperative margins, many will perform re-resection when feasible or ablation with cautery or radiofrequency when re-resection is not feasible, yet these practices are not supported by data (12,16). There is only one study that specifically addressed this topic. Wray and collleagues from the University of Cincinnati reported in 2007 a retrospective single-institution review of 118 surgically resected cases of CRCLM over a 13-year time span (30). Clinical outcomes were compared between patients undergoing intraoperative margin re-resection and patients with resection margins greater or less than 1-cm. Their study showed that patients with >1 cm margins after intraoperative margin re-resection had higher local recurrence rates and worse overall survival than those individuals initially undergoing >1 cm margin resection ($P<0.05$). They also showed that initial margins >1 cm were associated with favorable disease-free survival (39.2 *vs.* 22.9 mo, $P=0.023$).

The results of this study suggest several points. First, and probably most important, tumor biology plays a dominant role in patient outcome. Intraoperative margins requiring re-resection to achieve margins >1 cm resulted in higher local recurrence and lower disease-free survival than individuals with initial margins greater than 1 cm. If margin status were the absolute determining factor for survival, one would expect similar outcomes in both groups. The observation that this was not the case suggests that it is tumor biology and not margin that drives clinical outcome. For example, it is plausible to conceive that a rate-limiting factor precluding an initial R0 resection may be an infiltrative growth pattern near major vascular or biliary structures indicative of aggressive cancer. If one analyzes the recent French and Dutch studies on surgical margins in the context of the University of Cincinnati, the dominant role of tumor biology on clinical outcome is undeniable.

Second, preoperative computed tomography and/or magnetic resonance imaging and intraoperative ultrasonography are critical imaging modalities for the surgeon to utilize in operative planning for hepatectomy. The fact that margin re-resection does not convey the same favorable disease-free survival as an initial negative margin implies that careful preoperative surgical planning and intraoperative ultrasound are important tools for the surgeon to utilize to maximize the chance for an initial margin negative resection. However if intraoperative margin re-resection is performed, the surgeon and medical oncologist must appreciate that the patient is at higher risk for local recurrence and may benefit from additional chemotherapy.

Other points concerning intraoperative margin re-resection relate to surgical technology and specimen interpretation by the pathologist. Surgeons must use caution when interpreting results of intraoperative frozen sections because accurate assessment of surgical margin in liver surgery can be difficult. Intraoperative interpretation of frozen sections may overestimate the true positive margin rate because the commonly used ultrasonic dissector partly aspirates liver parenchyma between tumor and normal tissue. This may decrease the resection margin up to 2-mm, potentially overestimating the proportion of R1, rather than R0, resections. Also the remnant cut section of the liver in contact with the previously removed specimen is commonly treated with argon beam coagulation "sterilizing" another 1 to 2 mm of hepatic tissue. Some surgeons now incorporate radiofrequency energy to coagulate along the margins of the tumor prior to resecting the liver (31). Thus, tumors interpreted as "margin-positive" may incorrectly receive this designation because of failing to take into consideration the false positives secondary to modern surgical technology.

Finally, more effective chemotherapy regimens could reduce the proportion of R1 resections that develop secondary liver metastases, thus minimizing residual micrometastatic disease. It seems that the microscopic margin of resection is less important when effective modern systemic therapy is applied to treat residual occult disease. This concept is supported by recent studies showing R0 resections are not required to achieve optimal outcomes given the efficacy of modern systemic agents (22-25).

The substantial improvements in the effectiveness of newer agents for systemic therapy in metastatic CRC should be taken into account when there is surgical consideration of intraoperative margin re-resection. Re-resection should be performed for an R2 resection since, at minimum, an R1 resection should always be sought for optimal clinical outcomes. However intraoperative margin re-resection is probably of no value in the setting of R1 or sub-centimeter R0 resection. Recent studies show no outcome differences between negative sub-centimeter and >1 cm margins, and between negative and microscopically positive margins. Effective modern chemotherapy, false positives from ultrasonic dissectors, and coagulation necrosis from argon beam coagulators and radiofrequency energy favor this

approach. However if margin re-resection is required clinicians must be wary that this represents a marker for more aggressive cancer and consideration should be made for prolonged systemic therapy.

In summary, definitive surgical resection is critical to the treatment of appropriately selected patients with CRCLM. The definition of what constitutes an ideal margin resection has evolved, with current evidence indicating similar outcomes with R1 or R0 resections with use of modern systemic therapies. Intraoperative margin re-resection should be used selectively and may play less of role in the current practice of liver surgery in light of modern systemic therapies, imaging modalities that allow careful operative planning, and advances in surgical technology. When margin re-resection is undertaken, it should be with the understanding that margin status can be skewed by surgical technique, and that regardless of margin status, margin re-resection is associated with worse clinical outcome. Perhaps the most important point regarding intraoperative margin re-resection is not necessarily whether or not it should be done, but rather that it is an indicator of more aggressive tumor biology and higher rates of local recurrence.

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References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
2. Jemal A, Center MM, DeSantis C, et al. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893-907.
3. Yoo PS, Lopez-Soler RI, Longo WE, et al. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. Clin Colorectal Cancer 2006;6:202-7.
4. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-25; discussion 825-7.
5. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-53.
6. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
7. Bradley AL, Chapman WC, Wright JK, et al. Surgical experience with hepatic colorectal metastasis. Am Surg 1999;65:560-6; discussion 566-7.
8. Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. World J Surg 1995;19:59-71.
9. Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. Dis Colon Rectum 1988;31:1-4.
10. Adson MA, van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colorectal cancer. Arch Surg 1984;119:647-51.
11. Ekberg H, Tranberg KG, Andersson R, et al. Determinants of survival in liver resection for colorectal secondaries. Br J Surg 1986;73:727-31.
12. Fuhrman GM, Curley SA, Hohn DC, et al. Improved survival after resection of colorectal liver metastases. Ann Surg Oncol 1995;2:537-41.
13. Cady B, Jenkins RL, Steele GD Jr, et al. Surgical margin in hepatic resection for colorectal metastasis: a critical and improvable determinant of outcome. Ann Surg 1998;227:566-71.
14. Steele G Jr, Bleday R, Mayer RJ, et al. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group Protocol 6584. J Clin Oncol 1991;9:1105-12.
15. Shirabe K, Takenaka K, Gion T, et al. Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. Br J Surg 1997;84:1077-80.
16. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241:715-22, discussion 722-4.
17. Muratore A, Ribero D, Zimmitti G, et al. Resection margin and recurrence-free survival after liver resection of colorectal metastases. Ann Surg Oncol 2010;17:1324-9.
18. Kokudo N, Miki Y, Sugai S, et al. Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 2002;137:833-40.
19. Nuzzo G, Giuliante F, Ardito F, et al. Influence of surgical margin on type of recurrence after liver resection for colorectal metastases: a single-center experience. Surgery 2008;143:384-93.
20. Ohlsson B, Stenram U, Tranberg KG. Resection of colorectal liver metastases: 25-year experience. World J Surg 1998;22:268-76; discussion 276-7.

21. Figueras J, Burdio F, Ramos E, et al. Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. Evidences from 663 liver resections. Ann Oncol 2007;18:1190-5.
22. de Haas RJ, Wicherts DA, Flores E, et al. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg 2008;248:626-37.
23. Bodingbauer M, Tamandl D, Schmid K, et al. Size of surgical margin does not influence recurrence rates after curative liver resection for colorectal cancer liver metastases. Br J Surg 2007;94:1133-8.
24. Inoue Y, Hayashi M, Komeda K, et al. Resection margin with anatomic or nonanatomic hepatectomy for liver metastasis from colorectal cancer. J Gastrointest Surg 2012;16:1171-80.
25. Ayez N, Lalmahomed ZS, Eggermont AM, et al. Outcome of microscopic incomplete resection (R1) of colorectal liver metastases in the era of neoadjuvant chemotherapy. Ann Surg Oncol 2012;19:1618-27.
26. Scheithauer W, Rosen H, Kornek GV, et al. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. BMJ 1993;306:752-5.
27. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
28. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45.
29. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8:347-53.
30. Wray CJ, Lowy AM, Matthews JB, et al. Intraoperative margin re-resection for colorectal liver metastases. J Surg Educ 2007;64:150-7.
31. Pai M, Frampton AE, Mikhail S, et al. Radiofrequency assisted liver resection: analysis of 604 consecutive cases. Eur J Surg Oncol 2012;38:274-80.

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Surgical treatment of colorectal liver metastases

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Abstract: The incidence of colorectal cancer is rising in China. Since nearly 50% of these patients will ultimately develop liver metastases, an understanding of the surgical management of hepatic metastases is important. Surgical strategies for the management of liver metastases have evolved in recent years and now include adjunctive procedures such as portal vein embolization and radiofrequency ablation, which can help increase the number of patients eligible for potentially curative surgical management. In addition, innovations in treatment sequencing, including the use of peri-operative chemotherapy and the liver-first approach to the management of synchronous liver metastases have helped improve outcomes in these patients. Along with such changes in surgical management come new risks, such as chemotherapy-induced liver damage, with which the surgeon must be prepared to contend.

Keywords: Chemotherapy-associated liver injury; radiofrequency ablation; reverse approach to synchronous colorectal liver metastasis; portal vein embolization

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Epidemiology and background

Colorectal cancer is the 3rd most common cancer worldwide (1) and the 5th most common cancer in Eastern Asia (2). The incidence is rising in China (3) and it ranks among the top 5 most common cancers in residents of Shanghai with an incidence of 56 cases per 100,000 residents (4). Approximately 40-50% of patients affected with colorectal cancer will develop liver metastases at some point during the course of their disease, making liver metastases the most common cause of death for these patients (3,5,6). Complete surgical resection offers the only hope of cure and long-term survival for these patients. Using contemporary multimodality therapy, 5-year survival rates of 47-58% have been achieved for the 20-30% of patients who are able to undergo surgical resection (3,7,8).

According the general international classification system, colorectal liver metastases are considered synchronous if they are discovered at the time of initial diagnosis of the primary tumor or within six months of resection of the primary tumor (9). Metastases discovered in the liver more than six months after resection of the primary cancer, on the other hand, are considered metachronous.

Imaging and staging work up

The Chinese Guidelines for the Diagnosis and Comprehensive Treatment of Hepatic Metastasis of Colorectal Cancer recommend that the initial staging work-up for patients with colorectal cancer include measurement of serum AFP, CEA, and CA 19-9 as well as an hepatic ultrasound and abdominal and pelvic computed tomography (CT) scan with contrast to categorize the number and location of liver metastases and exclude additional sites of metastatic disease (9). For patients with suspected liver metastases, the guidelines recommend a liver magnetic resonance imaging (MRI) scan for further evaluation. It should be noted that while MRI has higher sensitivity for detection of tumors within the liver, CT provides superior imaging of extrahepatic disease (10). In addition, the guidelines recommend against routine percutaneous biopsy of suspected liver metastases due to the risks of needle track seeding and false negative

results; however, incisional or excisional biopsy should be performed if any suspicious liver lesions are encountered during resection of the primary tumor.

Following resection of a primary colorectal tumor in a patient without known metastatic disease, the recommended imaging follow up includes liver ultrasound every 3-6 months for the first two years and then every 6 months for 5 years (9). For patients undergoing surveillance after resection for stage II or III disease, the guidelines also recommend annual chest, abdomen, and pelvis CT with contrast with use of liver MRI to confirm any lesions seen on CT that are suspicious for new liver metastases. In patients who have previously undergone resection of liver metastases, the guidelines suggest that CT of the chest, abdomen, and pelvis with contrast be performed every 3 months for 2 years and then every 6-12 months for an additional 5-7 years (9). For each of these patient groups evaluation of the CEA level should be performed every 3-6 months for two years and then every 6 months for an additional 3-5 years.

Positron emission tomography (PET)/CT is not recommended as part of the routine staging work up for colorectal cancer (9). A retrospective British study showed a similar sensitivity and specificity of liver MRI and PET/CT for the detection of liver metastases, with a greater accuracy of MRI for lesions less than a centimeter in size--although it should be noted that this study also found a benefit of PET/CT over contrast-enhanced CT scan for the detection of extrahepatic metastatic disease (11). Similarly, a U.S. study identified the use of PET imaging as an independent predictor of a lower rate of nontherapeutic laparotomy in patients with hepatic colorectal metastases (12). No studies, however, have shown a survival benefit associated with the use of PET/CT. PET/CT is also limited in its detection of tumors less than 1 cm and mucinous tumors. PET-positive lesions are nonspecific, particularly in settings where inflammation may be present. Additionally, prior treatment with chemotherapy may decrease the sensitivity of PET for detection of disease (10).

Although not useful for pre-operative staging, intra-operative ultrasound is an important component of the surgical management of patients with hepatic metastases from colorectal cancer. Intra-operative ultrasound has been shown to detect tumors not seen on helical CT scan in as many as 27% of patients undergoing resection of primary or metastatic liver tumors, with even higher rates of detection of unsuspected lesions in patients with increasing numbers of tumors (13). For this reason, intra-operative ultrasound should be utilized at the time of liver resection for cancer.

Resectability and operability

Operability refers to a patient's ability to tolerate a liver resection (14) and includes factors such as comorbidities and baseline performance status. The resectability of a tumor has do with both technical and oncologic factors (14). Tumors are technically resectable when all metastases can be removed with negative margins with sparing of at least two adjacent segments of liver, and with preservation of adequate blood inflow and outflow, biliary drainage, and remnant parenchyma (generally accepted as at least 20% of estimated total liver volume) (10,15).

Oncologic factors which have previously been considered at least relative contraindications to the surgical treatment of liver metastases include the presence of four or more metastases and the presence of extrahepatic sites of metastases (16,17). Two recent retrospective studies have shown that long-term survival is possible even for patients with four or more metastases if complete resection can be accomplished (18,19). In one of these studies, even though the presence of multiple tumor nodules was independently associated with a lower rate of overall survival, it was not associated with disease-free survival (18). In the other study patients with four or more colorectal liver metastases had a 5-year actuarial disease-free survival rate of 21.5% with an overall survival rate of 50.9% after treatment with multimodality therapy (19). Additionally recent studies have shown favorable survival for patients with liver metastases and limited sites of resectable extrahepatic disease, including lung (20), limited peritoneal disease, and portal lymph nodes (21,22). Patients who develop new liver metastases or new sites of extrahepatic disease while on chemotherapy, however, should not be considered for resection unless a response to other therapy can be demonstrated (14).

Response to therapy

Emerging data suggest that the pathologic response to chemotherapy may represent an important endpoint that is highly correlated with overall survival (23,24). Four to nine percent of patients treated with neoadjuvant oxaliplatin or irinotecan-based chemotherapy may achieve a pathologic complete response (23,24), which has been shown on multivariate analysis to be an independent predictor of improved overall survival, overwhelming other previously established predictors of survival such as disease-free

interval, tumor size, and tumor multiplicity, with a hazard ratio of 4.8 for patients with a major pathologic response (defined as 49% or fewer viable tumor cells) (23). In addition, morphologic response to chemotherapy as seen on CT scan has been shown to correlate with overall survival (25). A study from the M.D. Anderson Cancer Center defined the "optimal" morphologic response as the presence of homogeneous low attenuation lesions with a thin, sharply defined interface between the tumor and the surrounding liver parenchyma and showed that patients treated with bevacizumab were significantly more likely to achieve such a response than those not treated with bevacizumab (47% *vs.* 12%) (25). The patients in the optimal morphologic response group had overall 3- and 5-year survival rates of 82% and 74%, respectively, *vs.* 60% and 45% (P<0.001) for those with a suboptimal response (25).

Synchronous metastases and treatment sequencing

Liver metastases are discovered synchronously with the primary tumor in approximately 25% of patients (26) and can be approached via three different strategies. The Chinese Guidelines for treatment of hepatic metastasis of colorectal cancer recommend either synchronous resection of both the primary and metastatic tumors or two-stage resection with resection of the primary tumor followed by resection of the hepatic metastases either with or without systemic chemotherapy in between the two operations (9). Classically, resection of the primary tumor followed by liver resection for the metastatic disease has been the approach taken to synchronous disease. There are several disadvantages to this approach, however, including the potential for progression of the metastatic disease prior to any systemic therapy, complications from the colorectal resection which may significantly delay or even preclude all together systemic therapy and/or resection of the liver metastases, and a substantial interval between presentation and administration of systemic therapy for stage IV disease. For these reasons, two alternative strategies have also been utilized. The first of these is simultaneous resection of both the primary tumor and the liver metastases. Several studies have shown the feasibility of this approach and have suggested that it can be accomplished without an increase in postoperative morbidity or mortality rates (26-29). Such an approach, however, is typically recommended for patients who either require a low-risk colon resection (e.g., right hemicolectomy) or a limited liver resection (e.g., wedge resection) if a more complex colorectal resection is required (10).

The second alternative strategy for the management of synchronous metastases is the reverse approach, whereby the liver resection is undertaken prior to the colorectal resection. This approach may include administration of neoadjuvant chemotherapy prior to any surgical resection and is feasible when the primary tumor is asymptomatic, without evidence of obstruction or bleeding. The major advantage to this approach is treatment of the metastatic disease prior to progression to an unresectable status (30,31). Progression of the primary tumor during the administration of systemic therapy is rare (32,33), but does require a change in treatment plan, so it is important that surveillance of the primary tumor be performed throughout the period of treatment for the metastatic disease. Once resection of the metastatic disease has been accomplished, focus can be turned to locoregional control of the primary tumor (i.e., resection for a colonic tumor or chemoradiation followed by resection for a locally advanced rectal tumor). In general, the decision regarding operative strategy for management of synchronous colorectal liver metastases should be prioritized based on whether the primary or metastatic tumor is causing symptoms, followed by which of the two sites presents the greatest oncologic risk. Evaluation of these factors is best undertaken by a multidisciplinary team at the outset of therapy.

Cautionary notes on neoadjuvant chemotherapy

Timing of surgery after chemotherapy

A Japanese study reported the results of sequential measurements of 15 minute indocyanine green retention (ICG R15) in patients following neoadjuvant chemotherapy. This study showed a significant improvement in the ICG R15 following the final dose of chemotherapy after a 2-week interval with further nonsignificant improvements at increasing time points up to 8 or more weeks after cessation of chemotherapy (34). Based on this data the authors concluded that resection should be delayed for at least 2-4 weeks following completion of chemotherapy. Another retrospective study of patients undergoing liver resection for colorectal metastases showed that receipt of 5 or fewer cycles of 5-FU-based preoperative chemotherapy was associated with a markedly lower rate of postoperative complications (19% *vs.* >40%) relative to patients receiving greater numbers of cycles (35).

Chemotherapy-induced liver injury

Several studies have described histologic changes in the livers of patients treated with certain chemotherapeutic agents. The first to be described of these was sinusoidal obstruction and veno-occlusive disease [the sinusoidal obstruction syndrome (36)] occurring in up to 78% of patients treated with oxaliplatin (37-40). These histologic changes do not seem to correlate with the total oxaliplatin dose received and may persist for months after chemotherapy (37,38). Although the presence of the sinusoidal obstruction syndrome has not been associated with increased rates of postoperative complications in most studies (38-40), in one French study it was associated with a longer length of hospital stay and a higher morbidity rate (41), and in another it was associated with an increased risk of transfusion (39).

Use of irinotecan has been associated with the development of steatohepatitis in approximately 20% of patients (38,40) and has been associated with higher rates of postoperative mortality (38), and may be correlated with higher rates of postoperative hepatic insufficiency (42). The development of steatohepatitis has also been shown to occur primarily in patients with a high body mass index (43), suggesting that rather than inducing steatohepatitis, irinotecan may cause progression of it (42). Increased rates of postoperative complications have also been correlated with longer durations of preoperative chemotherapy, with the most conservative cutoff occurring after 5 cycles of chemotherapy (35,39,41,44).

The effectiveness of modern chemotherapy regimens has resulted in a phenomenon known as disappearing liver metastases—metastases that become radiologically undetectable during neoadjuvant therapy. A retrospective study of patients treated with liver resection for colorectal metastases who had been treated with preoperative chemotherapy reported that almost 25% of patients had at least one liver metastasis that disappeared during treatment (45). In the patients whose missing tumors were not resected, nearly 60% eventually recurred at that site; however, the overall survival rates were not adversely impacted despite these local recurrences. Another retrospective study of disappearing metastases showed that persistent macroscopic disease was identified intraoperatively in 30% of the lesions, 80% of resected lesions without macroscopic evidence of residual disease had microscopic disease identified, and 74% of unresected lesions without macroscopic evidence of residual disease developed local recurrences with 1 year of surgery (46).

Perioperative chemotherapy

The use of perioperative chemotherapy in patients with resectable colorectal liver metastases was studied in a multicenter randomized trial—the EORTC Intergroup Trial 40983 (5). In this trial oxaliplatin-naïve patients were randomized to either 6 cycles of pre-operative and 6 cycles of post-operative FOLFOX4 or to surgery alone. The trial demonstrated that peri-operative chemotherapy increased the probability of 3-year progression-free survival by 35% (with a 7% absolute risk reduction) (5). Reversible post-operative complications were significantly more common in the peri-operative chemotherapy group (25% *vs.* 16%). A partial or complete response by RECIST criteria was seen in 40% of patients and on average the total tumor diameter decreased by about 25% (5).

A meta-analysis of randomized trials comparing surgery alone with peri-operative chemotherapy plus surgery in patients with stage IV colorectal cancer showed no evidence of a survival benefit for use of hepatic arterial chemotherapy, whereas the survival advantage for patients receiving peri-operative systemic chemotherapy approached significance (HR 0.74, P=0.08) (47). Both hepatic arterial chemotherapy (HR 0.78, P=0.01) and systemic peri-operative chemotherapy (HR 0.75, P=0.003) were associated with a significant recurrence-free survival benefit, however.

Functional liver remnant and portal vein embolization

A Japanese study of liver volumes in living transplant donors showed that in 25% of patients the left liver represents 30% or less of the total liver volume (48). For such patients, an extended right hepatectomy would carry a prohibitive risk of postoperative liver failure due to an inadequate functional liver remnant. The concept of portal vein embolization to induce hypertrophy of the functional liver remnant and thereby decrease the risk of postoperative liver insufficiency was first introduced by Makuuchi in 1990 to allow surgical resection in such patients (49). Since that time, additional studies have clarified the safety of and indications and techniques for the appropriate use of portal vein embolization. Preoperative portal vein embolization is typically recommended for patients with an anticipated functional liver remnant that is less than 20-25% of estimated total liver volume (50,51), with an expected average increase in volume of the remnant liver of 12% of the total liver volume (50). The rate of hypertrophy

has been shown to correlate with the degree of increase in the portal blood flow velocity in the nonembolized segment on postembolization day 1 (52). Portal blood flow in the nonembolized segments remains elevated for at least 14 days after embolization (52), providing the rationale for a 2-4 week waiting period between embolization and resection (50). The rate of hypertrophy after embolization is slower and the degree of hypertrophy is less in patients with cirrhosis (53) and diabetes (54,55). If an interventional radiology suite is unavailable for the performance of percutaneous portal vein embolization, then a transileocolic venous approach for embolization can be undertaken during laparotomy (49).

The technique of right portal vein ligation with in situ splitting (also known as ALPPS-associating liver partition and portal vein ligation staged hepatectomy) has been proposed as an alternate strategy for approaching the treatment of patients with a marginal or inadequate functional liver remnant (56). This technique involves two operations—the first during which the right portal vein is ligated and the hepatic parenchyma is completely (or nearly-completely) transected and a second (occurring after a variable period of delay, but during the same hospital stay) during which the resection is completed. Proponents of this approach feel that the hypertrophy achieved is more rapid and, perhaps, greater than that realized after portal vein embolization (57,58). Critics of the approach, however, feel that the high morbidity rate (68%), in-hospital mortality rate (12%), and lack of data on long-term oncologic outcomes should limit the use of this technique to clinical trials (56,59).

Repeat hepatectomy

Approximately 65-85% of patients who undergo liver resection for colorectal metastases will eventually develop a recurrence, of which 20-30% will be isolated to the liver (60). Repeat hepatic resection for recurrent liver metastases has been shown to have equivalent long-term survival without significant increases in perioperative morbidity or mortality in several studies, provided that a margin negative resection can be obtained (61-64).

(Metachronous metastases) - unresectable with downstaging

Retrospective studies have shown that use of contemporary chemotherapy regimens that include oxaliplatin and irinotecan can convert 12.5-38% of patients with initially unresectable liver metastases into surgical candidates (21,65). While such patients experience a high rate of recurrent disease (approximately 80% of patients will recur), 33-50% of them will be 5-year survivors and 23% of them will be 10-year survivors if an aggressive approach to resection of recurrent disease is used (21,65,66).

Second-line chemotherapy

For patients with marginally resectable or unresectable liver metastases from colorectal cancer who do not respond to first line chemotherapy, a switch to second-line chemotherapy may result in a response to therapy. The question of whether or not liver resection is reasonable in such patients if they respond to second-line chemotherapy has been addressed in a retrospective analysis (67). This study showed that 1-, 3-, and 5-year survival rates of 83%, 41%, and 22%, respectively, with 1- and 3-year disease-free survival rates of 37% and 11%, respectively, can be achieved in this setting with reasonable postoperative morbidity and mortality rates.

Biological agents

Biological agents, such as vascular endothelial growth factor (VEGF) inhibitors and epidermal growth factor receptor (EGFR) inhibitors in combination with cytotoxic chemotherapy frequently have activity in patients with metastatic colorectal cancer. There is emerging evidence from phase II and III randomized clinical trials that chemotherapy regimens that include biological agents may improve the ability to convert unresectable liver metastases into resectable ones (68).

Randomized controlled trials comparing FOLFOX or FOLFIRI with or without the vascular endothelial growth factor inhibitor bevacizumab have shown that the addition of bevacizumab significantly increases the duration of survival, the progression-free survival, and rates of response in both previously treated and previously untreated patients with metastatic colorectal cancer (69,70). The addition of bevacizumab to FOLFOX has been shown in a retrospective study to result in a lower percentage of viable tumor cells, although not a higher complete pathologic response rate, in resected specimens, and a decrease in the frequency and severity of sinusoidal obstruction syndrome was also noted (71). Similar results were obtained in another retrospective study where bevacizumab was

shown to result in decreased severity of the sinusoidal obstruction syndrome, but not to improve the likelihood of response according to RECIST criteria (72). No published randomized controlled trials of bevacizumab have measured rates of resection as a pre-specified endpoint.

Cetuximab is a monoclonal antibody that blocks the EGFR, which is frequently present on colon cancer cells (73). A randomized phase II trial of cetuximab plus either FOLFOX or FOLFIRI in patients with unresectable liver metastases from colorectal cancer showed high rates of partial or complete clinical response by RECIST criteria (68% *vs.* 57%, P=NS) (74). A retrospective analysis of the data from this study showed that partial or complete responses were significantly more likely in patients with KRAS-wide type tumors (70%) *vs.* those with KRAS-mutations (41%), and that chemotherapy with cetuximab increased the baseline resectability rate from 32% to 60% (P<0.0001) (74). A randomized phase III trial of FOLFIRI with and without cetuximab in patients with metastatic colorectal cancer (including, but not limited to patients with liver metastases) showed that the rates of surgery for metastases (7% *vs.* 3.7%) and the rates of R0 resection (4.8% *vs.* 1.7%, P=0.002) were higher in the group receiving cetuximab, although these were not pre-specified endpoints of the study (75). In addition, other EGFR inhibitors, such as panitumumab, have been shown to have activity in patients with metastatic colorectal cancer whose tumors are KRAS-wild type (76), and may eventually show similar rates of conversion to resectability.

Radiofrequency ablation

The EORTC 40004 study, a randomized phase II trial, randomized patients with unresectable liver metastases to either systemic therapy or systemic therapy plus radiofrequency ablation (RFA) (77). This study reported a non-significant improvement in 30-month overall survival and a significantly improved 3-year progression-free survival rate in the patients treated with RFA plus chemotherapy.

A retrospective German study has suggested that RFA may result in equivalent disease-free and overall survival to surgical resection for patients with a small number of metastases <5 cm in diameter (78). The RFA and surgery groups in this study were well-matched except for a significantly larger median tumor diameter in the surgery group (3 *vs.* 5 cm). The incidence of local recurrence was significantly higher and the time to progression was significantly shorter in the group treated with RFA; however, a higher rate of salvage therapy in the RFA group resulted in similar disease-free survival rates (78).

In contrast, another retrospective study concluded that RFA, alone or in combination with hepatectomy, results in significantly poorer overall survival (4-year survival of 22% *vs.* 65%) (7). This study also demonstrated higher rates of local recurrence in the group of patients treated with RFA relative to those treated with resection. While the role of radiofrequency ablation in the management of patients with liver metastases from colorectal cancer is still being defined, it is at the very least a useful adjunctive procedure in certain situations where resection is not technically feasible or would leave a patient with a marginal/inadequate functional liver remnant.

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References

1. The World Health Organization. Cancer Fact Sheet No 297. 2013.
2. International Agency for Research on Cancer. GLOBOCAN 2008. accessed on 2/10/13.
3. Dexiang Z, Li R, Ye W, et al. Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. Ann Surg Oncol 2012;19:2860-8.
4. Chen XR. Seniors to get free cancer screenings. Global Times 2013-2-3.
5. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.
6. Vibert E, Canedo L, Adam R. Strategies to treat primary unresectable colorectal liver metastases. Semin Oncol 2005;32:33-9.
7. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-25; discussion 825-7.
8. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
9. Xu J, Qin X, Wang J, et al. Chinese guidelines for the diagnosis and comprehensive treatment of hepatic

metastasis of colorectal cancer. J Cancer Res Clin Oncol 2011;137:1379-96.
10. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006;13:1261-8.
11. Kong G, Jackson C, Koh DM, et al. The use of 18F-FDG PET/CT in colorectal liver metastases--comparison with CT and liver MRI. Eur J Nucl Med Mol Imaging 2008;35:1323-9.
12. Pawlik TM, Assumpcao L, Vossen JA, et al. Trends in nontherapeutic laparotomy rates in patients undergoing surgical therapy for hepatic colorectal metastases. Ann Surg Oncol 2009;16:371-8.
13. Scaife CL, Ng CS, Ellis LM, et al. Accuracy of preoperative imaging of hepatic tumors with helical computed tomography. Ann Surg Oncol 2006;13:542-6.
14. Tzeng CW, Aloia TA. Colorectal liver metastases. J Gastrointest Surg 2013;17:195-201; quiz p.201-2.
15. Ribero D, Abdalla EK, Madoff DC, et al. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. Br J Surg 2007;94:1386-94.
16. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.
17. Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 1999;189:291-9.
18. Minagawa M, Makuuchi M, Torzilli G, et al. Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 2000;231:487-99.
19. Pawlik TM, Abdalla EK, Ellis LM, et al. Debunking dogma: surgery for four or more colorectal liver metastases is justified. J Gastrointest Surg 2006;10:240-8.
20. Brouquet A, Vauthey JN, Contreras CM, et al. Improved survival after resection of liver and lung colorectal metastases compared with liver-only metastases: a study of 112 patients with limited lung metastatic disease. J Am Coll Surg 2011;213:62-9; discussion 69-71.
21. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.
22. Elias D, Ouellet JF, Bellon N, et al. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. Br J Surg 2003;90:567-74.
23. Blazer DG 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol 2008;26:5344-51.
24. Adam R, Wicherts DA, de Haas RJ, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol 2008;26:1635-41.
25. Shindoh J, Loyer EM, Kopetz S, et al. Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. J Clin Oncol 2012;30:4566-72.
26. Martin R, Paty P, Fong Y, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg 2003;197:233-41; discussion 241-2.
27. Slupski M, Wlodarczyk Z, Jasinski M, et al. Outcomes of simultaneous and delayed resections of synchronous colorectal liver metastases. Can J Surg 2009;52:E241-4.
28. Capussotti L, Ferrero A, Viganò L, et al. Major liver resections synchronous with colorectal surgery. Ann Surg Oncol 2007;14:195-201.
29. Lyass S, Zamir G, Matot I, et al. Combined colon and hepatic resection for synchronous colorectal liver metastases. J Surg Oncol 2001;78:17-21.
30. Mentha G, Majno PE, Andres A, et al. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg 2006;93:872-8.
31. Mentha G, Roth AD, Terraz S, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. Dig Surg 2008;25:430-5.
32. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? J Am Coll Surg 2010;210:934-41.
33. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 2009;27:3379-84.
34. Takamoto T, Hashimoto T, Sano K, et al. Recovery of liver function after the cessation of preoperative chemotherapy for colorectal liver metastasis. Ann Surg Oncol 2010;17:2747-55.
35. Karoui M, Penna C, Amin-Hashem M, et al. Influence

of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006;243:1-7.
36. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). Semin Liver Dis 2002;22:27-42.
37. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004;15:460-6.
38. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065-72.
39. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 2006;24:4983-90.
40. Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007;11:860-8.
41. Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. Ann Surg 2008;247:118-24.
42. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. J Clin Oncol 2005;23:9073-8.
43. Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. J Am Coll Surg 2005;200:845-53.
44. Kishi Y, Zorzi D, Contreras CM, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. Ann Surg Oncol 2010;17:2870-6.
45. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg 2010;14:1691-700.
46. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939-45.
47. Wieser M, Sauerland S, Arnold D, et al. Peri-operative chemotherapy for the treatment of resectable liver metastases from colorectal cancer: A systematic review and meta-analysis of randomized trials. BMC Cancer 2010;10:309.
48. Leelaudomlipi S, Sugawara Y, Kaneko J, et al. Volumetric analysis of liver segments in 155 living donors. Liver Transpl 2002;8:612-4.
49. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107:521-7.
50. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. Br J Surg 2001;88:165-75.
51. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-80; discussion 680-1.
52. Goto Y, Nagino M, Nimura Y. Doppler estimation of portal blood flow after percutaneous transhepatic portal vein embolization. Ann Surg 1998;228:209-13.
53. Lee KC, Kinoshita H, Hirohashi K, et al. Extension of surgical indications for hepatocellular carcinoma by portal vein embolization. World J Surg 1993;17:109-15.
54. Nagino M, Nimura Y, Kamiya J, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. Hepatology 1995;21:434-9.
55. Shindoh J, Truty MJ, Aloia TA, et al. Kinetic growth rate after portal vein embolization predicts posthepatectomy outcomes: toward zero liver-related mortality in patients with colorectal liver metastases and small future liver remnant. J Am Coll Surg 2013;216:201-9.
56. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.
57. Alvarez FA, Ardiles V, Sanchez Claria R, et al. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS): Tips and Tricks. J Gastrointest Surg 2013;17:814-21
58. de Santibañes E, Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the "ALPPS" approach. Ann Surg 2012;255:415-7.
59. Aloia TA, Vauthey JN. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): what is gained and what is lost? Ann Surg 2012;256:e9; author reply e16-9.
60. Wanebo HJ, Chu QD, Avradopoulos KA, et al. Current perspectives on repeat hepatic resection for colorectal

carcinoma: a review. Surgery 1996;119:361-71.
61. Neeleman N, Andersson R. Repeated liver resection for recurrent liver cancer. Br J Surg 1996;83:893-901.
62. Antoniou A, Lovegrove RE, Tilney HS, et al. Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases. Surgery 2007;141:9-18.
63. Adair RA, Young AL, Cockbain AJ, et al. Repeat hepatic resection for colorectal liver metastases. Br J Surg 2012;99:1278-83.
64. Andreou A, Brouquet A, Abdalla EK, et al. Repeat hepatectomy for recurrent colorectal liver metastases is associated with a high survival rate. HPB (Oxford) 2011;13:774-82.
65. Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 1999;10:663-9.
66. Bismuth H, Adam R, Lévi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 1996;224:509-20; discussion 520-2.
67. Brouquet A, Overman MJ, Kopetz S, et al. Is resection of colorectal liver metastases after a second-line chemotherapy regimen justified? Cancer 2011;117:4484-92.
68. Nordlinger B, Van Cutsem E, Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol 2009;20:985-92.
69. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
70. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-44.
71. Ribero D, Wang H, Donadon M, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 2007;110:2761-7.
72. Klinger M, Eipeldauer S, Hacker S, et al. Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. Eur J Surg Oncol 2009;35:515-20.
73. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45.
74. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 2010;11:38-47.
75. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-17.
76. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-705.
77. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619-26.
78. Otto G, Düber C, Hoppe-Lotichius M, et al. Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery. Ann Surg 2010;251:796-803.

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The surgical treatment of patients with colorectal cancer and liver metastases in the setting of the "liver first" approach

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Abstract: A surgical resection is the only curative method in the therapy of colorectal carcinoma and liver metastases. Along with the development of interventional radiological techniques the indications for surgery widen. The number of metastases and patients age should not present a contraindication for surgical resection. However, there are still some doubts concerns what to resect first in cases of synchronous colorectal carcinoma and liver metastases and how to ensure the proper remnant liver volume in order to avoid postoperative liver failure and achieve the best results. Through this review the surgical therapy of colorectal carcinoma and liver metastases was revised in the setting of "liver-first" approach and the problem of ensuring of remnant liver volume.

Keywords: Colorectal liver metastases; liver resections; remnant volume; "liver-first" approach

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Introduction

Treatment of colorectal cancer and liver metastases are an extremely important clinical issue since that there are nearly a million newly diagnosed cases and nearly half of the million reported deaths worldwide (1). In large number of countries the incidence continue to rise (2), although the standardized prevention national programs of early detection have developed and brought to an earlier detection and diagnosed cases in early stage of tumor (3-5). In Asian countries, such as China, Japan, Republic of Korea, and Singapore, a 2-4-fold increase in the incidence of colorectal cancer in the past few decades is experienced (6). In Western World the colorectal cancer is reported as the third the most frequent cancer and the most frequent cancer in population older than 75 years (7).

Approximately 25% of newly diagnosed patients with colorectal cancer will have liver metastases at the time of diagnosis, another 25% will develop liver metastases during the course of the disease and two-thirds of all patients with liver metastases will die of them (8). The 10-year survival rate for patients with stage I disease is 90%, but for patients with inoperable stage IV disease, it is currently only 5% (9). For patients with liver metastases, the treatment strategy should be directed toward resectability (10).

The multidisciplinary therapeutic approach, consisting of new and more effective chemotherapeutic agents in single or combined therapy, an advanced role of interventional radiology with portal vein embolization (PVE) and tumor ablation and new strategies and techniques for hepatic resections, brought improved resectability rate of metastases to 20-30% of cases and has resulted in 5-year survival of 35-50% for selected cases (11-13). A need has been recognized for a new staging system that acknowledges the improvements in surgical techniques for resectable metastases and the impact of modern chemotherapy on rendering initially unresectable liver metastases from colorectal carcinoma resectable while distinguishing between patients with a chance for cure at presentation and those for whom only palliative treatment is possible (14).

There have been presented the predictive factors for survival and local recurrence (15,16). Traditionally, a staged approach (colorectal first) has been used in the management of patients with synchronous colorectal cancer and liver metastases. This involves the initial extirpation of the primary tumor. Systemic chemotherapy followed the operation, after which liver-directed operation was performed. The last 2 decades have brought an increased understanding of the biology of colorectal liver metastases, resulting in more effective targeted therapies in addition to decreased mortality after liver-directed operations (17,18).

The goal of this review is to focus onto the doubts concerning the operators all around the world in the context of reassuring the proper remnant liver volume and especially what to resect first in the cases of synchronous liver metastases of colorectal carcinoma.

The preoperative imaging and planning the surgical resection

The R0 resection is the ultimate goal of the surgical therapy. However the proper indication is essential in order to achieve adequate result of resection. Resectability depends onto the multiple factors: the number and location of metastases, the remnant liver volume and quality of the liver tissue that is not infiltrated by tumor. All lesions identified at the initial imaging records (CT or MRI) before any therapy is performed have to be accounted during planning the liver resection in order to predict the total risk and the outcome of surgical procedure. It is recognized that chemotherapy can induce toxic injury of liver tissue, primarily steatohepatitis and sinusoidal injury. Non-contrast CT and MRI could be used to assess steatosis (19-21), but steatohepatitis cannot be diagnosed with imaging. Sinusoidal injury can be judged by indirect signs of portal hypertension, particularly spleen size (22), or by using the liver-specific MRI contrast agent gadoxetic acid (23). The essential three points that are ultimate for complete resection are preservation of liver vascularity, the adequate remnant liver volume with reference to body weight and total liver volume, and that the quality of the remnant liver parenchyma is acceptable (24). The ultrasound (US), especially contrast enhanced ultrasound (CEUS) presents a unique imaging method for intraoperative assessment of unrevealed metastases, and the relation between tumor and vascular and biliar structures (25), sometimes even significantly more sensitive than CT and/or MRI preoperative imaging records (26). For the detection of extra hepatic metastases and local recurrence at the site of the initial colorectal surgery, apart from CT the use of FDG-PET is widespread. A high quality CT can detect the majority of extrahepatic disease, however the FDG-PET may reveal additional signs of disease as high metabolic activity. Although some studies showed a change in management in 10-20% of patients according to record of FDG-PET (27,28), some reports lower percentage and even seem to be more suspicious in its cost-effective role (29), especially in the context of FDG-records following the preoperative chemotherapy which reduces its sensitivity.

The surgical resection—what to resect first in synchronous metastases?

Surgical treatment of colorectal liver metastases remains the only treatment associated with a long survival time in patients with liver metastases from colorectal carcinoma, with a 40% survival at 5 years and almost 25% postoperative survival up to 10 years in specialized centers (30). The very important issue that the liver surgeon has to deal with is to proceed decide what to resect first liver or colon and/or when to undertake simultaneous surgical resections of both. The perfect solution seems to be a single stage colon and liver operation. The advantage of the one stage procedure could be less psychological stress for the patient, lower financial cost and shorter hospitalization time. On the other hand the advantages of the staged procedure are that there is no accumulation of the risks of liver and bowel resections at the same time. Neoadjuvant chemotherapy may be given before liver resection, and an extended hepatectomy or demanding bowel resection could be performed with the full attention of the surgical team focused on the liver or bowel disease, although, the key point for decision-making is the patient's safety (1). According to the reported initial experience with simultaneous versus staged resections, a French multicenter study showed an operative mortality of 7% for simultaneous 2% for staged surgery (31), while in a single center US study the mortality was 12% for simultaneous and 4% for staged resections (32). Several studies reported simultaneous operations performed without mortality, however patients were selected by experienced hepatobiliary surgeons and the major hepatectomies were avoided in elderly patients the same as in those with demanding colorectal surgery (33-36). In addition, since the surgical mortality rate is significantly higher when surgery of extensive hepatic resections is combined with colorectal resection (37), this approach should be only performed in carefully selected patients.

The standard staged operative treatment recommendations

in the literature suggest resection of the primary tumor followed by chemotherapy for 3-6 months and second stage of surgical treatment that includes liver surgery. The problem with this approach lies in the fact that liver metastases determine survival more intensive than the primary colorectal tumor. Chemotherapy can sometime not be performed after the surgical treatment of the primary tumor, especially when complicated by anastomotic leak or dehiscence, which occurs in 6-12% of patients (38,39). In cases of advanced rectal cancer usually a long term of radio-chemotherapy of 5 weeks is recommended and the second stage of operative treatment is planned 6-10 weeks following the neoadjuvant therapy. Therefore the patients do not receive a therapy of liver metastases for almost 15 weeks, which brings to the progress of liver metastatic disease (40). On the other hand some experimental studies have reported the rapid growth of metastases after removal of primary tumor (41,42). The underlying mechanism for those experimental results could be the loss of primary tumor-induced inhibition of angiogenesis in the metastases, which supports the founding of the increase of vascular density in humans after resection of primary tumor (43).

The reverse surgical approach onto the surgical treatment of colorectal liver metastases known as "liver-first" approach is reported as feasible and safe procedure with promising results, although it brings along the risk of bowel obstruction following the growth of primary tumor, which can be avoided by Hartmanns procedure (39,44). Results from the Liver Met Survey, involving 13,334 patients from 330 centers in 58 countries who underwent surgery for liver metastases, reported a better survival outcome in patients who undergo first resection of liver metastases than in those who do not (45). A recent systematic review of studies published in 1999-2010 confirmed these results and revealed 5-year survival rates for patients with liver metastases in the range of 16-74% (median, 38%) after liver resection (46).

The main idea of the "liver first" approach was to avoid the time loss between the operative therapy of primary tumor and the oncological therapy. Since the patients with rectal cancer often require a complex oncological therapy (chemotherapy, radiotherapy, and a complex pelvic operation), they could be the most proper candidates for such an approach (47). Despite liver-first patients usually have a greater hepatic disease burden and undergoing major resection more often, the reverse strategy was found safe and had long-term outcomes comparable to those of the other approaches (48).

How to achieve resectability without chemotherapy?

A large number of liver metastases should not be an absolute contraindication to surgery combined with chemotherapy provided that resection can be complete, with preservation of a functioning liver remnant of 25-30% (49). However, the problem is the loss of the proper functioning remnant volume of normal liver tissue, which presents an absolute contraindication for surgical resection. Advances in interventional radiology, particularly PVE in which the hypertrophy of normal liver tissue is provoked in order to ensure the proper remnant volume (50) and radiofrequency thermal ablation (RFA) widened the indications for surgical treatment of patients with colorectal cancer and liver metastases. In patients planned for major hepatectomies and with an otherwise normal liver, preoperative PVE is recommended when the ratio of the remnant liver to total liver volume is estimated to be less than 30%, whereas in patients with neoadjuvant chemotherapy this ratio is considered to be 40% (51,52). PVE is a safe procedure, but manipulation of the embolic material to the main portal vein or into branches that supply the future remnant liver remains a risk (1). RFA was initially anticipated for local treatment of hepatocellular carcinoma but has recently found application for the management of colorectal liver metastases, where its indications are still under doubt. Critical review of the results of RFA shows that it must be restricted in cases with a maximum of 3 lesions with the size of the biggest lesion less than 3 cm (53). Another limitation for the use of RFA in the management of colorectal liver metastases is the anatomic location of the lesion near big vessels, which increases the risk of incomplete ablation due to reduced heat effect that is used (54). A great indication of RFA is actually recurrence after resection, detected as small lesions, so it is possible not to interrupt chemotherapy (55).

A novel method in liver surgery that can solve the problem of remnant volume is the associating of liver partition and portal vein ligation (ALPPS) firstly reported 3 years ago (56). In ALPPS approach, the portal vein ligation associated with in situ splitting is able to induce enormously accelerated hypertrophy (57). The neovascularization and persistence of interlobar perfusion are prevented by performing parenchymal dissection and complete devascularization of segment IV (56). The nearly total parenchymal dissection induced a median hypertrophy of 74%, which is markedly above the range that can be achieved by portal vein ligation or PVE alone (58,59).

Conclusions

Surgical R0 resection still remains the only curative therapeutic tool in patients with colorectal cancer and liver metastases. The proper diagnostic algorithm is ultimate. The indications for surgical treatment are enlarged by the progress in neoadjuvant chemotherapy, diagnostic imaging, interventional radiology procedures especially the usage of PVE and radio frequent ablation. On the other hand the surgical techniques still develop producing the new pathways of treatment such as "liver-first approach" in the context of 2-stage operative therapy and ALPPS for the ensuring the remnant liver volume. Simultaneous liver and colorectal operations are feasible at carefully selected patients but should be avoided in cases of major hepatectomies, in elderly patients, and in patients with too complex intraoperative asset of colorectal tumor. The 2-stage hepatectomies as well as the "liver first" approach seem to become the new treatment strategies that improved the prognosis in patients in whom an R0 resection can be achieved with curative intention. The multidisciplinary treatment therapeutic approach in patients with colorectal cancer and liver metastases is essential to make the proper treatment plan and achieve the best results.

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References

1. Dimitroulis D, Nikiteas N, Troupis T, et al. Role of surgery in colorectal liver metastases: too early or too late? World J Gastroenterol 2010;16:3484-90.
2. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008, Version 1.2, Cancer Incidence and Mortality Worldwide. IARC Cancer Base No.10. Available online: http://globocan.iarc.fr. accessed November 23, 2011.
3. Jurisić I, Paradzik MT, Jurić D, et al. National program of colorectal carcinoma early detection in Brod-Posavina County (east Croatia). Coll Antropol 2013;37:1223-7.
4. Milas J, Samardzić S, Miskulin M. Neoplasms (C00-D48) in Osijek-Baranja County from 2001 to 2006, Croatia. Coll Antropol 2013;37:1209-22.
5. Samardzić S, Mihaljević S, Dmitrović B, et al. First six years of implementing colorectal cancer screening in the Osijek-Baranja County, Croatia--can we do better? Coll Antropol 2013;37:913-8.
6. Sung JJ, Lau JY, Goh KL, et al. Increasing incidence of colorectal cancer in Asia: implications for screening. Lancet Oncol 2005;6:871-6.
7. Boyle P, Leon ME. Epidemiology of colorectal cancer. Br Med Bull 2002;64:1-25.
8. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: is there a limit? J Clin Oncol 2005;23:8490-9.
9. Van den Eynde M, Hendl isz A. Treatment of colorectal liver metastases: a review. Rev Recent Clin Trials 2009;4:56-62.
10. Aloia TA, Adam R, Azoulay D, et al. Outcome following hepatic resection of metastatic renal tumors: the Paul Brousse Hospital experience. HPB (Oxford) 2006;8:100-5.
11. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125-35.
12. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759-66.
13. Krebs B, Kozelj M, Potrc S. Rectal cancer treatment and survival--comparison of two 5-year time intervals. Coll Antropol 2012;36:419-23.
14. Poston GJ, Figueras J, Giuliante F, et al. Urgent need for a new staging system in advanced colorectal cancer. J Clin Oncol 2008;26:4828-33.
15. Boras Z, Kondza G, Sisljagić V, et al. Prognostic factors of local recurrence and survival after curative rectal cancer surgery: a single institution experience. Coll Antropol 2012;36:1355-61.
16. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.
17. Mayo SC, Heckman JE, Shore AD, et al. Shifting trends in liver-directed management of patients with colorectal liver metastasis: a population-based analysis. Surgery 2011;150:204-16.
18. Asiyanbola B, Chang D, Gleisner AL, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 2008;12:842-51.
19. Kodama Y, Ng CS, Wu TT, et al. Comparison of CT methods for determining the fat content of the liver. AJR Am J Roentgenol 2007;188:1307-12.
20. Reeder SB, Sirlin CB. Quantification of liver fat with magnetic resonance imaging. Magn Reson Imaging Clin N Am 2010;18:337-57.

21. van Werven JR, Marsman HA, Nederveen AJ, et al. Assessment of hepatic steatosis in patients undergoing liver resection: comparison of US, CT, T1-weighted dual-echo MR imaging, and point-resolved 1H MR spectroscopy. Radiology 2010;256:159-68.
22. Overman MJ, Maru DM, Charnsangavej C, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol 2010;28:2549-55.
23. Shin NY, Kim MJ, Lim JS, et al. Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases. Eur Radiol 2012;22:864-71.
24. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274-86.
25. Chami L, Lassau N, Malka D, et al. Benefits of contrast-enhanced sonography for the detection of liver lesions: comparison with histologic findings. AJR Am J Roentgenol 2008;190:683-90.
26. Leen E, Ceccotti P, Moug SJ, et al. Potential value of contrast-enhanced intraoperative ultrasonography during partial hepatectomy for metastases: an essential investigation before resection? Ann Surg 2006;243:236-40.
27. Necib H, Garcia C, Wagner A, et al. Detection and characterization of tumor changes in 18F-FDG PET patient monitoring using parametric imaging. J Nucl Med 2011;52:354-61.
28. Hendlisz A, Golfinopoulos V, Garcia C, et al. Serial FDG-PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy. Ann Oncol 2012;23:1687-93.
29. Moulton C, Levine MN, Law C, et al. An Ontario Clinical Oncology Group (OCOG) randomized controlled trial (RCT) assessing FDG PET/CT in resectable liver colorectal adenocarcinoma metastases (CAM). J Clin Oncol 2011;29:abstr 3520.
30. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125-35.
31. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer 1996;77:1254-62.
32. Bolton JS, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. Ann Surg 2000;231:743-51.
33. Weber JC, Bachellier P, Oussoultzoglou E, et al. Simultaneous resection of colorectal primary tumour and synchronous liver metastases. Br J Surg 2003;90:956-62.
34. Chua HK, Sondenaa K, Tsiotos GG, et al. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Colon Rectum 2004;47:1310-6.
35. Tanaka K, Shimada H, Matsuo K, et al. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery 2004;136:650-9.
36. Minagawa M, Yamamoto J, Miwa S, et al. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. Arch Surg 2006;141:1006-12; discussion 1013.
37. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol 2007;14:3481-91.
38. Chiappa A, Biffi R, Bertani E, et al. Surgical outcomes after total mesorectal excision for rectal cancer. J Surg Oncol 2006;94:182-93; discussion 181.
39. Tran CL, Udani S, Holt A, et al. Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer. Am J Surg 2006;192:873-7.
40. Verhoef C, van der Pool AE, Nuyttens JJ, et al. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. Dis Colon Rectum 2009;52:23-30.
41. O'Reilly MS, Holmgren L, Shing Y, et al. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 1994;79:315-28.
42. O'Reilly MS, Holmgren L, Chen C, et al. Angiostatin induces and sustains dormancy of human primary tumors in mice. Nat Med 1996;2:689-92.
43. Peeters CF, de Waal RM, Wobbes T, et al. Outgrowth of human liver metastases after resection of the primary colorectal tumor: a shift in the balance between apoptosis and proliferation. Int J Cancer 2006;119:1249-53.
44. Mentha G, Roth AD, Terraz S, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. Dig Surg 2008;25:430-5.
45. Registry of patients operated for Colorectal Liver Metastasis. Available online: http://www.livermetsurvey.org. International livermetsurvey.org, accessed November 23, 2011.

46. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol 2012;4:283-301.
47. Andres A, Toso C, Adam R, et al. A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. Ann Surg 2012;256:772-8; discussion 778-9.
48. Mayo SC, Pulitano C, Marques H, et al. Surgical Management of Patients with Synchronous Colorectal Liver Metastasis: A Multicenter International Analysis. J Am Coll Surg 2013;216: 707-16.
49. Adam R, De Gramont A, Figueras J, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist 2012;17:1225-39.
50. Makuuchi M, Thai BL, Takayasu K, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery 1990;107:521-7.
51. Abdalla EK, Barnett CC, Doherty D, et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-80; discussion 680-1.
52. Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery 2000;127:512-9.
53. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol 2005;23:1358-64.
54. Terraz S, Constantin C, Majno PE, et al. Image-guided multipolar radiofrequency ablation of liver tumours: initial clinical results. Eur Radiol 2007;17:2253-61.
55. Mentha G, Majno P, Terraz S, et al. Treatment strategies for the management of advanced colorectal liver metastases detected synchronously with the primary tumour. Eur J Surg Oncol 2007;33 Suppl 2:S76-83.
56. Baumgart J, Lang S, Lang H. A new method for induction of liver hypertrophy prior to right trisectionectomy: A report of three cases HPB (Oxford, England) 2011;13:71-2.
57. Torres OJ, Moraes-Junior JM, Lima e Lima NC, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a new approach in liver resections. Arq Bras Cir Dig 2012;25:290-2.
58. de Santibañes E, Alvarez FA, Ardiles V. How to avoid postoperative liver failure: a novel method. World J Surg 2012;36:125-8.
59. Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012;255:405-14.

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Surgery for liver metastasis from gastric cancer

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Surgical management of hepatic metastases from gastric cancer is becoming one of the hot topics in gastric oncology. This is matter of satisfaction for the Italian Research Group on Gastric Cancer, who actively explored this particular subject. On the basis of our data and those from the literature, in a recent editorial we sponsored a "μετάνοια" (change of mind) that could lead to include surgery among the therapeutic options for a subgroup of metastatic gastric cancer patients (1).

We note that review articles follow each other with increasing frequency and almost parallel the number of research article but, fortunately, we also observe that the number of cases begins to rise. In fact, in 2010 Kerkar and colleagues (2) reviewed 436 patients collected from 19 surgical series published over a 20-year time-span, in 2014 Fitzgerald and colleagues (3) collected 481 cases published in the period 1990 to 2013, but the last review and meta-analysis, published on line in the spring of 2016 (4), considered 991 patients who underwent liver resection for hepatic metastases from gastric cancer, recruited from 1990 to 2015. It really seems that seeds planted by a handful of Pioneers begin to grow and surgery, at least in referring centres, begins to be considered as one of the possible therapeutic options for these patients. Furthermore, the fact that a group of preeminent scientists and surgeons dedicates to this topic a full meta-analysis suggests that the route we explored may be correct.

The work by Markar and colleagues we were asked to comment shows some points of unequivocal agreement among the different authors that published in this domain, resumed as follows:

(I) Surgical indications are well established: liver only metastatic disease, preservation of postoperative liver function and surgical resection aimed to full control of hepatic and gastric disease (R0);

(II) In the above conditions surgery suffers very low mortality (median 0%, range, 0–30%) and morbidity rates typical of all major surgical procedures (median 24%, range, 0–48%);

(III) Pooled 1-, 3-, and 5-year survival were 68%, 31% and 27%, respectively, with a median survival of 21 months (range, 9–52 months);

(IV) Eastern patients display better survival performances than their Western counterparts: at the considered time-point survival was 79% *vs.* 59%, 34% *vs.* 24.5% and 27.3% *vs.* 16.5%. Furthermore, the meta-analysis performed on comparative studies showed that:

  (i) Surgical resection of hepatic metastases is associated to improved survival if compared to no surgical resection (HR =0.50; 95% CI: 0.41–0.61; P<0.001);

  (ii) Patients with solitary hepatic metastasis have better 5-year survival than those affected by multiple metastases who were operated on (OR =0.31; 95% CI: 0.13–0.76; P=0.011);

  (iii) There is no difference in 5-year survival after resection of synchronous and metachronous metastases (OR =1.28; 95% CI: 0.46–3.57, P=0.631).

In extreme synthesis, the meta-analysis we are commenting gives official approval to the clinical experiences that originated the literature on this particular topic: surgery has a role in the management of a well defined subset of

metastatic gastric cancer.

We would like to add another statement to those listed above. It is self-explaining and immediate: multi-disciplinary approach offers the best results and adjuvant chemotherapy is a major prognostic factor in this subgroup of patients (5).

To these editorialists, however, some critical points raised by the review merit special discussion.

The first and the one with greatest impact in every-day clinical practice is the selection of candidates to curative surgery. At present the curve that describes survival after surgery suffers a step drop during the first year, suggesting that some abusive procedures are performed: mortality is around 40% after 6 months and reaches 70–80% 1 year after surgery.

Some indications arise from six papers that (6-11) considered cohorts of patients as observed in every-day clinical practice and not upon super-selected populations submitted to surgical treatment.

In the different settings of the disease, synchronous and metachronous presentation, simple clinical variables may be employed to select the best candidates for curative surgery (7,8,11) and those to be excluded from hepatic resection. In the synchronous setting (7) gastric cancer T>2 and scattered bilobar metastases (H3) are negative prognostic factors: median and 5-year survival was respectively 23 months and 27% for the 10% of cases which did not display the two risk factors, while patients affected by T≥3 gastric cancer and H3 metastases (30% of cases) displayed a median survival of 6 months and did not survive more than 16 months. Accordingly, in the metachronous setting (11) the variable T4, N+ and G3 showed a negative prognostic role. Patients not presenting these variables (7%) had a 5-year survival rate of 40%, those affected by two or three negative prognostic factors (48%) had a median survival of 4±3 months. Upon these bases, it is possible to select the best candidates for curative resection, those for whom an aggressive treatment should be mandatory, from those who will not benefit from hepatectomy. All together, they represent 40–55% of cases. In the middle one finds the huge group of cases presenting one risk factor. They do not display an astonishing survival performance (median survival is around 8–9 months). Yet among these it is possible to find long-term survivors. We think that in these cases the therapeutic decision should be discussed on a case by case basis, considering that a major prognostic factor emerging from the literature is represented by the possibility to achieve a curative resection.

The second point we want to discuss concerns the different prognostic factors in the subgroup of patients submitted to hepatectomy. Two of them have special importance. Gastric cancer progression through the serosa (T4) is a negative prognostic determinant that must always be considered, as it opens the door of the peritoneal cavity (5,12-14). Beside this, we would like to insist here that the completeness of tumor bulk removal is the key-point of the therapeutic strategy. The expansion of the experience and the most recent series focusing on surgical subgroups, indicate this point precisely. In a recent review of our cases (5), we were surprised by the absence, once excluded the factor T of the gastric primary, of other gastric cancer or metastasis-related prognostic variables emerging from our data. Indeed, this enhances the surgeon's role in the management of these cases.

In the synchronous setting R0 resection must be achieved both on the hepatic metastases and on the gastric primary, thus gastrectomy must be routinely associated to D≥2 lymphectomy.

In our experience, once R0 resection can be achieved, the extent of hepatic involvement no longer influences the prognosis. This finding is in contrast with data from some of the most numerous cohorts published (6,8,10,15,16) but merits full attention. From a speculative point of view, this enforces the idea that hepatic metastases may still be included in the concept of regional disease, which may benefit from regional surgery. This concept is well validated for metastases from colorectal cancer, but it is absolutely new for metastases from gastric cancer.

The third point concerns the prognostic role displayed by the timing of metastatic disease.

Clinicians consider the metachronous presentation as more favorable. The conclusion of the commented meta-analysis seems to contradict this certitude. It must be noted, however, that they only considered the 5-year survival and not the entire survival curve. Patients submitted to hepatectomy for metachronous metastases benefit of a better selection and display better survival performance in the short and medium term; at 5 years, however, survival curves tend to approximate each-other (5).

Concluding this editorial we'd like to comment the observation by Markar and co-authors concerning the limits of literature as far as the performance status and co-morbidity of studied patients are considered. We are confident that in this phase the majority of surgeons reserved their attention to the best patients, those fit for surgery and with the more favourable hepatic involvement. We fully appreciate the scientific biases linked to these limits

but also the results emerging from the simple, common-sense oriented clinical practice. These results encourage the surgical treatment of these cases, at least in the best conditions. The biologic impact of this kind surgery is also unknown, but we noted in our outpatient activity that the postoperative period is easy, that patients perform well and are generally satisfied of the treatment they received. These are all the reasons that encourage our activity in promoting this relatively neglected topic.

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Footnote

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References

1. Tiberio GA, Roviello F, Donini A, et al. Hepatic metastases from gastric cancer: A surgical perspective. World J Gastroenterol 2015;21:11489-92.
2. Kerkar SP, Kemp CD, Avital I. Liver resections in metastatic gastric cancer. HPB (Oxford) 2010;12:589-96.
3. Fitzgerald TL, Brinkley J, Banks S, et al. The benefits of liver resection for non-colorectal, non-neuroendocrine liver metastases: a systematic review. Langenbecks Arch Surg 2014;399:989-1000.
4. Markar SR, Mikhail S, Malietzis G, et al. Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis. Ann Surg 2016;263:1092-101.
5. Tiberio GA, Ministrini S, Gardini A, et al. Factors influencing survival after hepatectomy for metastases from gastric cancer. Eur J Surg Oncol 2016;42:1229-35.
6. Cheon SH, Rha SY, Jeung HC, et al. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. Ann Oncol 2008;19:1146-53.
7. Tiberio GA, Coniglio A, Marchet A, et al. Metachronous hepatic metastases from gastric carcinoma: a multicentric survey. Eur J Surg Oncol 2009;35:486-91.
8. Ueda K, Iwahashi M, Nakamori M, et al. Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer. Langenbecks Arch Surg 2009;394:647-53.
9. Hwang SE, Yang DH, Kim CY. Prognostic factors for survival in patients with hepatic recurrence after curative resection of gastric cancer. World J Surg 2009;33:1468-72.
10. Makino H, Kunisaki C, Izumisawa Y, et al. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. Anticancer Res 2010;30:2367-76.
11. Tiberio GA, Baiocchi GL, Morgagni P, et al. Gastric cancer and synchronous hepatic metastases: is it possible to recognize candidates to R0 resection? Ann Surg Oncol 2015;22:589-96.
12. Takemura N, Saiura A, Koga R, et al. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. Langenbecks Arch Surg 2012;397:951-7.
13. Ambiru S, Miyazaki M, Ito H, et al. Benefits and limits of hepatic resection for gastric metastases. Am J Surg 2001;181:279-83.
14. Sakamoto Y, Sano T, Shimada K, et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. J Surg Oncol 2007;95:534-9.
15. Schildberg CW, Croner R, Merkel S, et al. Outcome of operative therapy of hepatic metastatic stomach carcinoma: a retrospective analysis. World J Surg 2012;36:872-8.
16. Kinoshita T, Kinoshita T, Saiura A, et al. Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases. Br J Surg 2015;102:102-7.

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Is there any role for liver resection in the treatment of liver metastases from gastric carcinoma?

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Hepatectomy is an increasingly utilised treatment for liver-limited metastatic disease. While this is usually in the setting of colorectal metastases, occasionally there is a role for this in other malignancies (1). Markar *et al*. (2) have recently published a systematic review and pooled analysis on the role of hepatectomy for gastric adenocarcinoma metastases. Primary outcome was assessed as overall survival following liver resection; secondary outcomes examined were morbidity and mortality rates and prognostic factors that may impact survival following resection. These aims were similar to those of an earlier review (3) of the same topic published some two years ago, and four new studies have been published since that time and were included in this present review, providing an update on current evidence.

Markar *et al*. (2) reviewed a total of 39 reports, including close to 1,000 patients who had undergone hepatectomy for gastric adenocarcinoma liver metastases. It was noted that the majority of patients included were from Asian (737 patients) rather than Western (254 patients) centres, which probably reflects the higher incidence of gastric adenocarcinoma in the East (4). Of the studies identified, none were randomized controlled trials. The majority of included studies were case series, with eight papers providing survival data on patients with metastatic gastric adenocarcinoma who hadn't undergone hepatectomy as a comparative cohort. Additionally, the case series were generally small, with the median number of patients undergoing hepatectomy being 21; only four studies included more than 50 patients (5-8).

This review confirms that, while hepatectomy for gastric adenocarcinoma is rare, it can be performed safely, with 30-day mortality as low as 0% and 30-day morbidity ranging from 0–47%. Median survival was 21 months and 1-, 3- and 5-year survivals were reported as 68%, 31% and 27%. These outcomes are in keeping with previously reported outcome data (2). Interestingly, survival outcomes were better in Asian centres, which may be a reflection of higher-volume centres treating more patients.

The authors have conducted a pooled-analysis including nine identified studies of survival outcome comparing patients who underwent resection of hepatic metastases with patients who had not undergone resection. They concluded that there was a significantly improved survival benefit (HR =0.5; 95% CI: 0.41–0.61; P<0.001) for patients undergoing hepatic resection. The major drawback with such a statistical comparison is the variation of cohorts being included for comparison. None of these studies were randomized controlled trials. In the eight studies that included a cohort who did not undergo hepatectomy, the usual reason for not undergoing resection was that the extent of intra-hepatic disease was such that hepatectomy was not feasible. In this instance, it is difficult to ascertain if the improved survival was due to a benefit of hepatectomy or simply a reflection of extent of disease. Of note, one of the studies included in the pooled-analysis comparing resection with non-resection did not include any data for cohort that did not undergo resection. (9)

Seven studies were included in a pooled analysis comparing outcomes following hepatectomy in patients with solitary metastasis to that of patients with multiple metastases. 5-year survival was demonstrated to be greater

(OR =0.31; 95% CI: 0.13–0.76; P=0.011) in patients following resection of a solitary metastasis.

Survival following resection of synchronous and metachronous metastases were compared by pooled analysis of seven studies, and interestingly, no difference was demonstrated in 5-year survival. Our own earlier review (3) concluded that patients with metachronous metastases may have a better prognosis than patients with synchronous metastases. We included three studies, all of which were included in the present review, which demonstrated greater survival in patients with metachronous metastases, particularly when comparing survival within 3 years of resection (10-12).

This current review confirms that in very select patients, there may be a role for hepatectomy in the treatment of liver-limited metastases from gastric adenocarcinoma. Reported survival following resection is greater than what may be expected for patients with metastatic gastric adenocarcinoma, and there seemed to a favourable prognosis following liver resection when compared to those patients who did not undergo resection. It must be borne in mind that patients included as comparators were generally those with more extensive disease not suitable for resection, and therefore better survival may simply be a reflection of less extensive or less aggressive disease, rather than solely as a consequence of liver resection.

We agree with the reviewers' conclusion that a prospective study would be required to more accurately assess the benefit of hepatectomy in these patients, however recruitment to such a trial would prove challenging, as fewer than 3% of patients who undergo gastrectomy have hepatic metastases that meet the highly selective criteria described in previously published studies (3).

In conclusion, we concur with the authors of the present review that there may be a place for liver resection with curative/long-term survival intent in a limited number of highly selected patients with gastric adenocarcinoma that metastasised to the liver.

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References

1. Elias D, Cavalcanti de Albuquerque A, Eggenspieler P, et al. Resection of liver metastases from a noncolorectal primary: indications and results based on 147 monocentric patients. J Am Coll Surg 1998;187:487-93.
2. Markar SR, Mikhail S, Malietzis G, et al. Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis. Ann Surg 2016;263:1092-101.
3. Grimes N, Devlin J, Dunne DF, et al. The role of hepatectomy in the management of metastatic gastric adenocarcinoma: a systematic review. Surg Oncol 2014;23:177-85.
4. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137-50.
5. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. Ann Surg 2006;244:524-35.
6. Aizawa M, Nashimoto A, Yabusaki H, et al. Clinical benefit of surgical management for gastric cancer with synchronous liver metastasis. Hepatogastroenterology 2014;61:1439-45.
7. Takemura N, Saiura A, Koga R, et al. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. Langenbecks Arch Surg 2012;397:951-7.
8. Tiberio GA, Baiocchi GL, Morgagni P, et al. Gastric cancer and synchronous hepatic metastases: is it possible to recognize candidates to R0 resection? Ann Surg Oncol 2015;22:589-96.
9. Wang YN, Shen KT, Ling JQ, et al. Prognostic analysis of combined curative resection of the stomach and liver lesions in 30 gastric cancer patients with synchronous liver metastases. BMC Surg 2012;12:20.

10. Ambiru S, Miyazaki M, Ito H, et al. Benefits and limits of hepatic resection for gastric metastases. Am J Surg 2001;181:279-83.
11. Okano K, Maeba T, Ishimura K, et al. Hepatic resection for metastatic tumors from gastric cancer. Ann Surg 2002;235:86-91.
12. Schildberg CW, Croner R, Merkel S, et al. Outcome of operative therapy of hepatic metastatic stomach carcinoma: a retrospective analysis. World J Surg 2012;36:872-8.

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Hepatic resection, hepatic arterial infusion pump therapy, and genetic biomarkers in the management of hepatic metastases from colorectal cancer

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Abstract: The liver is the most common site of colorectal cancer metastasis. Fortunately, improvements have been made in the care of patients with colorectal liver metastasis (CRLM). Effective management of CRLM requires a multidisciplinary approach that is tailored to individuals in order to achieve long-term survival, and cure. Resection and systemic chemotherapy provides benefit in selected individuals. An adjunct to resection and/or systemic chemotherapy is the use of hepatic arterial infusion pump (HAIP) therapy. Many studies show HAIP provides benefit for select patients with CRLM. Added to the crucible of a multidisciplinary approach to managing CRLM is the ever growing understanding of tumor biology and genetic profiling. In this review, we discuss the outcomes of resection, systemic therapies and HAIP therapy for CRLM. We also discuss the impact of recent advances in genetic profiling and mutational analysis, namely mutation of KRAS and BRAF, for this disease.

Keywords: Colorectal liver metastasis (CRLM); resection; parenchymal-sparing; hepatic artery infusion pump (HAIP); KRAS; BRAF; FOLFOX

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Introduction

About 132,700 new cases of colorectal cancer (CRC) are diagnosed each year in the United States. The liver is the most common site of metastatic disease, with up to 60% of patients ultimately developing liver metastases (CRLM) (1). Fortunately, significant improvements have been made for patients with metastatic colorectal cancer (mCRC).

Initial reports of hepatic resection for CRLM demonstrated an unexpected, prolonged long-term survival (2). Long-term follow up documented the curative potential of hepatic resection for limited CRLM in 15 to 25% of patients (3). Up until the 1990's, hepatic resections were fraught with significant blood loss, subsequent peri-operative complications, and a high mortality rate (4). Better understanding of hepatic anatomy, resection techniques, intraoperative anesthetic management, and postoperative care, have improved peri-operative outcomes. Currently, hepatic resection for CRLM is effective when performed at high volume specialty centers achieving a perioperative mortality rate of 1% (5,6). Parallel to this, evidence supports the use of hepatic artery infusion (HAI) of chemotherapy as an adjunct to managing CRLM. Likewise, our understanding of genetic aberration in CRLM emerges as important factor in treatment plans and prognosis.

In this review, we discuss surgical treatment and associated outcomes in the treatment of CRLM. In addition, the role and efficacy of HAI therapy are examined. Finally, we outline how genetic profiling and mutational

analysis can impact management of this disease in this era of molecular-based targeted therapies.

Surgical management of CRLM

Resection for CRLM has been well established over the last three decades. Patient selection with preoperative multidisciplinary review and improved perioperative management make resection a safe and effective treatment modality for patients with operable CRLM.

Patients' disease burden and future liver remnant are analyzed with cross-sectional imaging, volumetric studies, and evaluation of hepatic synthetic function. In general, patients with CRLM are considered resectable if their tumor burden can be removed with a negative margin while leaving a viable liver remnant that is able to drain bile and provide adequate synthetic function. Twenty percent of patients are estimated to have resectable disease at presentation (7).

Despite being technically resectable, outcomes are varied, and associated with a number of clinical and pathologic factors. Multivariate analysis of retrospective studies have shown that patient age, hepatic margin status, extrahepatic disease, number and size of tumors, CEA level, disease-free interval (DFI), and lymph node status of the primary tumor are associated with recurrence and survival after hepatic resection for CRLM (8,9). Many studies have combined these prognostic factors into clinical risk scores in attempts to improve prognostication. Stratifying patients into low and high-risk scores can predict survival following resection. In one example, a low-risk score was associated with a 60% 5-year survival while a high-risk score had an associated 14% 5-year survival. Despite effective stratification with clinical risk scores, patients with high-risk scores that undergo complete resection still have the potential for long-term survival and cure. These statistics underscore the need for better risk-stratification tools. The only factors that appear to make cure extremely unlikely, however, are a persistent positive hepatic margin and presence of extrahepatic disease (3,10). In summary, for patients with resectable liver-limited CRLM, the presence of adverse prognostic factors and high-risk scores do not preclude the potential for cure with complete resection and should not trump sound clinical judgment.

Hepatic parenchymal sparing techniques in lieu of extensive resections should now be routine in contemporary surgical management of CRLM and have been associated with significant improvements in perioperative outcomes (5,6). House *et al*. published a retrospective study of 1,600 consecutive patients who underwent resection for CRLM to determine the outcomes in two separate eras [1985-1998, 1999-2004]. The incidence of hemi-hepatectomy and wedge resections decreased in the latter era. Segmental resections are being performed more frequently with improved perioperative outcomes, and without jeopardizing oncologic principles (11). Historically, mortality following hepatic resection was high but now the 90-day mortality related to resection for CRLM is less than 1% in experienced high volume centers (5).

Despite 5-year survival rates of 20-50% following complete resection, recurrence rates approach 70-80% with long-term follow up (12). The high recurrence rates provide the rationale for treating microscopic disease with adjuvant chemotherapy, in an attempt to improve outcomes. Early randomized trials demonstrated that the addition of adjuvant 5-FU chemotherapy as compared to resection alone was not associated with improved progression-free (PFS), or overall survival (OS) (13).

The EORTC intergroup 40983 randomized trial evaluated perioperative FOLFOX for patients with limited and resectable CRLM (14,15). Patients were randomized to receive perioperative FOLFOX or surgery alone. The initial publication on this trial documented a significant 7.3% absolute increase in PFS. However, with longer term follow up, OS was not statistically different between the two groups. This trial demonstrated that perioperative FOLFOX chemotherapy may improve early PFS but was not associated with improved survival. While this trial was not powered to detect small differences, it ruled out a major impact on OS. However, this patient cohort was heterogenous. It is clear that select patients in each treatment group had durable survival while others did not. This again adds mounting evidence for the need of improved predictive factors and that CRLM is a heterogenous disease process.

In summary, multidisciplinary management that incorporates both patient and tumor-related factors should be performed in order to individualize treatment plans. Hepatic resection for CRLM is the standard of care for patients who are able to undergo operation and with resectable disease, due to associated long-term survival and potential for cure. Of those undergoing a potentially curative resection, survival is approximately 50% at 5-year, and the cure rate ranges from 20-25%, which is superior to chemotherapy alone (3). Unfortunately, the benefit of neoadjuvant and adjuvant systemic chemotherapy is not

well understood in the context of curative surgery. The high recurrence rates after resection underscore the continued need for development of effective adjuvant therapies in patients undergoing resection of CRLM.

HAI pump therapy

Contemporary systemic therapies include 5-FU in combination with either oxaliplatin (FOLFOX), irinotecan (FOLFIRI) or both (FOLFOXIRI) (16-18). These provide response rates of 50% and median survivals of 16-24 months for untreated mCRC (17,19,20). Biologic agents targeting vascular endothelial growth factor (bevacizumab) or epidermal growth factor receptor (cetuximab) improve responses rates in select patients (21,22). Salvage with second and third line chemotherapeutic regimens once progression occurs provides diminutive benefit, with response rates no greater than 10% or 15% (23). These outcomes provide a benchmark with which to compare the efficacy of HAI chemotherapy.

HAI chemotherapy has been studied for decades (24,25). The therapy has not been universally embraced, perhaps because of the surgical training and expertise required for pump placement, the requirement for diligent and frequent follow-up, and the ability to recognize and manage complications. HAI chemotherapy requires establishment of a multi-disciplinary program consisting of a specialist surgeon, medical oncologist, interventional radiologist, gastroenterologist, nuclear medicine radiologist, technologists, and nursing staff.

The rationale for HAI therapy is based upon anatomic and pharmacologic principles. The hepatic arteries exclusively perfuse CRLM, while the portal vein and hepatic arteries jointly perfuse normal hepatocytes (26). The use of drugs that are extracted by the liver during first-pass metabolism results in high local concentrations of drug with minimal systemic exposure. Ensminger and colleagues showed that 94% to 99% of floxuridine (FUDR) is extracted by the liver during the first pass compared with 19% to 55% for 5-FU (27). In fact, mean tumor FUDR levels are increased 15-fold when the drug is injected via the hepatic artery (28). FUDR is therefore an ideal drug for HAI, providing a high hepatic concentration of drug with minimal systemic spill over and resultant toxicity. The development of an implantable infusion pump allowed for the safe administration of hepatic arterial chemotherapy in the outpatient setting (29).

Hepatic artery anatomy has a predilection for variation, with one third of patients possessing aberrant anatomy (30). Currently, computed tomography (CT) angiography provides accurate determination of patient anatomy. A surgeon experienced with dissection of the porta hepatis is required for HAI pump placement. The gastroduodenal artery (GDA) is the preferred conduit for the pump catheter, since other conduits are associated with increased rates of pump-related complications (30).

Hepatic arterial chemotherapy in first-line treatment of unresectable colorectal liver metastases

One of the first randomized trials of HAI therapy for unresectable CRLM was conducted at MSKCC (31). This prospective randomized trial compared HAI therapy with systemic chemotherapy using FUDR in both groups. Of the 99 enrolled patients, 2 complete responses and 23 partial responses (53%) were observed in the group undergoing HAI therapy, compared to 10 partial responses (21%) in the systemic chemotherapy group (P=0.001). The crossover rate from systemic chemotherapy to HAI therapy was 60%, of whom 25% subsequently underwent a partial response. The median survival for the HAI therapy and systemic chemotherapy groups was 17 and 12 months, respectively (P=0.424), despite the high cross over of the patients from the systemic chemotherapy group to the HAI therapy group.

The Cancer and Leukemia Group B (CALGB) completed trial 9481, which compared systemic chemotherapy with 5-FU/LV to HAI therapy using FUDR, LV, and dexamethasone (32). One hundred thirty-four patients were randomized without crossover. Most patients (70%) had greater than 30% liver involvement and 78% had synchronous metastases. Ninety-seven percent of patients had not received any chemotherapy. Response rates were significantly higher in the HAI therapy-only group (47% *vs.* 24%; P=0.012), but time to progression was not significantly different (5.3 *vs.* 6.8 months; P=0.8). Time to hepatic progression was significantly improved in the HAI therapy arm (9.8 *vs.* 7.3 months; P=0.017), median OS was significantly better in the HAI therapy arm (24.4 *vs.* 20 months; P=0.0034). At 3- and 6-month follow-up, physical functioning, as measured with quality of life instruments, was improved in the HAI therapy group.

A total of 10 randomized phase III trials comparing HAI to systemic therapy have been completed. Most of these demonstrate a higher response rate with HAI therapy as compared to systemic chemotherapy in patients with unresectable CRLM. Whether improved response rates

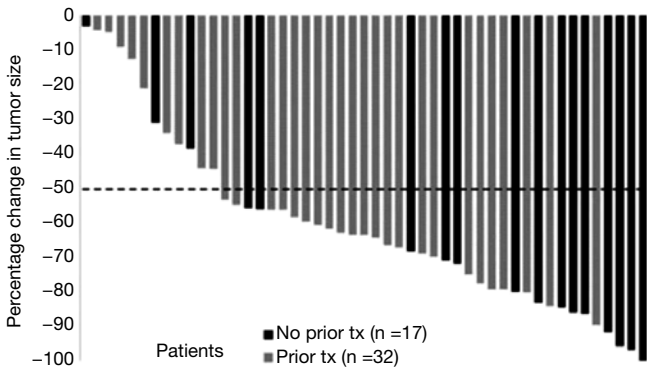

Figure 1 Waterfall plot of response to hepatic arterial infusion pump (HAIP) in phase II trial at MSKCC (40).

translate into prolonged survival is unknown, and most trials were underpowered to detect survival differences. In addition, many of these studies allowed crossover to the HAI therapy. Many trials also used HAI with 5-FU, which is considered less effective than FUDR. Some trials included patients with extrahepatic disease, for which HAI alone is ineffective. Lastly, many trials utilized ports with high failure rates and inability to deliver therapy.

Two meta-analyses of the original seven trials were conducted and included more than 600 patients. The first confirmed the increased response rates seen with HAI therapy over systemic chemotherapy (41% *vs.* 14%) (33). A second meta-analysis published the same year found an absolute survival difference of 12.5% at 1 year (P=0.002) and 7.5% at 2 years (P=0.026) in favor of HAI therapy (34).

Combined hepatic arterial and systemic chemotherapy for treatment of unresectable colorectal liver metastases

Extrahepatic disease progression develops in 40% to 70% of patients who undergo HAI therapy for unresectable CRLM. Since HAI with FUDR results in minimal systemic exposure, combining HAI with FUDR and systemic chemotherapy was the next logical therapeutic strategy. Safi *et al.* studied whether intra-arterial FUDR alone or a combination of intra-arterial FUDR and IV FUDR given concurrently would improve survival (35). Response rates were 60% in both groups. However, the incidence of extrahepatic disease progression was significantly lower in patients who received combined systemic and hepatic therapy.

In a MSKCC phase I study, 36 patients with unresectable CRLM received HAI FUDR and systemic oxaliplatin plus irinotecan or oxaliplatin plus 5-FU/LV. Eighty-nine percent of patients were previously treated and 69% had previously received irinotecan. Both regimens were well tolerated, and response rates for the two groups were 90% and 88% (36). In a non-randomized study analyzing HAI therapy with FUDR and systemic irinotecan after cytoreduction of unresectable hepatic mCRC, 71 patients received therapy and were compared with a historic control group that received cytoreduction alone. Time to progression was 19 *vs.* 10 months, and median survival was 30.6 *vs.* 20 months for the HAI therapy *vs.* control groups, respectively (37). Similarly, a Japanese group examined HAI therapy with 5-FU and systemic irinotecan in previously treated patients and demonstrated response rates of 76.5%, with median OS of 20 months (38). Therefore, as compared systemic therapy alone, HAI therapy combined with modern systemic chemotherapy is associated with higher response rates.

Utilizing chemotherapy to convert unresectable patients to complete resection is an achievable goal of chemotherapy. Adam *et al.* presented their French experience of patients with unresectable CRLM. Of 1,104 patients considered unresectable at presentation, 12.5% were converted to surgical candidates with contemporary systemic cytotoxic chemotherapy (39). The patients who underwent resection realized a 3-year OS of 52%; a number far greater than the benchmark of 2 years for systemic therapy without resection. Importantly, most recurrences were extrahepatic providing the rationale for continued systemic chemotherapy. In a recent prospective phase II trial of HAI therapy and modern systemic chemotherapy combined with bevacizumab for patients with unresectable CRLM, 49 patients underwent evaluation of the conversion rate from unresectable liver metastases to complete resection as the primary outcome (40). Sixty-five percent of patients had received previous systemic chemotherapy. The median number of metastases was 14. The overall response rate was 76%. Importantly as depicted in a waterfall plot, most patients had a greater than 50% reduction in tumor volume (*Figure 1*). Such a dramatic improvement in tumor burden allows for resection to be considered. Twenty-three patients (47%) achieved conversion to resection at a median of 6 months from treatment initiation. Median OS and PFS were 38 and 18 months, respectively, with resection being the only factor associated with prolonged OS and PFS on multivariate analysis (3-year OS of 80% when resected compared with 26% in unresectable patients). Ten patients had no evidence of disease at the time of publication with a median follow up of 39 months. Importantly, a high

biliary toxicity rate was found in the first 24 patients whose treatment included bevacizumab, but without any positive impact on outcome. As a result, bevacizumab is no longer used in HAI therapy combinations (41).

Moreover, Elias *et al.* presented their French experience of 87 patients with isolated CRLM between 1999 and 2003 who were treated with both HAI of oxaliplatin and systemic 5-FU. Importantly, 79% of patient had received prior contemporary systemic chemotherapy. Twenty-six percent of the cohort were converted to resectability and realized median OS of 42 months (42). Therefore, in two separate studies, HAI therapy converts unresectable patients to surgical candidates which confers long-term survival.

Adjuvant hepatic arterial chemotherapy following liver resection

Following resection of CRLM, at least 60% to 70% of patients recur at a median of 16 months (12). Patterns of recurrence are important to consider when devising adjuvant treatment strategies. At least half of all recurrences involve the liver, and, in one study, 64% of patients had their first site of recurrence in the liver (12). This provides rationale for targeting the liver as an adjunct to adjuvant systemic therapies.

There are four randomized trials evaluating adjuvant HAI chemotherapy following hepatic resection of CRLM. In an MSKCC study, 156 patients with resected hepatic metastases were randomized to either 6 months of systemic 5-FU/LV or systemic 5-FU/LV plus HAI therapy with FUDR (43). Randomization was performed intraoperatively after complete resection. Patients were stratified based on the number of metastases and prior treatment history. The primary endpoint was 2-year survival and was 86% in the combined-therapy group *vs.* 72% for those who received systemic chemotherapy alone (P=0.03), with median survival of 72.2 and 59.3 months, respectively. In an updated analysis, with a median follow-up of 10 years, OS was 41% in the HAI group versus 27% in the systemic chemotherapy only group (P=0.10) (8,44). Overall PFS was significantly greater in the combined-therapy group (31.3 *vs.* 17.2 months; P=0.02). The median hepatic PFS was not yet reached in the combined-therapy group, whereas it was 32.5 months in the monotherapy group (P<0.01).

In a German multi-institutional study, 226 patients were randomized to resection alone without systemic therapy or resection plus 6 months of HAI therapy with 5-FU/LV given as a 5-day continuous infusion every 28 days (20). The study was terminated early, due to an interim analysis suggesting a low chance of survival benefit with HIA therapy. The impact of HAI therapy in this study is difficult to assess because only 74% of patients assigned to HAI therapy received this treatment, and only 30% completed it. There was no difference in time to progression, time to hepatic progression, and median OS in an intention-to-treat analysis. When patients were analyzed "as treated", time to hepatic progression (45 *vs.* 23 months) and time to progression or death (20 *vs.* 12.6 months) was improved in the HAI therapy arm. Despite this trial's shortcomings, when analyzed appropriately it was still a positive trial showing HAI efficacy.

The intergroup study randomized 109 patients to resection alone without systemic therapy, or resection followed by 4 cycles of HAI therapy with FUDR and infusional systemic 5-FU, followed by systemic 5-FU (45). The endpoint was disease-free survival (DFS). The 4-year (DFS) (46% *vs.* 25%; P=0.04) and 4-year hepatic DFS (67% *vs.* 43%; P=0.03) favored HAI therapy but no difference was reported in median or 4-year OS between the groups when analyzed on an intention-to-treat basis.

Finally, a study conducted in Greece on 122 patients used mitomycin C, 5-FU, and interleukin (IL)-2 by both HAI therapy and the IV route *vs.* the IV route alone. The 2-year survival, 5-year survival, DFS, and hepatic DFS were all significantly longer for the HAI therapy plus systemic chemotherapy group (46).

The potential benefit of combination HAI FUDR therapy when combined with modern systemic chemotherapy in the adjuvant setting is unknown since no randomized trials addressing this have been performed. In a retrospective analysis, House and colleagues retrospectively compared 125 patients who underwent HAI therapy with FUDR with 125 consecutive similar patients who received modern systemic therapy alone, and noted an associated prolonged OS, hepatic recurrence-free survival (RFS), and disease-specific survival (DSS) with adjuvant combination HAI and systemic therapy; 75%, 48%, and 79%, *vs.* 55%, 25%, and 55%, respectively (P<0.01) (47). Therefore, despite contemporary cytotoxic chemotherapy, HAI FUDR continues to provide better outcomes for those with CRLM.

To further illustrate this point, a phase I trial combining adjuvant HAI FUDR with escalating doses of oxaliplatin and 5-FU was performed. Safety and feasibility were established and the 4-year OS and PFS were a very promising 88% and 50%. In a randomized phase II

trial of patients treated with HAI FUDR and modern systemic chemotherapy (depending on prior treatment) randomized to receive bevacizumab or not, the 4-year OS was 85% (32,48).

In another study from France, 98 patients underwent curative resection of CRLM. Forty-four patients received combined HAI of oxaliplatin with systemic 5-FU. Fifty-four patients received contemporary systemic therapy alone. Three-year disease free survival was 33% compared to 5% (P=0.0001) for those treated with HAI oxaliplatin versus systemic alone. Additionally, OS showed a trend for improvement for those treated with HAI oxaliplatin (49).

A new review comparing patients treated with adjuvant HAI and systemic therapy after liver resection prior to 2003 or after 2003 show a 5-year survival of 56% and 80% for those treated before or after 2003, respectively (50).

In summation, these data show combination HAI and systemic chemotherapy therapy provide improved benefit compared to each alone. The findings provide the rationale for a randomized trial comparing adjuvant HAI therapy plus systemic chemotherapy versus modern systemic chemotherapy alone in the treatment of resected CRLM.

Genetic profiling and prognosis for colorectal liver metastases

Cancer is frequently associated with genetic aberrations. These aberrations lead to over or under production of proteins, which, in turn, lead to cellular transformation and autonomous growth potential. KRAS and BRAF mutations have emerged as important genetic aberrations affecting the management CRLM.

About 20% to 40% of CRC harbor mutations in KRAS (51-53). These mutations are conserved through all stages of a patient's metastatic disease. This suggests that KRAS mutation may be a driving genetic alteration. KRAS mutations may also be prognostic (54). At MSKCC, a retrospective study was performed to determine the impact of KRAS mutation on DSS following hepatic resection for CRLM. KRAS mutation was independently associated with a worse DSS compared to wild-type tumors (2.6 *vs.* 4.8 years) (51). KRAS mutations were also associated with a short DFI and higher numbers of hepatic tumors. In a MD Anderson Cancer Center (MDACC) analysis, all patients undergoing hepatic resection for CRLM received preoperative contemporary cytotoxic chemotherapy and bevacizumab (53). Tumors harboring wild-type KRAS had fewer than 50% viable cells 58% of the time, compared to 38% of the time in mutated KRAS tumors. Hepatic and pulmonary recurrence rates were decreased for wild-type KRAS patients compared to mutated KRAS patients. These differences were associated with a prolonged OS for patients with wild-type KRAS tumors (81% compared to 52% at 3 years). In the Johns Hopkins experience, patients harboring mutated KRAS CRLM had a median RFS of 11 months compared 18 months for those with wild-type KRAS patients following curative resection of CRLM (52).

In another study, 169 patients with resected CRLM received adjuvant HAI therapy and systemic chemotherapy, of whom 118 were wild-type KRAS, and 51 had KRAS mutated tumors (55). The 3-year RFS for patients with wild-type KRAS tumors was 46%, compared with 30% for patients with mutated KRAS tumors (P=0.005). The 3-year OS was 95% *vs.* 81%, respectively. Interestingly, KRAS was an independent predictor of RFS (HR 1.9) on multivariate analysis. In summary, these data suggest that KRAS mutation is associated with an aggressive disease biology and worse outcome after resection of CRLM.

As stated, KRAS mutation is a poor prognostic factor for CRC. Additionally, KRAS mutation predicts a poorer outcome with systemic cytotoxic chemotherapy as illustrated in the MDACC and Johns Hopkins data. In the MSKCC experience, this holds true as well (*Table 1*). However, multimodality treatment for select patients utilizing resection, HAI, and systemic therapy appears to mitigate these poor outcomes. In an updated review of MSKCC experience, patients with CRLM and wild-type KRAS have a 3-year survival of 97% when treated with HAI FUDR and systemic therapy. Those with KRAS mutation realize a 3-year survival of 89% with HAI FUDR and systemic therapy. Both of these survivals are compelling evidence that HAI is providing benefit to those with CRLM above and beyond that provided by systemic therapies alone despite KRAS mutation status.

BRAF is a serine/threonine-protein kinase downstream in the signaling cascade from *ras* produced by the proto-oncogene BRAF. The gene is mutated in multiple tumors including CRC. In general, BRAF mutations portend worse outcome for patients with CRC. In a population-based analysis, OS for patients with mCRC harboring BRAF mutations was 8 months compared to 17 months for wild-type patients and was independently associated with worse outcome (HR 10.6, P <0.001) (56). In the context of metastasectomy for mCRC, the MSKCC experience was analyzed (57). Only 41% of patients with mutated BRAF had isolated liver disease as compared to 63% of those with

Table 1 Differential survival of CRLM treated at three institutions

Study	Pts (n)	Median FU (month)	3-Year RFS (%)		3-Year OS (%)	
			KRAS WT	KRAS MUT	KRAS WT	KRAS MUT
MSKCC (50)	148	80	50	32	97	89
Johns Hopkins (52)	202	18	34	28	70	60
MDACC (53)	193	33	34	14	81	52

Pts, patients; CRLM, colorectal liver metastasis; RFS, recurrence-free survival; OS, overall survival.

wild-type BRAF. Metastases were more likely to be in the peritoneum (26%) or lung (12%) for BRAF mutants. Even in the context of curative metastasectomy, OS was 61% at 2 years for patients with BRAF mutations compared to 86% for wild-type. Despite resections with curative intent, BRAF mutation appears to be a poor prognostic factor.

Micro-array technology to assess mRNA expression in tumors has allowed investigators to study the prognostic impact of genetic expression signatures. Using high throughput RNA and genetic analysis methods, MSKCC has been able to improve accuracy of predicting 3-year outcomes following resection of CRLM by developing an expression molecular risk score (58). This molecular risk score was more prognostic of outcome compared to previously validated clinical risk scores. These results remain in their infancy and require external validation but provide the promise of improving our knowledge of CRLM management.

Conclusions

During the last three decades, there has been progressive improvement in the management of CRLM. Hepatic resection is performed with low risk at high-volume specialized centers, and has been established as the standard of care for resectable disease with associated prolonged survival and potential for cure. Likewise, systemic therapies have improved, with the advent of novel cytotoxic systemic chemotherapeutic agents. Furthermore, targeted therapies are now applied to contemporary drug regimens and have modestly improved outcomes in patients with mCRC. HAI chemotherapy has also evolved, and provides a unique and effective therapy both in the unresectable setting and as an adjuvant therapy following resection seemingly beyond that of systemic therapies alone. Multidisciplinary care for each patient with CRLM is crucial to orchestrate the multiple management strategies to extent survival. Combining clinical features with molecular profiling may provide superior prognostication for patients with CRLM. The promise of individualized therapy, tailored according to specific genetic mutations and disease patterns, is now being realized and continues to evolve.

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Footnote

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Wanebo HJ, Semoglou C, Attiyeh F, et al. Surgical management of patients with primary operable colorectal cancer and synchronous liver metastases. Am J Surg 1978;135:81-5.
3. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575-80.
4. Ekberg H, Tranberg KG, Andersson R, et al. Major liver resection: perioperative course and management. Surgery 1986;100:1-8.
5. Kingham TP, Correa-Gallego C, D'Angelica MI, et al. Hepatic parenchymal preservation surgery: decreasing morbidity and mortality rates in 4,152 resections for malignancy. J Am Coll Surg 2015;220:471-9.
6. House MG, Ito H, Gönen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. J Am Coll Surg 2010;210:744-52, 752-5.
7. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer.

Ann Surg 2006;244:254-9.
8. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.
9. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer 1996;77:1254-62.
10. Carpizo DR, Are C, Jarnagin W, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol 2009;16:2138-46.
11. Gold JS, Are C, Kornprat P, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 2008;247:109-17.
12. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440-8.
13. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol 2008;26:4906-11.
14. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14:1208-15.
15. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.
16. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30.
17. Price TJ, Segelov E, Burge M, et al. Current opinion on optimal systemic treatment for metastatic colorectal cancer: outcome of the ACTG/AGITG expert meeting ECCO 2013. Expert Rev Anticancer Ther 2014;14:1477-93.
18. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343:905-14.
19. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697-705.
20. Lorenz M, Müller HH, Schramm H, et al. Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German Cooperative on Liver Metastases (Arbeitsgruppe Lebermetastasen). Ann Surg 1998;228:756-62.
21. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
22. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45.
23. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-37.
24. Ramming KP, Sparks FC, Eilber FR, et al. Hepatic artery ligation and 5-fluorouracil infusion for metastatic colon carcinoma and primary hepatoma. Am J Surg 1976;132:236-42.
25. Bern MM, McDermott W Jr, Cady B, et al. Intraaterial hepatic infusion and intravenous adriamycin for treatment of hepatocellular carcinoma: a clinical and pharmacology report. Cancer 1978;42:399-405.
26. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol 1954;30:969-77.
27. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. Semin Oncol 1983;10:176-82.
28. Sigurdson ER, Ridge JA, Kemeny N, et al. Tumor and liver drug uptake following hepatic artery and portal vein infusion. J Clin Oncol 1987;5:1836-40.
29. Blackshear PJ, Dorman FD, Blackshear PL Jr, et al. The design and initial testing of an implantable infusion pump. Surg Gynecol Obstet 1972;134:51-6.
30. Allen PJ, Stojadinovic A, Ben-Porat L, et al. The management of variant arterial anatomy during hepatic arterial infusion pump placement. Ann Surg Oncol

2002;9:875-80.
31. Kemeny N, Daly J, Reichman B, et al. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. Ann Intern Med 1987;107:459-65.
32. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol 2006;24:1395-403.
33. Meta-Analysis Group in Cancer, Piedbois P, Buyse M, et al. Reappraisal of hepatic arterial infusion in the treatment of nonresectable liver metastases from colorectal cancer. J Natl Cancer Inst 1996;88:252-8.
34. Harmantas A, Rotstein LE, Langer B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. Cancer 1996;78:1639-45.
35. Safi F, Bittner R, Roscher R, et al. Regional chemotherapy for hepatic metastases of colorectal carcinoma (continuous intraarterial versus continuous intraarterial/intravenous therapy). Results of a controlled clinical trial. Cancer 1989;64:379-87.
36. Kemeny N, Jarnagin W, Paty P, et al. Phase I trial of systemic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver metastases from colorectal cancer. J Clin Oncol 2005;23:4888-96.
37. Bilchik AJ, Wood TF, Allegra D, et al. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms: a proposed algorithm. Arch Surg 2000;135:657-62; discussion 662-4.
38. Shitara K, Munakata M, Kudo T, et al. Combination chemotherapy with hepatic arterial infusion of 5-fluorouracil (5-FU) and systemic irinotecan (CPT-11) in patients with unresectable liver metastases from colorectal cancer. Gan To Kagaku Ryoho 2006;33:2033-7.
39. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.
40. D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. Ann Surg 2015;261:353-60.
41. Cercek A, D'Angelica M, Power D, et al. Floxuridine hepatic arterial infusion associated biliary toxicity is increased by concurrent administration of systemic bevacizumab. Ann Surg Oncol 2014;21:479-86.
42. Goéré D, Deshaies I, de Baere T, et al. Prolonged survival of initially unresectable hepatic colorectal cancer patients treated with hepatic arterial infusion of oxaliplatin followed by radical surgery of metastases. Ann Surg 2010;251:686-91.
43. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341:2039-48.
44. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med 2005;352:734-5.
45. Kemeny MM, Adak S, Gray B, et al. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy--an intergroup study. J Clin Oncol 2002;20:1499-505.
46. Lygidakis NJ, Sgourakis G, Vlachos L, et al. Metastatic liver disease of colorectal origin: the value of locoregional immunochemotherapy combined with systemic chemotherapy following liver resection. Results of a prospective randomized study. Hepatogastroenterology 2001;48:1685-91.
47. House MG, Kemeny NE, Gönen M, et al. Comparison of adjuvant systemic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer. Ann Surg 2011;254:851-6.
48. Kemeny N, Capanu M, D'Angelica M, et al. Phase I trial of adjuvant hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone plus systemic oxaliplatin, 5-fluorouracil and leucovorin in patients with resected liver metastases from colorectal cancer. Ann Oncol 2009;20:1236-41.
49. Goéré D, Benhaim L, Bonnet S, et al. Adjuvant chemotherapy after resection of colorectal liver metastases in patients at high risk of hepatic recurrence: a comparative study between hepatic arterial infusion of oxaliplatin and modern systemic chemotherapy. Ann Surg 2013;257:114-20.
50. Kemeny N, Chou J, Boucher T, et al. Improvement in long-term survival in patients with metastatic colorectal cancer (CRC) after liver resection with modern chemotherapy and hepatic arterial infusion (HAI). J Clin Oncol 2015;33:abstr 3563.
51. Nash GM, Gimbel M, Shia J, et al. KRAS mutation correlates with accelerated metastatic progression in patients with colorectal liver metastases. Ann Surg Oncol 2010;17:572-8.

52. Karagkounis G, Torbenson MS, Daniel HD, et al. Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. Cancer 2013;119:4137-44.
53. Vauthey JN, Zimmitti G, Kopetz SE, et al. RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg 2013;258:619-26; discussion 626-7.
54. Ahnen DJ, Feigl P, Quan G, et al. Ki-ras mutation and p53 overexpression predict the clinical behavior of colorectal cancer: a Southwest Oncology Group study. Cancer Res 1998;58:1149-58.
55. Kemeny NE, Chou JF, Capanu M, et al. KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. Cancer 2014;120:3965-71.
56. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer 2011;117:4623-32.
57. Yaeger R, Cercek A, Chou JF, et al. BRAF mutation predicts for poor outcomes after metastasectomy in patients with metastatic colorectal cancer. Cancer 2014;120:2316-24.
58. Ito H, Mo Q, Qin LX, et al. Gene expression profiles accurately predict outcome following liver resection in patients with metastatic colorectal cancer. PLoS One 2013;8:e81680.

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Radiofrequency ablation or resection for small colorectal liver metastases - a plea for caution

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Colorectal cancer (CRC) is among the leading causes for cancer death worldwide (1) and remains a serious problem for the public healthcare systems due to continuously growing costs of the treatment, and relatively low cure rates, especially in advanced stages of disease. The liver is secondary only to lymph nodes as a site for metastasis from primary CRC - about 50% of the patients developed liver metastases (CLM) during their course of disease, and in approximately ¾ of these the liver is the only site of distant spread (2). To date, resection of the metastases (LR) is the only proven potentially curative treatment option for the patients with CLM. However, despite the current advances in the concepts and techniques in liver surgery, the vast majority of the patients with CLM as well as those with other liver malignancies are not amenable to curative surgery. There is a growing need for efficient and minimally invasive techniques for the treatment of unresectable primary and metastatic liver cancer. In these circumstances several liver-directed local treatment modalities were developed and intensively explored during the years, with the aim to achieve local control, initially in patients with unresectable liver tumors, and eventually to compare further the results with those of hepatic resection. Among these local treatment options, the radiofrequency ablation (RFA) has become most popular and widely accepted local ablation modality during the past two decades. The accumulated evidence from several studies, including randomized trials, proved the safety and efficacy of RFA in the treatment of patients with hepatocellular carcinoma on cirrhosis (HCC) and even the superiority of RFA over hepatic resection in some subgroups of patients with HCC (3). None of these evidences can be directly applied to the patients with CLM.

The benefit from RFA for the patients with unresectable CLM in terms of prolonged progression-free survival (PFS) can be regarded as proven by several nonrandomized and one randomized study - EORTC 40004 (4). In the latter, RFA plus systemic chemotherapy are compared with systemic treatment alone. The median overall survival (OS), 30-month OS, and PFS are respectively 45.3 months, 61.7% and 16.8 months for the combined treatment *vs.* 40.5 months, 57.6% and 9.9 months for systemic treatment group. The EORTC 40004 does not demonstrate OS advantage from RFA and all non-randomized studies which demonstrate the OS benefit from adding RFA to systemic treatment have used historical and/or not well matched control groups. There is no any prospective, randomized trial comparing the efficacy of RFA with that of LR for CLM currently available. The literature data suggests that if local control is achieved by RFA as a sole procedure or as an adjunct to LR, the combination with current systemic therapy can reflect in prolonged OS compared to chemotherapy alone (5). Some authors go further ahead and propose RFA as a first-line treatment for the patients with resectable CLM, in order to "spare" patients from "unnecessary" LR if local control is achieved by RFA (6,7), however they have been criticized by several arguments (8,9).

Recently Solbiati *et al.* (10) reports the long-term results of the treatment of small CLM with percutaneous RFA plus irinotecan- or oxaliplatin-based systemic therapy. This report includes 99 patients with minimum of 3 years follow-up. No patient has had liver dysfunction or poor performance status and has been included in the study because of ineligibility (80.1%) or refusal (19.9%) of LR. The vast majority of the patients in this report - 73.7% have had one or two CLM, and the mean size of metastases has

been 2.2 cm. The authors report 88.1% overall complete ablation rate in this highly selected group of patients. At a median follow-up of 53 months, 40.4% of the patients have developed new CLM and almost each third patient (32.3%) has reported to have local tumor progression at the ablation site. 67.7% of the patients have died (67 of 99), and 18.1% have been disease-free at last follow-up. The median survival of the patients with incomplete ablation in this study has been 30 months. Estimated 1-, 5- and 10-year OS rates have been 98%, 47.8% and 18% respectively. The authors conclude that these results are equivalent to results from surgical resection. Is it really true?

Strong scientific evidence is needed in order to propose a change in the paradigm of the treatment of CLM, and all the published results should be carefully interpreted, keeping in mind available evidence about the effectiveness of RFA, as well as some important rules when comparing results with those of LR. In concordance with the available evidence, the above study confirms the benefit from RFA for patients with unresectable CLM, when complete ablation is achieved. But the reported difference between incomplete ablation rate of 11.9% and local tumor growth at the ablation site of 32.3% ultimately demonstrates the limited possibilities to evaluate the effectiveness of RFA with current imaging. As the tumor progression at the RFA site is a consequence of incomplete ablation, this report shows again that even in the treatment of small CLM with percutaneous RFA by most experienced team, the local control is not achieved in about one third of the patients. This result is too far from the reported local control rate of any study of LR of CLM. The oncologic safety and efficacy of RFA is further questioned by the meta-analysis of the percutaneously treated 3046 CLM, because of the lack of safety margin at the ablation site in 88.4% of treated lesions (11). Furthermore, there is no clinical data to confirm strong radiological/pathological correlation when the local control after RFA of CLM is estimated. Another limitation for percutaneous RFA comes from the unability of the current imaging studies to detect small hepatic and/or extrahepatic lesions compared with intraoperative staging, which includes intraoperative ultrasound (12). The latter fact adds unpredictable bias in estimating "new" lesions in any study of percutaneous RFA of CRLM.

The argument that even an incomplete tumor ablation can be beneficial is also questionable - the median survival of 30 months achieved in this group of patients in Solbiati's report compares unfavorably with the median survival of 40.5 months in patients with comparable extent of disease in EORTC 40004 study, treated with systemic chemotherapy alone. When comparing long-term oncologic outcomes of percutaneous RFA of CLM with those of LR it is important also to follow some rules to avoid misleading conclusions. Most of the reported series of LR of CLM include patients with various extents of disease which have had different prognosis according to widely accepted and externally validated prognostic scoring systems as Fong's score or Basingstoke predictive index (13,14). By these, the number and the size of CLM both are independent predictors of outcome. In almost all of the studies of percutaneous RFA for CLM these variables are limited by exclusion criteria. So, the comparison with the results of LR should be done with carefully matched groups. The team from the MD Anderson Cancer Center reported the results of such nonrandomized comparison of RFA to LR in patients with solitary CLM: 5-year overall- and disease-free survival 27% versus 71% and 0% versus 50% for RFA versus resection, respectively (15). Apart from the clear demonstration that resection determines outcome, the latter report opens again the question about the influence of the RFA on the natural course of disease as even if in 60% of the patients RFA achieves local control, there have been no 5-year disease-free survivors. Finally, as the estimated 18% 10-year survival in the above RFA study by Solbiati *et al.* is compared with those of LR of CLM without any attempt for matching the extent of disease, the authors' conclusion that their results are equivalent to results from surgical resection should be questioned. Moreover a median follow-up of 53 months is too short to draw such conclusion. The need for longer follow-up was noted by all the studies of 10-year survival after LR of CLM, as substantial part of the patients can develop new metastases even after 5-year of disease-free survival (16-19). A report of the long-term results of a randomized study of adjuvant treatment after LR of CLM with a follow-up of minimum 6 years (median 10.3 years) demonstrates that 38.7% 10-year survival can be achieved with combined aggressive treatment of resectable CLM (20). Importantly this study also confirms that patients with limited disease (Fong's score 0 to 2) have better prognosis after LR irrespective of the adjuvant treatment regimen - median survival has been 82.8 months in the fluorouracil monotherapy group. These figures are still much better than any reported results of RFA of CLM.

The evidence-based use of RFA in CLM is still evolving and is far from definitive conclusions. There is still no strong evidence that RFA of CLM can be beneficial in terms of overall survival, as selection bias regarding the

number and size of the CLM exists in all of the RFA studies. However the PFS benefit from RFA has been considered proven, even in the presence of limitations regarding the estimation of completeness of the ablation of CLM. Comparison between well matched groups of patients with CLM demonstrates that LR offers significant advantage over RFA in terms of local control, long-term overall- and disease-free survival. As it is still not clear whether incomplete ablation is beneficial or harmful, larger-scale randomized studies on patients with unresectable CLM are needed to draw conclusions. The currently available data does not justify proposing RFA as an alternative to LR in resectable CLM, even in order to use RFA as a part of "test of time" approach. In these circumstances it is also highly unlikely for any design of a randomized trial aiming to compare LR to RFA in resectable CLM to pass the institutional review boards. The oncologic safety and efficacy of RFA should be further carefully explored in unresectable CLM.

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References

1. El-Tawil AM. Colorectal cancer and pollution. World J Gastroenterol 2010;16:3475-7.
2. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254-9.
3. Tombesi P, Di Viece F, Sartori S. Resection vs thermal ablation of small hepatocellular carcinoma: What's the first choice? World J Radiol 2013;5:1-4.
4. Ruers T, Punt C, Van Coevorden F, et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 2012;23:2619-26.
5. Julianov A. Expanding Local Control Rate in Liver Cancer Surgery – The Value of Radiofrequency Ablation. In: Liver Tumors, Julianov A. ed. InTech 2012. Available online: http://www.intechopen.com/books/liver-tumors/expanding-local-control-rate-in-liver-cancer-surgery-the-value-of-radiofrequency-ablation
6. Livraghi T, Solbiati L, Meloni F, et al. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 2003;97:3027-35.
7. Otto G, Düber C, Hoppe-Lotichius M, et al. Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery. Ann Surg 2010;251:796-803.
8. Figueras J, Lladó L. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 2003;98:2303-4.
9. Julianov AE, Karashmalakov AG. Percutaneous radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery: is it justified? Ann Surg 2011;254:178.
10. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. Radiology 2012;265:958-68.
11. Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005;242:158-71.
12. Elias D, Sideris L, Pocard M, et al. Incidence of unsuspected and treatable metastatic disease associated with operable colorectal liver metastases discovered only at laparotomy (and not treated when performing percutaneous radiofrequency ablation). Ann Surg Oncol 2005;12:298-302.
13. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18.
14. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125-35.
15. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 2006;141:460-6; discussion 466-7.
16. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575-80.
17. Viganò L, Ferrero A, Lo Tesoriere R, et al. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. Ann Surg Oncol 2008;15:2458-64.
18. Pulitanò C, Castillo F, Aldrighetti L, et al. What defines

'cure' after liver resection for colorectal metastases? Results after 10 years of follow-up. HPB (Oxford) 2010;12:244-9.
19. Chua TC, Saxena A, Chu F, et al. Predictors of cure after hepatic resection of colorectal liver metastases: an analysis of actual 5- and 10-year survivors. J Surg Oncol 2011;103:796-800.
20. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. N Engl J Med 2005;352:734-5.

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"Vanishing liver metastases"—A real challenge for liver surgeons

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Abstract: Expanded surgical intervention in colorectal liver metastasis (LM) and improved chemotherapy led to increasing problem of disappearing liver metastases (DLM). Treatment of those continues to evolve and poses a real challenge for HPB surgeons. This review discusses a clinical approach to DLM, emphasizing crucial steps in clinical algorithm. Particular issues such as imaging, intraoperative detection and surgical techniques are addressed. A step-by-step algorithm is suggested.

Keywords: Disappearing liver metastases (DLM); complete pathological response; liver imaging; contrast-enhanced intraoperative ultrasound (CE-IOUS)

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Introduction

Colorectal cancer (CRC) is one of the most common cancers in the world. Advances in treatment have led to a decrease in the death rate for CRC over past two decades (1). Despite these advances, approximately half of all patients diagnosed with CRC will develop liver metastasis (LM) during the course of their disease (2-5). When left untreated, colorectal LM is rapidly and uniformly fatal with a median survival measured in months (6,7). Surgical resection provides the best opportunity for long-term survival and even the chance for cure, and so it is the current paradigm of treatment (8-17). Unfortunately, only 10-25% of patients with LM are candidates for surgical resection at the time of presentation (18-20). In patients with unresectable metastases, chemotherapy is the treatment of choice, either as a palliative treatment or in attempt to convert them into surgical candidates (21-24). Chemotherapy can also be administrated as a neoadjuvant strategy for selected cases of colorectal LM (23-25). Thus, an increasing number of patients receive chemotherapy prior to liver resection (26,27). The introduction of new, more effective systemic cytotoxic and biologic agents have been an important advance in the management of CLM. Tumor response has significantly improved with modern combination regimens, with up to 50% response rates for unresectable LM and 20% proceeding to liver resection with curative intent (28). Along with an improvement in chemotherapy treatment, there has been an increasing evidence of "disappearing" liver metastases (DLM) (27-31). DLM defined as a disappearance of liver metastases on cross-sectional imaging after administration of preoperative chemotherapy, which means a complete radiological response. That phenomenon occurs in 5-38% of patients who undergo preoperative systemic therapy (27,29-32). The logic basis behind the decision-making algorithm for DLM built on understanding of correlation between the complete radiological response and complete pathological response or durable complete clinical response. The complete pathological response defined as an absence of residual tumor in the resection specimen. The durable complete clinical response means no recurrence during a satisfactory period of time, when the site of disappearing lesion in not resected (left *in situ*). Both are desirable outcomes promising a chance for cure.

In this review we propose a decision-making algorithm for management of DLM which discuss step-by-step how to improve a clinical approach to DLM, emphasizing upfront improvements in imaging, intraoperative detection and surgical techniques.

DLM prevention—Overtreatment is not advisable

The reported risk factors for the occurrence of DLM are:

small size of LM (<2 cm), initial number of metastasis (over 3) and a prolonged preoperative chemotherapy (26,30). Therefore, for those patients selected to receive neoadjuvant treatment for a resectable disease, preoperative chemotherapy should be given for a fixed short duration. There is no strict evidence for number of cycles to treat. Van Vledder and colleagues showed that patients with DLM received 7.7 cycles of chemotherapy versus 5.5 cycles in patients without DLM (26). In addition, an 18 % increase in chance of DLM with each additional cycle of treatment was noted. The majority of DLMs arose 3-6 months following the start of chemotherapy (25). Based on that evidence, some writers proposed the numbers of 4-6 cycles (32,33). After that initial course the clinician should reevaluate the patient in order to avoid disappearing and to promptly resect it. It is important to remember, that patients that receive chemotherapy for resectable disease do not need to demonstrate objective response, although radiological response is a good prognostic factor. As far as conversion treatment for unresectable disease concerned, it should be continued until the patient has a resectable disease, not until maximum response (28,33).

In fact, prolonged chemotherapy can cause liver toxicity, and thus to disturb the management of LM by two mechanisms. First, it leads to decreased ability of preoperative imaging to detect LM, by increased fatty content (26,33,34). Second, it makes the surgery more difficult technically, causing an obvious increase in intra and postoperative morbidity (23).

Preoperative imaging—Are the metastases missing indeed?

The rate of complete radiological response varies in different series as much as 4% and 38% (25,26,28,33-37). It can be explained by differences in chemotherapy regimens and by the quality and competence of preoperative imaging. Numbers of modalities are in use to image patients with LM.

Computed tomography (CT)

Since its introduction into clinical practice in the 1970s, the quality and accuracy of CT in detecting LM has continued to improve, with a sensitivity ranging currently between 63% and 90%, and specificity between 85% and 90%, approaching 100% in some series (26,33,34,38,39).

Preoperative chemotherapy can induce parenchymal changes to the liver, defined as steatosis or steatohepatitis (33,40). In that setting the background liver appears darker, allowing less contrast between the parenchyma and the hypovascular metastases, hindering their detection (34,41,42).

Several risk factors have been reported causing an inadequate staging of LM by CT, such as steatosis > 30%, more than 3 LM and lesions smaller than 1 cm (32-34).

Based on this evidence, we assume that all missing metastases on triple-phase CT should be confirmed by another imaging modality.

PET-FDG and PET-CT

That modality shows high sensitivity, up to 97%, for detecting LM in some series (43,44). Other publications reported wider range of sensitivities—51-90% (40,45-48). This data reflects several factors, which reduce the sensitivity of FDG uptake, such as small lesions (especially less than 1 cm) and impaired glucose uptake in tumor cells due to chemotherapy (49,50). Nevertheless, some series emphasized an important role of PET-FDG, changing the treatment plan in up to 30-40%, either by finding an extrahepatic disease or correctly predicting a complete pathological response (51,52). In a prospective study of 104 patients with CRC, PET-CT revealed unsuspected disease in 19%, changed stage in 13.5% and resulted in modified surgery in 11.5% (53). As the likelihood of extrahepatic disease increases along with the degree of liver involvement, PET-CT should be considered as a routine examination in staging patients prior to surgical resection (34). This is important when considering extensive surgery to avoid the morbidity of futile laparotomies.

In summary, remaining an important tool in primary staging, PET scan is not a good test for looking at viable cancer within the liver after chemotherapy (54).

MRI

MRI appears to be the best hepatic imaging modality, especially in the setting of chemotherapy-induced steatosis and for small lesions (28,55). Compared with CT, it has better sensitivity and specificity (34). Recent advances in MRI techniques, such as diffusion-weighted imaging (DWI) and hepatobiliary contrast agents even strengthen that superiority. DWI is a measure of the ability of water molecules to diffuse freely between tissues and hence directly correlates with underlying cellular density. Metastases tend to restrict diffusion and the addition of

DWI to the typical liver MRI protocol improves sensitivity and specificity for lesion detection and characterization (56-60). In addition to DWI, hepatobiliary phase MRI using liver-specific contrasts has demonstrated improved sensitivity to metastasis detection over routine MRI (61-64). Examples of such contrast agents are Gadoxetic acid and super paramagnetic iron oxide (SPIO). These agents help to improve the contrast between hepatocytes and tumor cells during the late hepatobiliary phase, in which peak parenchymal enhancement happens.

In summary, MRI is an optimal modality to image LM missing on CT scan. Moreover, in recent study an inability to observe a DLM on MRI was associated with an increased chance for complete pathological or durable clinical response (30).

Following adequate imaging—Should we always operate?

Since no preoperative imaging modality, including MRI, has a sensitivity of 100%, there is a subset of DLM that will be found only at the time of surgical exploration. In other words, if we do not proceed to surgical exploration in setting of DLM even after performing comprehensive imaging, we may leave the tumor behind. So one should always consider surgical exploration when feasible, especially in presence of DLM risk factors, mentioned previously, such as small and multiple lesions, prolonged chemotherapy and significant chemotherapy induced liver damage. The literature hasn't faced the difference between per patient versus per metastases approach to exploration. Obviously, a patient with multiple metastases, which only part of them disappeared on imaging, will undergo exploration, demanding resection of remaining lesions in any case. It is less clear how safe is a possibility to avoid surgery in rare patient with completely "clean" post-chemotherapy liver. Such specific cases should be discussed in a multidisciplinary team, taking in consideration favorable prognosis in good treatment responders. That fact promotes an aggressive approach with meticulous intraoperative assessment.

Intraoperative assessment—Could we do better?

The role of exploratory laparoscopy as a first step in operative approach to DLM is still being controversial. The main importance of laparoscopy in such cases is probably to rule out a disseminated peritoneal disease. The ability of laparoscopy to identify small lesions missing on preoperative imaging is significantly limited.

Using formal laparotomy, all patients with DLM should undergo a full liver mobilization, visual inspection, palpation and finally intraoperative ultrasonography (IOUS). Systematic examination by IOUS can lead to an increase in the detection of DLM. In the published experience, a macroscopic residual disease was observed in as much as 27-45% of the patients with DLM by combination of palpation and IOUS (25,26,36,37). As mentioned previously, that frequency was lowered by the use of preoperative MRI (26,28,36).

Contrast-enhanced intraoperative ultrasound (CE-IOUS) is a novel technique that was proposed in 2004 for both CLM and hepatocellular carcinoma detection. The preliminary results were inconclusive for CLM (64-66). Further investigations showed that it is capable of detecting a larger proportion of CLM, in comparison with other imaging modalities including IOUS (53,67,68). Arita *et al.* assessed a usefulness of CE-IOUS in identifying DLM (69). Out of 32 DLM, 4 were identified by IOUS, all confirmed as tumor by pathology. Out of remaining 28, 12 we found by CE-IOUS, all were resected and a vast majority (11 of 12) consisted of malignancy. The authors concluded that CE-IOUS might be necessary for identifying DLM.

Possible factors influencing the surgeon ability to discover DLM include the degree of hepatic steatosis, the depth of DLM, the location relative to anatomical landmarks and surgeon skill with IOUS (28,66,70).

How to treat missing LM during surgery

When a surgeon cannot identify DLM during the operation, he has two options to manage that situation. First is to treat surgically the site of anatomical location of the metastases, and check for complete pathological response in pathology regimen. Second, he can leave it *in situ*. In that scenario the outcome will be assessed by the follow-up imaging, looking for recurrence al the site of DLM. The duration of the follow-up to define a complete clinical response is not well defined. According to the fact that the median time of recurrence is 6-8 months, it is makes sense to define a durable clinical response as no recurrence at cross-sectional imaging at 1 year (26,28,30).

The literature is not is not convincing when facing the dilemma of resecting the site of metastasis versus leaving it *in situ*. Several predicting factors for a good correlation between a complete radiological and complete pathological response were described. Most significant of them were

initial higher number of LM, more metastases with partial response, young patients (<60 years), low initial CEA level (<30) which normalizes during chemotherapy, small lesions (<3 cm) and an absence of lesion on preoperative MRI (26,37). Another independent predicting factor was a use of hepatic artery infusion (HAI) therapy (28,36,37).

Proponents of aggressive resection present high rates of recurrence while left *in situ* (above 70%) and low rates of complete pathological response when resected (20%) (27,28). van Vledder *et al*. showed a significant advantage in 3-year intrahepatic recurrence-free survival rates for resection versus follow-up group (26). On the other hand, there was no difference in overall survival (26,27). The possible explanation is the fact that about a half of the patients experience recurrence in any other location, different from the DLM sites or even extrahepatic (33). The aggressive biologic nature of disease in those patients may neutralize the local control of disease by DLM sites resection, thus moderating overall survival benefit (25,26,33).

From the practical point of view, the decision should be made based on aggressiveness of the disease, the patient condition and operative risk, an ability to treat all sites surgically and predictive factors for true complete pathological response as described above.

Advances in surgeon arsenal—From "blind" hepatectomy to NanoKnife

When the lesion cannot be identified, incorporation of the original site to hepatectomy or even performing segmental hepatectomy for a DLM site alone should be considered (26). The clear disadvantage of such "blind" hepatectomy technique is an inadequate residual liver volume and increased surgical risk. In fact, performing a major hepatectomy to resect the site of the DLM may not decrease the recurrence rate (27). On the contrary, the prognosis could be worsened by reducing the possibility of second hepatectomy. Along with the general trend of liver sparing in hepatobiliary surgery, in the field of DLM technological improvements allow more precise intervention. The key point is an exact site location. One option is to mark the LM with coils using percutaneous interventional radiology techniques (71). Although discussed in the chapter of operative treatment, its real place in decision-making algorithm is before starting chemotherapy. One can consider that tool, when dealing with an aggressive disease, which requires prolonged therapy, or when mentioned risk factors for DLM exist. Additional aids to assist in surgical planning are new software and applications that alleviate determining surgical planes, evaluating FLR and depicting anatomy (34).

Radiofrequency ablation (RFA) is a gaining momentum alternative for liver lesion resection (72). The idea of ablating a previously marked site of DLM is promising in avoiding massive resections. It is timely influencing the debate about the necessity of DLM site resection. The problem in analyzing that modality is to compare it to surgical resections. Unlike in surgical resection, an evidence for complete response rates can be collected by looking for recurrence in follow-up imaging.

In spite of its widespread use and noted efficacy, RFA has some limitations. Its dependence on heating of the tissue to denature proteins means adjacent thermosensitive structures such as colon, stomach, bile ducts, gallbladder, and hepatic capsule can be damaged resulting in complications, and large vessels within or close to the treatment zone may cause thermal sinks ("heat-sink" effect) that will prevent complete treatment of the target lesion (72,73). Although there are new thermal technologies such as microwave ablation, which may potentially generate a larger ablation zone in a shorter time, they still have the limitations associated with thermal technologies. These limitations have generated interest in other methods of ablation and have forced an integration of irreversible electroporation (IRE) method into treatment options list of hepatic tumors.

IRE, commercially available as NanoKnife, is a new ablative technology that uses high-voltage, low-energy DC current to create nanopores in the cell membrane, disrupting the homeostasis mechanism and inducing cell death by initiating apoptosis (74). Its major advantage is the lack of heat-sink effect and the ability to treat zones near vessels, bile ducts, and critical structures. IRE comes with its own share of limitations. Human experiences are still limited, whereas thermal ablative techniques such as RFA have been time-tested for nearly three decades. The procedure has a learning curve because multiple needle placements are required within a prescribed distance, which can be challenging, and parallel placement of the probes may be hindered by issues, such as intervening ribs. In addition, this is a very expensive technology. We doubt a routine use of it when dealing with the lesion that is not even visible and the need for resection is controversial.

Computer assisted liver surgery can be an elegant way to locate and ablate the site of DLM. Indeed, the integration of the prechemotherapy imaging to the US imaging along with the navigation system can allow the surgeon to locate and ablate precisely the metastatic site (75).

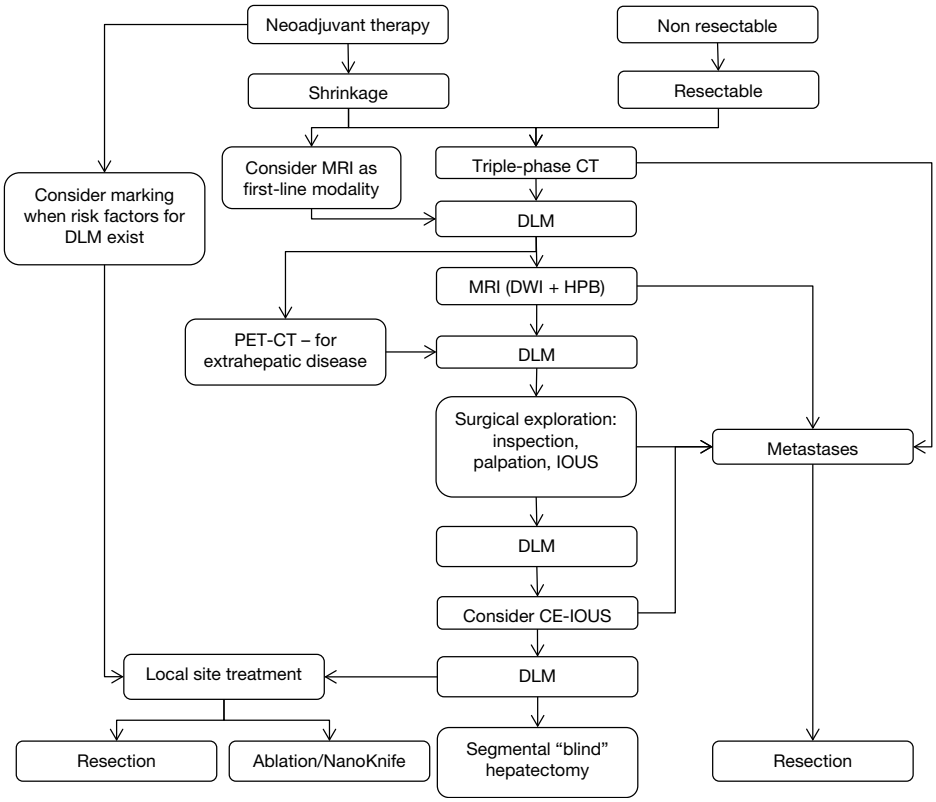

Figure 1 Algorithm for clinical approach to DLM. DLM, disappearing liver metastases.

Summary

Our review suggest an algorithm for clinical approach to DLM (*Figure 1*). The most crucial steps are a comprehensive preoperative imaging, including MRI, careful surgical exploration, using IOUS and possibly CE-IOUS, and to be assisted by variety of operative techniques, such as local ablation of previously marked sites. The algorithm might serve as a helpful tool, but it definitely does not replace a multidisciplinary team, which should carry out the treatment of such a complicated patients. As the technology is improving fast, we look forward for the future improvements. The desirable navigation system may give an answer for difficulties to locate previous sites of DLM.

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References

1. American Cancer Society. Detailed Guide: Colon and Rectum Cancer page. Available online: http://www.cancer.org, accessed 4/15/2010.
2. Van Cutsem E, Nordlinger B, Adam R, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer 2006;42:2212-21.
3. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10-30.
4. Stangl R, Altendorf-Hofmann A, Charnley RM, et al. Factors influencing the natural history of colorectal liver metastases. Lancet 1994;343:1405-10.
5. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol 2005;23:2038-48.
6. Bengmark S, Hafström L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer 1969;23:198-202.
7. Bengtsson G, Carlsson G, Hafström L, et al. Natural history of patients with untreated liver metastases from

colorectal cancer. Am J Surg 1981;141:586-9.
8. Alberts SR, Poston GJ. Treatment advances in liver-limited metastatic colorectal cancer. Clin Colorectal Cancer 2011;10:258-65.
9. Berri RN, Abdalla EK. Curable metastatic colorectal cancer: recommended paradigms. Curr Oncol Rep 2009;11:200-8.
10. Kopetz S, Vauthey JN. Perioperative chemotherapy for resectable hepatic metastases. Lancet 2008;371:963-5.
11. Scheele J, Stang R, Altendorf-Hofmann A, et al. Resection of colorectal liver metastases. World J Surg 1995;19:59-71.
12. Fortner JG, Silva JS, Golbey RB, et al. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. Ann Surg 1984;199:306-16.
13. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15:938-46.
14. Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. Surgery 1986;100:278-84.
15. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer 1996;77:1254-62.
16. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309-18; discussion 318-21.
17. Figueras J, Valls C, Rafecas A, et al. Resection rate and effect of postoperative chemotherapy on survival after surgery for colorectal liver metastases. Br J Surg 2001;88:980-5.
18. Scheele J. Hepatectomy for liver metastases. Br J Surg 1993;80:274-6.
19. Petrelli NJ, Abbruzzese J, Mansfield P, et al. Hepatic resection: the last surgical frontier for colorectal cancer. J Clin Oncol 2005;23:4475-7.
20. Adam R. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases. Ann Oncol 2003;14 Suppl 2:ii13-6.
21. Meric F, Patt YZ, Curley SA, et al. Surgery after downstaging of unresectable hepatic tumors with intra-arterial chemotherapy. Ann Surg Oncol 2000;7:490-5.
22. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644-57; discussion 657-8.
23. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 2008;371:1007-16.
24. Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 2009;27:1829-35.
25. Allen PJ, Kemeny N, Jarnagin W, et al. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. J Gastrointest Surg 2003;7:109-15; discussion 116-7.
26. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg 2010;14:1691-700.
27. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol 2006;24:3939-45.
28. Bischof DA, Clary BM, Maithel SK, et al. Surgical management of disappearing colorectal liver metastases. Br J Surg 2013;100:1414-20.
29. Elias D, Goere D, Boige V, et al. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. Ann Surg Oncol 2007;14:3188-94.
30. Auer RC, White RR, Kemeny NE, et al. Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. Cancer 2010;116:1502-9.
31. Lubezky N, Geva R, Shmueli E, et al. Is there a survival benefit to neoadjuvant versus adjuvant chemotherapy, combined with surgery for resectable colorectal liver metastases? World J Surg 2009;33:1028-34.
32. Thomay AA, Charpentier KP. Optimizing resection for "responding" hepatic metastases after neoadjuvant chemotherapy. J Surg Oncol 2010;102:1002-8.
33. Gaujoux S, Goéré D, Dumont F, et al. Complete radiological response of colorectal liver metastases after chemotherapy: what can we expect? Dig Surg 2011;28:114-20.
34. Fowler KJ, Linehan DC, Menias CO. Colorectal liver metastases: state of the art imaging. Ann Surg Oncol 2013;20:1185-93.
35. Chun YS, Vauthey JN, Ribero D, et al. Systemic

chemotherapy and two-stage hepatectomy for extensive bilateral colorectal liver metastases: perioperative safety and survival. J Gastrointest Surg 2007;11:1498-504; discussion 1504-5.
36. Elias D, Youssef O, Sideris L, et al. Evolution of missing colorectal liver metastases following inductive chemotherapy and hepatectomy. J Surg Oncol 2004;86:4-9.
37. Tanaka K, Takakura H, Takeda K, et al. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. Ann Surg 2009;250:935-42.
38. Kamel IR, Choti MA, Horton KM, et al. Surgically staged focal liver lesions: accuracy and reproducibility of dual-phase helical CT for detection and characterization. Radiology 2003;227:752-7.
39. Kim YK, Park G, Kim CS, et al. Diagnostic efficacy of gadoxetic acid-enhanced MRI for the detection and characterisation of liver metastases: comparison with multidetector-row CT. Br J Radiol 2012;85:539-47.
40. Zorzi D, Laurent A, Pawlik TM, et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94:274-86.
41. Oliva MR, Mortele KJ, Segatto E, et al. Computed tomography features of nonalcoholic steatohepatitis with histopathologic correlation. J Comput Assist Tomogr 2006;30:37-43.
42. Albrecht T, Blomley MJ, Burns PN, et al. Improved detection of hepatic metastases with pulse-inversion US during the liver-specific phase of SHU 508A: multicenter study. Radiology 2003;227:361-70.
43. Bipat S, van Leeuwen MS, Comans EF, et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis--meta-analysis. Radiology 2005;237:123-31.
44. Kinkel K, Lu Y, Both M, et al. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. Radiology 2002;224:748-56.
45. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674-84.
46. van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012;19:2805-13.
47. Muhi A, Ichikawa T, Motosugi U, et al. Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. J Magn Reson Imaging 2011;34:326-35.
48. Kim YK, Park G, Kim CS, et al. Diagnostic efficacy of gadoxetic acid-enhanced MRI for the detection and characterisation of liver metastases: comparison with multidetector-row CT. Br J Radiol 2012;85:539-47.
49. Fong Y, Saldinger PF, Akhurst T, et al. Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. Am J Surg 1999;178:282-7.
50. Tan MC, Linehan DC, Hawkins WG, et al. Chemotherapy-induced normalization of FDG uptake by colorectal liver metastases does not usually indicate complete pathologic response. J Gastrointest Surg 2007;11:1112-9.
51. Huebner RH, Park KC, Shepherd JE, et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000;41:1177-89.
52. Ruers TJ, Wiering B, van der Sijp JR, et al. Improved selection of patients for hepatic surgery of colorectal liver metastases with (18)F-FDG PET: a randomized study. J Nucl Med 2009;50:1036-41.
53. Llamas-Elvira JM, Rodríguez-Fernández A, Gutiérrez-Sáinz J, et al. Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. Eur J Nucl Med Mol Imaging 2007;34:859-67.
54. Akhurst T, Kates TJ, Mazumdar M, et al. Recent chemotherapy reduces the sensitivity of [18F] fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. J Clin Oncol 2005;23:8713-6.
55. Kulemann V, Schima W, Tamandl D, et al. Preoperative detection of colorectal liver metastases in fatty liver: MDCT or MRI? Eur J Radiol 2011;79:e1-6.
56. Kenis C, Deckers F, De Foer B, et al. Diagnosis of liver metastases: can diffusion-weighted imaging (DWI) be used as a stand alone sequence? Eur J Radiol 2012;81:1016-23.
57. Taouli B, Sandberg A, Stemmer A, et al. Diffusion-weighted imaging of the liver: comparison of navigator triggered and breathhold acquisitions. J Magn Reson Imaging 2009;30:561-8.
58. Bruegel M, Holzapfel K, Gaa J, et al. Characterization of focal liver lesions by ADC measurements using a respiratory triggered diffusion-weighted single-shot echo-planar MR imaging technique. Eur Radiol 2008;18:477-85.

59. Bruegel M, Gaa J, Waldt S, et al. Diagnosis of hepatic metastasis: comparison of respiration-triggered diffusion-weighted echo-planar MRI and five t2-weighted turbo spin-echo sequences. AJR Am J Roentgenol 2008;191:1421-9.
60. Parikh T, Drew SJ, Lee VS, et al. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. Radiology 2008;246:812-22.
61. Holzapfel K, Eiber MJ, Fingerle AA, et al. Detection, classification, and characterization of focal liver lesions: Value of diffusion-weighted MR imaging, gadoxetic acid-enhanced MR imaging and the combination of both methods. Abdom Imaging 2012;37:74-82.
62. Zech CJ, Herrmann KA, Reiser MF, et al. MR imaging in patients with suspected liver metastases: value of liver-specific contrast agent Gd-EOB-DTPA. Magn Reson Med Sci 2007;6:43-52.
63. Hammerstingl R, Huppertz A, Breuer J, et al. Diagnostic efficacy of gadoxetic acid (Primovist)-enhanced MRI and spiral CT for a therapeutic strategy: comparison with intraoperative and histopathologic findings in focal liver lesions. Eur Radiol 2008;18:457-67.
64. Leen E, Ceccotti P, Moug SJ, et al. Potential value of contrast-enhanced intraoperative ultrasonography during partial hepatectomy for metastases: an essential investigation before resection? Ann Surg 2006;243:236-40.
65. Fioole B, de Haas RJ, Wicherts DA, et al. Additional value of contrast enhanced intraoperative ultrasound for colorectal liver metastases. Eur J Radiol 2008;67:169-76.
66. Torzilli G, Botea F, Donadon M, et al. Criteria for the selective use of contrast-enhanced intra-operative ultrasound during surgery for colorectal liver metastases. HPB (Oxford) 2014. [Epub ahead of print].
67. Torzilli G, Del Fabbro D, Palmisano A, et al. Contrast-enhanced intraoperative ultrasonography during hepatectomies for colorectal cancer liver metastases. J Gastrointest Surg 2005;9:1148-53; discussion 1153-4.
68. Takahashi M, Hasegawa K, Arita J, et al. Contrast-enhanced intraoperative ultrasonography using perfluorobutane microbubbles for the enumeration of colorectal liver metastases. Br J Surg 2012;99:1271-7.
69. Arita J, Ono Y, Takahashi M, et al. Usefulness of contrast-enhanced intraoperative ultrasound in identifying disappearing liver metastases from colorectal carcinoma after chemotherapy. Ann Surg Oncol 2014;21 Suppl 3:S390-7.
70. Takahashi M, Hasegawa K, Arita J, et al. Contrast-enhanced intraoperative ultrasonography using perfluorobutane microbubbles for the enumeration of colorectal liver metastases. Br J Surg 2012;99:1271-7.
71. Zalinski S, Abdalla EK, Mahvash A, et al. A marking technique for intraoperative localization of small liver metastases before systemic chemotherapy. Ann Surg Oncol 2009;16:1208-11.
72. Mahvi DM, Lee FT Jr. Radiofrequency ablation of hepatic malignancies: is heat better than cold? Ann Surg 1999;230:9-11.
73. Nahum Goldberg S, Dupuy DE. Image-guided radiofrequency tumor ablation: challenges and opportunities--part I. J Vasc Interv Radiol 2001;12:1021-32.
74. Kingham TP, Karkar AM, D'Angelica MI, et al. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. J Am Coll Surg 2012;215:379-87.
75. Sakamoto T. Roles of universal three-dimensional image analysis devices that assist surgical operations. J Hepatobiliary Pancreat Sci 2014;21:230-4.

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Major hepatectomy for complex liver trauma

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Abstract: The liver is the most frequently injured intraperitoneal organ, despite its relatively protected location. The liver consisting of a relatively fragile parenchyma contained within the Glisson capsule, which is thin and does not provide it with great protection. The management of hepatic trauma has undergone a paradigm shift over the past several decades with significant improvement in outcomes. Shifting from mandatory operation to selective nonoperative treatment, and, presently, to nonoperative treatment with selective operation. Operative management emphasizes packing, damage control, and utilization of interventional radiology, such as angiography and embolization. Because of the high morbidity and mortality, liver resection seems to have a minimal role in the management of hepatic injury in many reports, but in a specialized referral center, like our institute, surgical treatment becomes, in many cases, the only life-saving treatment. Innovations in liver transplant surgery, living liver donation, and the growth of specialized liver surgery teams have changed the way that surgeons and hepatic resection are done.

Keywords: Hepatectomy; laceration of liver; blunt liver trauma; liver fixation

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Case presentation

A 23-year-old male arrived to emergency room after being run over by a car. On his arrival, GCS 15, BP 136/90, HR 92, severe RUQ pain with large hematoma on the right chest and abdomen which was distended with localized peritonitis.

(I) FAST—large amount of fluid in the abdominal cavity.
(II) Chest X-ray—no signs of pneumothorax no ribs fractures.
(III) CT findings (*Figures 1*,*2*):
  (i) Severe liver injury Gr 4, extravasation of contrast material—"Blash";
  (ii) Irregularity in the right hepatic vein close to the IVC junction—suspected RT hepatic vein laceration;
  (iii) Large amount of blood in the abdominal cavity;
  (iv) Stable fracture of the pelvis.

Due to the CT finding and hemodynamically instability with tachycardia above 100 and hypotension, the patient was rushed to the OR for exploratory laparotomy. Angiography with embolization was not done, because in case of severe liver injury with hemodynamically instability the right course of action is an immediate surgery.

Surgical technique

The operative findings were a large central liver laceration with active bleeding which was not controlled by packing alone. A "Pringle" was placed over the hepato-duodenal ligament which decreased the bleeding but did not stop it. A complex hepatic injury involving the liver parenchyma, the right hepatic pedicle and the right hepatic vein was diagnosed. As a result of right pedicle tear, the attempts to release the clamping failed and were accompanied by massive bleedings. Several attempts to control the right pedicle were not successful; we considered putting a caval balloon catheter if the total vascular exclusion (TVE) was not successful. TVE (*Figure 3*) was performed due to the retroperitoneal bleeding and enabled the displacement

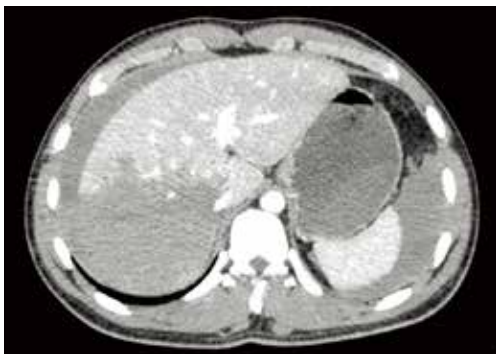

Figure 1 CT before surgery—hemoperitoneum with laceration of the liver.

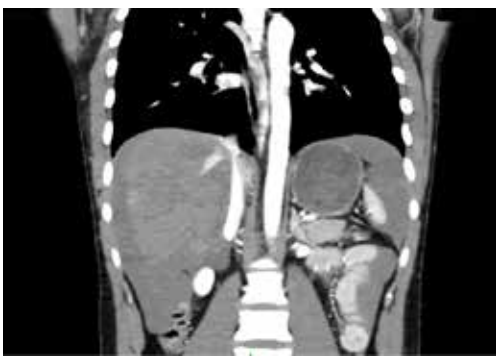

Figure 2 CT before surgery—suspected tear of the right hepatic vein.

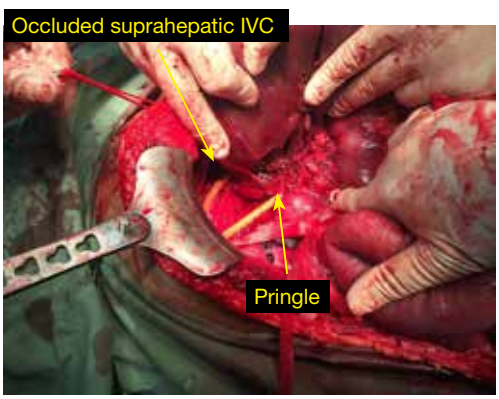

Figure 3 Total vascular exclusion before hepatectomy.

of the liver and the assessment of the IVC injury. After excluding the liver, exploration revealed that the liver was torn off from the IVC and the right hepatic vein was disconnected (*Figure 4*). A formal right hepatectomy was performed without dissection of the pedicle by an anterior

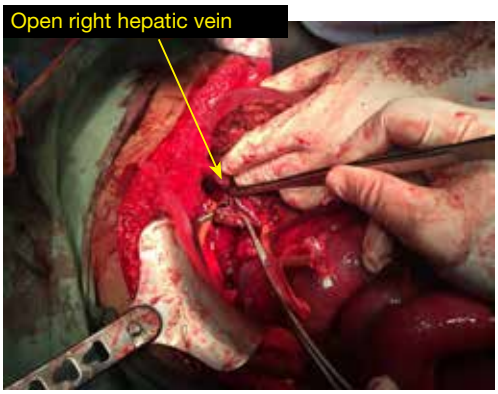

Figure 4 Torn right hepatic vein.

approach. Due to bowel edema the abdomen could not be closed primarily and the remaining left lobe of the liver could not be fixed within the abdominal wall, a temporary closure of the abdomen with VAC PAK was done. The patient was transferred to the ICU hemodynamically stable for further resuscitation.

Post-operative course

During the next 2 weeks, the patient was operated three times and had an open abdomen that was kept closed with a VAC PAC.

Immediately after the first operation the patient remained intubated and kept his hemodynamically stability with noradrenaline. A biliary leak was observed and the bowels were less edematous. On post-operative day 6 the abdomen was opened to change the VAC in the ICU, the liver was found twisted to the right and very congested. An intraoperative US showed a severe narrowing of the left and mid hepatic veins with a reduced blood flow, corresponding to a partial Budd Chiari. After putting the liver in its anatomic position the hepatic veins looked normal with a normal flow. Acute Budd-Chiari syndrome (ABCS) after major hepatic resection is rare but potentially lethal (1,2). After extended right hepatectomy, the remnant liver can be affected by outflow obstruction due to torsion of the IVC or kinking of the left hepatic vein (2,3). Fixing left remnant liver in the anatomic position has been demonstrated to improve hepatic vein flow and reduce ABCS incidence after extended right liver resection (4). In addition, the usage of expenders filled with fluids is common in dual liver transplants, which are taken off after a period of time after

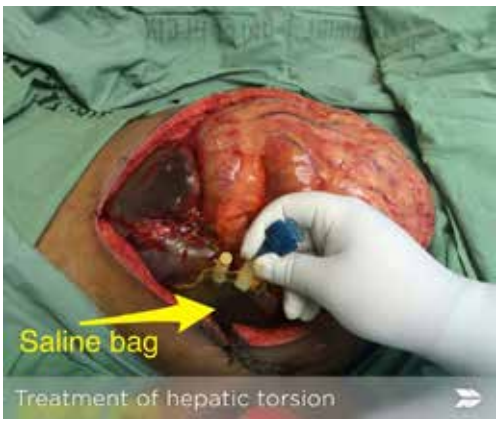

Figure 5 Saline bag for fixing the liver in place.

Figure 6 Granulation tissue over the abdomen before skin graft.

surgery (5). Under this special circumstance that the left lobe of the liver could not be fixed anatomically due to the open abdomen, an innovative solution was chosen: putting a sterile 500 cc saline bag within the abdominal cavity, keeping the left lobe of the liver in place (*Figure 5*). In the next 10 days the saline bag was replaced every 3 days in the ICU. The patient was transfer to the trauma unit after 2 weeks in the ICU, he went through a prolonged rehabilitation process and he is recovering from his injuries (*Figure 6*).

The patient was released from the hospital after a month. He is programmed for a reconstruction of the abdominal wall.

Summary

The management of liver trauma underwent a significant shift over the past several decades with an impressive improvement in outcomes. Shifting from mandatory operation to selective non-operative treatment and presently, to non-operative treatment in selected patients (6-8). The non-operative management (NOM) such as angiography with embolization (reserved only for hemodynamically stable patients) or intra-aortic balloon occlusion (IABO) which is useful for proximal vascular control, by clamping the descending aorta, in traumatic haemorrhagic shock (there are limited clinical studies regarding its effectiveness) (9).

We described a unique and innovative treatment for a complicated liver trauma, where the surgeons chose the unconventional trauma treatment due to an uncontrolled massive bleeding of patient.

The operation was executed by a well-experienced hepato-biliary team of surgeons, and took place in a tertiary trauma center. Procedures such as the one described here, have good success rates and low mortality rates when performed by an experienced team. In this case, the experienced and highly skilled team was also forced to exhibit creative thinking and unorthodox measures to save the patient's live.

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None.

Footnote

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

References

1. Poon RT, Chan J, Fan ST. Left hepatic vein kinking after right trisegmentectomy: a potential cause of postoperative liver failure. Hepatogastroenterology 1998;45:508-9.
2. Wang JK, Truty MJ, Donohue JH. Remnant torsion causing Budd-Chiari syndrome after right hepatectomy. J Gastrointest Surg 2010;14:910-2.
3. Di Domenico S, Rossini A, Petrocelli F, et al. Recurrent acute Budd-Chiari syndrome after right hepatectomy: US color-Doppler vascular pattern and left hepatic vein stenting for treatment. Abdom Imaging 2013;38:320-3.
4. Ogata S, Kianmanesh R, Belghiti J. Doppler assessment after right hepatectomy confirms the need to fix the remnant left liver in the anatomical position. Br J Surg 2005;92:592-5.

5. Inomata Y, Tanaka K, Egawa H, et al. Application of a tissue expander for stabilizing graft position in living-related liver transplantation. Clin Transplant 1997;11:56-9.
6. Ochiai T, Igari K, Yagi M, et al. Treatment strategy for blunt hepatic trauma: analysis of 183 consecutive cases. Hepatogastroenterology 2011;58:1312-5.
7. Morrison JJ, Bramley KE, Rizzo AG. Liver trauma--operative management. J R Army Med Corps 2011;157:136-44.
8. Kozar RA, Feliciano DV, Moore EE, et al. Western Trauma Association/critical decisions in trauma: operative management of adult blunt hepatic trauma. J Trauma 2011;71:1-5.
9. Irahara T, Sato N, Moroe Y, et al. Retrospective study of the effectiveness of Intra-Aortic Balloon Occlusion (IABO) for traumatic haemorrhagic shock. World J Emerg Surg 2015;10:1.

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