



AME Surgery Series 003

# COLORECTAL SURGERY

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# **Colorectal Surgery**

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# Colorectal Surgery (FIRST EDITION)

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# VI

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The Annals of Cardiothoracic Surgery, one of AME's peer-reviewed journals, is lucky to have an author from Rochester, USA. He is left-handed. When he began his training in surgery, he encountered huge obstacles. For example, when using scissors or knotting during a surgery, his actions were the opposite of what was described in textbooks. Therefore, he often "took a beating" from his mentors when performing a surgery.

Later, he summarized his experience and published it in a journal in an attempt to find other surgeons that "suffer from the same fate". Surprisingly, after his article was published, many surgeons e-mailed him, asking him how left-handed doctors should undergo surgical training, and so on. Then he met Professor Tristan D. Yan, the editor-in-chief of Annals of Cardiothoracic Surgery, who happens to be a left-handed doctor. Tristan encouraged him to become a heart surgeon because there are steps in cardiac surgery that require the use of the left hand to complete the suture threading technique. Tristan's view was that it was better if surgeons were trained to use both their left and right hands.

A few days ago, on my daughter's first day of kindergarten, I chatted with her teacher for a while; finally, she asked me if there was anything about my daughter that she should take note of . "Please do not correct my daughter's left-handedness," I said, "Just let it be." "Why?" the teacher asked in wonder.

On December 7, 2013, we held the second AME Academic Salon in the Hospital Affiliated to Nantong University. After dinner, Dr. Shen Yaxing from the Department of Thoracic Surgery of Shanghai Zhongshan Hospital invited several attendees to have tea in his room. The elevator was in the middle of the hotel. After we walked out of the elevator, he led us to the left, then to the left, then to the left, and finally to the door of his room. Although we were somehow confused and disoriented, some of us did find out that the door was just diagonally across the elevator. We all burst into laughter. Yaxing shared that he took this route the first time he entered his room, and so he decided to bring us on the same route on the second time. Yaxing then said that this was the behavior of a 'typical' surgeon!

During the training to be a surgeon, each step and each action are done under the strict direction and supervision of a senior surgeon. Thus, many surgeons like to affectionately address their mentors as their "masters".

How, then, can you become a master of surgery? In addition to your own intelligence and diligence, the expertise and mentorship offered by a "master" is also very important. Just like in the world of martial arts, there are many different schools that are independent from each other and have their own strength and weakness, and the surgical world is very much the same.

Therefore, it is important for a young surgeon to gain knowledge and skills from different masters by taking in only the essence and discarding the dregs. Therefore, we have planned to publish the AME Surgery series, in an attempt to share with our readers the surgical skills of some prominent surgical teams in China and abroad, as well as their philosophical thinking and some interesting stories. We sincerely hope that our colleagues in the surgical departments find these books insightful and helpful.

Stephen D. Wang Founder and CEO, AME Publishing Company The global burden of colorectal cancer (CRC) is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 (1). In China, CRC is the third most prevalent cancer and accounts for the fifth cause for death (2). But fortunately, the incidence and mortality of CRC have decreased in recent years due to effective screening programs and improvements in treatment modalities (3).

It is challenging for most clinicians to comprehensively and quickly grasp the forefront knowledge of colorectal cancer in an era of Big Data. In this book, therefore, we carefully collected a series of excellent articles contributed by international leading experts on colorectal cancer that cover the etiology, screening, surgical treatment and adjuvant radiochemotherapy of this malignancy by focusing on the hottest clinical issues and the most promising treatments. It includes practical chapters on single-port laparoscopic surgery, CT colonography, post-operative outcomes, transanal minimally invasive surgery, etc.

As the professors of Colorectal Surgery in Fudan University Shanghai Cancer Center, we are honored to serve as the editorial board members of this fantastic book. Our department has been established as an independent department since 2005, and colorectal cancer multidisciplinary therapy team was established in 2006. We perform about 2000 colorectal cancer surgeries every year, in which half of them are rectal cancers. As a leading institution in colorectal cancer treatment in China, hundreds of patients with recurrent disease were referred to our department each year.

We are grateful for this opportunity to publish this book with the cooperation of AME Publish Company and thank the editors and the publisher for their outstanding job in bringing out this wonderful textbook. We hope those who read this book will gain new insights about the similarities and differences in how the West and East deliver colorectal cancer care.

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#### Preface

In these twenty years, surgical treatments have been dramatically developed from open surgery to endoscopic surgery worldwide. Innovative techniques such as reduced port surgery, NOTE, trans-anal surgery or robotic surgery came to our clinical fields in these ten years. We watched some of them grew bigger and others were disappearing at that time.

Nowadays, many colorectal surgeons became to believe the clinical benefits not only in the minimum invasiveness but also in oncological outcomes laparoscopic surgery potentially had. Some qualified clinical trials were conducted in colon cancer and the long-term outcome in laparoscopic surgery was comparable to open surgery. However, recent clinical studies shown in rectal cancer had different results from colon cancers. COLOR II and COREAN trial concluded the good oncological results in laparoscopic surgery for rectal cancer treatment but, Australian trial and US trials shown in last year indicated that curative resection rate in laparoscopic surgery group was worse than one in open surgery. We should recognize the caution they made in laparoscopic surgery for rectal cancer and some technical difficulties in laparoscopic surgery might be one of the causes of the limitations. To overcome such a situation, well educational system should be provided for surgeons all over the world.

The Recent laparoscopic approach has been applied to advanced procedures and an intersphincteric resection, pelvic side-wall dissection and trans-anal procedures were expanding in clinical fields of rectal cancer treatment which could make numbers of patients with rectal cancer preserved their anus and the functions. Furthermore, robotic devices will be also expected to expand in future market of surgical fields in a few years. Actually, some international companies are creating new devices. The Clinical trial using available robotics showed that there was a little benefit in surgery performed by robots than by conventional laparoscopic surgery. This might indicate differences in surgical procedures between by robot and by human get less after surgeon's learning for laparoscopic skills was achieved. Robotic technology must be improved from now and surgeons would begin to use the new innovative devices.

Finally, we would like to hope the recent works included in this book would penetrate to clinical field deeply.



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#### Preface

It is a great pleasure for me to be invited as Co-Editor of this book on Colorectal Surgery, presented as a themed collection of related articles from journals of AME recently published. The authors are comprised of estimated collaborators in the field of colorectal cancer research worldwide.

Colorectal cancer is one of the most common cancers in the world and, in particular, in western populations. There are different known risk factors for colorectal cancer, including germline genetic mutations. Some types of polyps, mostly adenomas, are established pre-neoplastic lesions and their identification with endoscopy allows effective screening and early diagnosis, with good possibilities to address patients to the best treatment. The screening for colorectal cancer has gained importance in the last years, because it identifies pre-neoplastic lesions or early stage tumors and permits to perform an efficacious oncologic treatment. Surgery still represents the mainstay therapy for colorectal cancer and this book is focused in particular on this field. The type of surgery depends on the stage and location of the tumor: usually a colectomy is needed and a good surgical treatment includes adequate resection margins and an appropriate lymphadenectomy. To be oncologically correct, a colonic resection must comprise at least 12 lymph nodes, which must be harvested till the origins of the principal mesocolic arteries of the specimen. This is the most important oncologic principle of colorectal surgery and all surgeons who want to perform an appropriate resection must respect it. In rectal surgery this concept is extended to all the mesorectum and in this field the most important oncologic principle is the respect of the total mesorectal excision (TME). Described for the first time in the 1982 by Prof. Heald, this concept is at the basis of the modern colorectal cancer surgery and it has become the "gold standard" for the treatment of rectal cancer worldwide. Even after the introduction of minimally invasive techniques, these basic oncologic principles have not changed and continued to constitute the fundamentals of colorectal oncologic surgery. In effect minimally invasive surgery has gained importance over the past two decades. From the first colorectal laparoscopic procedure described by Jacobs in 1991, many authors have given further evidence on the noninferiority of laparoscopy over open surgery, focusing on morbidity and mortality and on the effectiveness of this approach in terms of oncologic outcomes. However this approach has been adopted very slowly, especially for rectal cancer resections, maybe for some critical issues, like the lack of dexterity, a challenging learning curve and a difficulty in the approach of narrow anatomic fields such as the pelvis. To overcome these limitations, robotic surgical systems have been introduced and quickly adopted in colorectal surgery. Actually this technique can overtake the limitations of laparoscopy with comparable results in terms of surgical and oncologic outcomes. Nevertheless the adoption of this approach has been slow and not so widespread mainly due to its high costs and the absence of clear advantages over standard laparoscopy.

Over 50% of colorectal cancer patients will present with liver metastases either at the time of diagnosis or after resection of the primary tumor. In addition to the advances of surgery, chemotherapy and targeted biologic therapies have progressively and significantly improved the prognosis of patients with hepatic metastases in the last years. It is for this reason that a multimodal management is at the basis of the modern treatment of colorectal cancer. This approach includes the collaboration of surgeons, oncologists, radiotherapists as well as those specialists involved in pain management, diagnostic imaging, and complementary medicine in order to offer a complete and effective approach to this disease.

For these reasons this book, even if focused on the role of surgery, is composed of a series of discussions about the importance of the multimodal management of colorectal cancer.

So, after an introduction on the etiology and screening of colorectal cancer, the book directly focuses on all the aspects of colorectal surgery, including the treatment of hepatic metastases. In the last part there is a discussion about the complementary treatments, neoadjuvant and adjuvant chemo-radiotherapy, which today play an important role in the multimodal management of this disease.



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In recent decades, we have witnessed tremendous improvements in the field of surgery, and no other area of surgery has had such intense and rapid development as colorectal surgery. New and exciting diagnostic procedures and operative approaches, which are continuing to evolve as we learn how they may be applied to routine clinical settings, help in the evaluation of patients and provide detailed knowledge about which treatment should be chosen. The gastrointestinal tract, more than any other abdominal organ, continues to open up fascinating surgical frontiers in both basic research as well as in clinical practice. Clinical studies supported by surgical technology have contributed to our further understanding of the clinical behaviour of the various colorectal diseases, resulting in more reasonable and appropriate clinical management. The cutting-edge knowledge and comments on recently published studies provided in this book bring together the accumulated experience of many of the leading surgeons and physicians and the latest clinical research. We have endeavored, with help of an international group of contributors, to provide an up-to-date and authoritative account of the management of colorectal disease in selected topics. Collectively, the chapters make a case for the need for new innovative approaches to integrating surgical technology into the management of patient care.

Our starting point is the bacteria-hypothesis of colorectal cancer, which addresses its pathogenetic and therapeutic implications. The second chapter is devoted to epidemiological issues, where the key issues are elaborated in three reviews and one comment. The latest developments in surgical techniques and treatments and different controversies in managing patient care are described in detail in chapter three, including single-incision laparoscopic surgery, robotic surgery, transanal TME, TAMIS and endoscopic techniques. Chapters four and five are focused on the medical and surgical treatment of colorectal metastases, including neo-adjuvant treatment, intraperitoneal therapy and HIPEC. Seven recent reviews and comments give a full insight into the latest knowledge and treatment principles in this area. The last chapter addresses the influence of anastomotic leakage on patients' outcomes and functional disturbances after rectal cancer surgery. Many challenges still remain, and we are at an early stage of acquiring the knowledge and skills needed to better understand the implications of surgical technology on clinical practice.

Special acknowledgement must be given to the authors, who are among the foremost experts in their fields, and who have contributed to the chapters. It would not be possible to publish this book without their cooperation and help. Also, we wish to express our deep appreciation to our publishers, AME publishing company, for giving us great support in publishing a book in such an innovative form and a very readable size. This book presents the state-of-the-art techniques at the cutting edge of the colorectal surgery field and makes a convincing case for what will be possible for future generations of surgeons. We hope that all clinicians involved in the treatment of colorectal disease will receive this volume with great interest.

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#### Preface

Rectal cancer had been reported to be the third most common malignancy worldwide. The treatment of rectal cancer is mainly surgery with the goal of tumor control and preservation of anorectal function. The treatment of rectal cancer has undergone tremendous improvements since Miles' introduction of the abdominoperineal resection (APR) in 1908. The APR procedure became the gold standard as most surgeons observed decrease in local recurrence. With its high morbidity, some surgeons began to question its need to all rectal cancer, for prevention of colostomy and restoration of bowel continuity. In 1948, Claude Dixon was the first to prove that anterior resections could be safely done. And in 1970, Sir Alan Parks, at Saint Marks Hospital, showed that rectal cancers even closer to the dentate line cutoff could be safely resected and a coloanal anastomosis (CAA) performed. He achieved comparable results for cancers treated with APR. With the improvement of morbidity and avoidance of permanent stoma, a 15% to 45% local recurrence still occurs. Then the introduction of total mesorectal excision (TME) by Bill Heald has reduced local recurrence rate by less than 10%. The TME in combination with neoadjuvant chemoradiation therapy decreased the rate of local recurrence from 8.2% to 2.4%. Neoadjuvant chemoradiation therapy coupled with the introduction of the circular (EEA®) stapler in 1979 even more facilitated the progress toward performing more sphincter-sparing operations. In 1977, 'intersphincteric resection' (ISR) was adopted by Lyttle to mean resection of the internal sphincter muscle for inflammatory bowel disease. The procedure has been gradually refined in the following decades, and during 1994 ISR procedure was initiated for very low rectal cancer located 5 cm from the anal verge. In a recent systematic review, Dr. Akagi concluded that ISR is oncologically acceptable compared with APR and CAA with excellent disease-free survival (69-86%) and overall 5-year survival rates (79-97%). In addition to these developments of surgery, adjuvant treatment has evolved greatly. Cytotoxic chemotherapy, targeted agents, and recent immune checkpoint inhibitor are now currently available armamentarium for colorectal cancer treatment. In this regards, this book includes crucial aspects of colorectal cancer treatment in terms of 'etiology of colorectal cancer, screening of colorectal cancer, surgical treatment of colorectal cancer, treatment of colorectal metastases, adjuvant radiochemotherapy of colorectal cancer, and treatment of postoperative complications after rectal cancer surgery'. This book will deliver up-to-date evidences for colorectal cancer treatment.

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#### Preface

The incidence of colorectal cancer (CRC) is increasing steadily worldwide. Despite major developments in the diagnosis and treatment of CRC, more efforts are needed for substantial improvements in the screening of asymptomatic individuals, early diagnosis, and refinement in the multimodality treatment and the multidisciplinary approach of these patients especially when advanced, recurrent or metastatic disease is faced.

This book on Colorectal Surgery is a collection of articles from AME journals. It aims to address the above-mentioned topics by providing contemporary, concise and integrated views on the diagnosis and screening, surveillance, and therapeutic approaches to CRC communicated by an international cohort of eminent authors.

Early chapters address the possible relationship between gut microbiota and colorectal carcinogenesis and the potential therapeutic implications. Novel stool and blood based tests as possible first-line effective tools for the screening of asymptomatic individuals are presented. The optimal intervals and duration of surveillance colonoscopies after detection and removal of adenomas are outlined.

Surgical resection is the cornerstone of CRC treatment offering the best chance for cure in these patients. In recent years, the development of laparoscopic and robotic surgery, the advent of different minimally invasive transanal approaches and innovative combination of techniques contributed to better quality of life and patient satisfaction, improved functional results and comparable to conventional techniques oncological outcomes when performed by an experienced operative team in properly selected patients. These issues are presented and highlighted in the third section of this book.

The following section focus on the management of colorectal liver metastases (CRLM). Development of liver metastases is a crucial event in CRC progression and a major determinant of patient survival. Approximately half of CRC patients ultimately develop liver metastases with nearly 25% presenting as synchronous metastases (at presentation or within 6 months after primary tumor resection) and the remaining 25% as metachronous metastases. Modern chemotherapeutic regimens are highly effective and improve the survival of patients with CRLM but are generally not curative. Surgical resection of CRLM is the only treatment modality offering the best chance of cure and enabling long-term survival with a five-year survival rate exceeding 50% and almost 20% of patients surviving more than ten years. Better knowledge of the molecular pathways and biological behavior of CRLM, the availability of targeted agents and the use of multi-agent therapies, the combination of loco-regional and ablative treatments, and the multidisciplinary approach improved profoundly the survival of patients with CRLM. The treatment strategy has evolved and the indications for resection of CRLM have expanded considerably over the last two decades. Currently, the focus has shifted to the future liver remnant (what remains after resection) rather than to the metastatic burden (number and size of metastases) thus offering the opportunity of CRLM resection in patients who traditionally would not have been candidates for resection. More recently, the laparoscopic resection of CRLM has been introduced and rapidly overcome factors such as the number, the size, the distribution and the accessibility of the lesions and progressed from minor to major hepatectomies. This is a highly demanding technique but experienced teams have shown its feasibility, safety and oncological efficiency in CRLM resection.

The final sections focus on some distinct conditions such as dissemination of CRC into the peritoneal cavity (peritoneal carcinomatosis) which is currently considered as loco-regional rather than systemic disease, and the role of cytoreductive surgery and intraperitoneal chemotherapy in targeting this condition. The current status of neoadjuvant chemoradiation for the treatment of rectal cancer as part of a multidisciplinary approach is also presented. Finally, the effect of anastomotic leakage after rectal cancer resection on immediate postoperative outcomes, postoperative bowel function and quality of life and possibly on the oncological results is outlined.

We would like to thank the authors for their precious contribution to accomplish our aim. We consider this book to be of interest and value to healthcare providers involved in the treatment of patients with CRC, to students and trainees, and to the wide audience.

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# The bacteria-hypothesis of colorectal cancer: pathogenetic and therapeutic implications

#### Debora Compare, Gerardo Nardone

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> **Abstract:** It is estimated that up to 20% of malignancies worldwide can be attributed to infections. The most convincing evidence, in this context, is the link between Helicobacter pylori and both gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. A growing body of evidence in the last years has raised up the question of the putative causal role of gut microbiota in the carcinogenetic process. Bacteria are an important component of the human body. The human intestine contains >500 different types of microorganisms, usually referred to as the commensal intestinal microbiota. A chronic alteration of the intestinal microbiota homeostasis or "dysbiosis" underlies many diseases, including cancer. The main mechanisms by which bacteria may induce carcinogenesis include chronic inflammation, immune evasion and immune suppression. If the microbiota is involved in cancer development, being the colon the site where the microbiota reaches its highest concentration, it is expected to be its major site of action. Numerous data from experimental, animal model and human studies support the gut-bacteria hypothesis of colorectal cancer (CRC). Germ-free rats, compared with conventionally reared animals, develop fewer and smaller tumors both spontaneously and after chemically-induced CRC. The absence of the physiological inflammation caused by the commensal microbiota may explain the capability of the germ-free rats to develop a more efficacious anti-cancer immune response. Several microorganisms, including Streptococcus bovis, Bacteroides fragilis and Escherichia coli have been implicated in the pathogenesis of CRC. The emerging relationship between gut microbiota and cancer prompts new ways of thinking about cancer prevention and leads to the development of innovative treatments such as probiotics. However, although in vitro and animal model studies suggest a protective anticancer effect of probiotics, the results of human epidemiological studies are still controversial and very few data are available from interventional studies.

Keywords: Gut microbiota; colorectal cancer (CRC); probiotics

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#### Introduction

Back to 1863 Rudolf Virchow, a German pathologist, affirmed that cancer may be considered the end result of a chronic inflammatory process triggered by an adverse toxic environment, including infections. The concept that bacterial infections could lead to cancer was first proposed in the late 19<sup>th</sup> century, following the pioneering work of Robert Koch and Louis Pasteur, based on the discovery of bacteria at the sites of tumors. Nowadays up to 20% of

malignancies worldwide can be attributed to infections with a global total of 1.2 million cases per year (1). The most convincing evidence, in this context, is the link between *Helicobacter pylori* and both gastric cancer and mucosaassociated lymphoid tissue (MALT) lymphoma. The hypothesis of the infectious origin of cancer is corroborated by the association of *Salmonella typbi* with gallbladder cancer, *Chlamydia pneumoniae* with lung cancer, and *Streptococcus bovis* (S. *bovis*) with colorectal cancer (CRC).

Based on these historical perspectives a growing body of

evidence in the last years has raised up the putative causal role of gut microbiota in the carcinogenetic process (2). If the microbiota is involved in cancer development, being the colon the site where the microbiota reaches its highest concentration, it is expected to be its major site of action.

Colorectal cancer is the third most common cause of cancer-related death in woman and the fourth leading cause of cancer mortality in males. Over 140,000 new cases of CRC are estimated for the U.S. in 2012 with diseasespecific mortality of up to 60,000 reported in 2011 (3). Colorectal cancer is classified as inherited (due to genetic instability), inflammatory (associated to inflammatory bowel disease) or sporadic, which accounts for more than 80% of all CRCs. Sporadic CRC, is the focus of both tremendous epidemiological research efforts, with the goal to determine potential causative and risk factors associated with the disease, and continuous basic research, aimed to clarify the pathogenetic mechanisms of the disease. Several potential risk factors have been identified, such as highfat diet, red meat consumption, alcohol intake, and obesity, but the list continues to evolve, and in the past few decades has expanded to include infectious agents, and in particular alterations of the gut microecology.

Here, we will address the link between gut microbiota and CRC focusing on pathogenetic and therapeutic implications.

#### **Gut microbiota and carcinogensis**

Our gut harbors the majority of mammalian-associated microbes. The fetal intestine is sterile but, following delivery, the colonization of the intestine by a variety of microorganisms begins. Gastrointestinal colonization involves a succession of bacterial populations varying as the diet changes and the host develops. This assemblage of bacteria inhabiting the gut is usually referred to as the commensal intestinal microbiota. Each human adult harbors approximately 10<sup>14</sup> bacteria in the gut, which is about 10 times the number of cells making up the human body (4). There are at least 500 different bacterial species and these species can again be divided into different strains, highlighting the enormous complexity of this ecosystem. The bacteria in the gut interact with their human host and, although some bacteria are potentially pathogenic and can become a source of disease, this host-bacterial interaction is mainly symbiotic and health-conferring. The result of this interaction may lead to a "physiological inflammation" that regulates the presence of the resident gut microbiota or, to

a "pathological inflammation", the degree of which depends on the number and virulence of the invading pathogens (5). Physiological inflammation maintains a dynamic yet fragile homeostatic balance; however, persistent inflammation may be the link between gut bacteria and carcinogenesis process. Chronic inflammation can profoundly alter local immune response and lead to the release of reactive oxygen species (ROS) and nitric oxide (NO) that in turn may induce DNA damage and consequently alter tissue homeostasis (6). Nevertheless, cytokines and chemokines can act as tumor growth and survival factors and may induce tumor development by promoting angiogenesis and suppressing immune-surveillance. Cancer-promoting cytokines include tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL)-6, and IL-1. By contrast, IL-10 and transforming growth factor beta (TGF- $\beta$ ) inhibit carcinogenesis (6). In summary, chronic inflammation, immune evasion and immune suppression are the mechanisms by which bacteria may induce carcinogenesis.

The gut microbiota elicits both innate and adaptive immune mechanisms that cooperate to protect the host and maintain intestinal homeostasis. Activation of innate host defense depends on specific pattern recognition receptors (PRRs) that recognize highly conserved microbial signature molecules called "pathogen-associated molecular patterns" (PAMPs). The PRRs include the family of toll-like receptors (TLRs), which scan the extracellular space, and Nod-like receptors (NLRs), which guard the intracellular cytoplasmatic compartment (7). Different TLRs recognize different classes of PAMPs, characterizing different pathogens. After PAMP ligation, TLRs dimerize and transmit intracellular signals through four adaptor proteins: myeloid differentiation primary response gene 88 (MyD88), toll/interleukin-1-receptordomain-containing adaptor inducing interferon- $\beta$  (TRIF), toll/interleukin-1-receptor-domain-containing adaptor protein (TIRAP), and TRIF-related adaptor molecule (TRAM), that have an important role in inflammation and tissue regeneration (8). Therefore, TLRs are likely candidates to mediate the effects of the innate immune response on tumorigenesis. Mice that lack either TLR4 or its MyD88 adaptor exhibit decreased epithelial cell proliferation and increased apoptosis in response to chemical-induced injury (9,10). Finally, the blockade of the TLR4 receptor in mice with CRC xenografts decreases the growth of colon tumors.

TLR4 has been associated with the process of tumor progression via the nuclear factor kappa-lightchain-enhancer of activated B cells (NF-κB) pathway



**Figure 1** Toll like receptor signaling in colorectal cancer. LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IκB, inhibitor of NF-κB; IAP, inhibitor of apoptosis; TNF-α, tumor necrosis factor alpha; IL, interleukin 6; COX2, cycloxigenase 2; PGE2, prostaglandin E2.

resulting in the transcription of inflammatory cytokines, chemokines and antimicrobial genes. How NF-κB-induced inflammatory process drives carcinogenesis is unclear, although IL-6 seems to have a pivotal role. IL-6 induces the procarcinogenic signal transducer and activator of transcription (Stat)3 pathway and transcriptionally activates proliferative, antiapoptotic and proangiogenic genes involved in cancer growth, such as c-IAP-1 and c-IAP-2, Fas ligand, c-myc, p53, and cyclin D1 (*Figure 1*) (11).

Findings from animal models of CRC are corroborated by human studies. The TLR4/MyD88 co-receptor complex is over-expressed in CRCs compared to the normal and adenomatous colonic epithelium, confirming that this signaling pathway is important in human sporadic CRC (12). Specific polymorphisms of toll receptors are also associated with an increased CRC risk and influence prognosis (13). In both murine models and human samples, TLR4 and IL-6 expression in the tumor microenvironment are associated with the presence of adenocarcinoma, and higher levels of TLR4 expression in the tumor stroma are noted with disease progression (14). TLR4 expression in the stroma of patients with stage 3 CRCs correlates with early relapse, suggesting the importance of this marker in predicting prognosis or as a therapeutic target (15).

The gut-mucosal arm of the adaptive immune system, localized predominantly in the small bowel, provides humoral and cell-mediated immunity against ingested antigens and luminal organisms. Effector lymphocytes are diffusely distributed in the lamina propria as isolated lymphoid follicles or are organized into structures termed "Peyer's patches". Locally recruited cells of the adaptive immune system may have either pro- or anti-tumorigenic roles. T cells, for instance, are required for inflammation, cancer development, and tumor progression (Figure 2), as well as for anticancer immunity (16). In sporadic CRC, there seems to be a well-defined balance between immunosurveillance (executed by CD8+ T cells, NK cells, and CD4<sup>+</sup> T cells) and tumor-promoting inflammation (executed by innate immune cells, B cells, and various subtypes of T cells) (8).



Figure 2 The role of immune cells in the gut microbiota-related colorectal carcinogenesis.

Three effector pathways of T helper (Th) cell differentiation have been characterized: Th1, Th2 and Th17 responses. While the Th1 response is typically anticarcinogenic, the contribution of Th2 or Th17 responses to cancer remains to be defined (17). Microbiotainduced Th17 cytokines in the lamina propria are crucial for protection against intestinal pathogens but, they can also contribute to inflammation. Indeed, IL-23-responsive innate lymphoid cells in the lamina propria contribute to colitis in Rag-/- mice by producing IL-17 and interferon gamma (IFN- $\gamma$ ) (18). Whether the highly inflammatory nature of Th17 cells is sufficient to cause or contribute to carcinogenesis is still debated. Experimental evidence

#### Compare and Nardone. Gut microbiota and colorectal cancer

shows that Th17 cells progressively increase in the tumor microenvironment during tumor development and that IL-17 up-regulates the expression of pro-inflammatory cytokines and pro-angiogenic factors. On the other hand, a number of reports have described tumor-inhibitory effects of IL-23 and IL-17 in mouse models genetically engineered to overexpress IL-23 or IL-17. Therefore, the activation of the IL-23/IL-17 pathway may promote tumorigenesis by inducing local inflammatory response, or inhibit it by stimulating anti-tumor immunity (19). More recently, a T regulatory response (TReg), driven by IL-10 and TGF-β has been shown to counterbalance the pro-inflammatory effect of the Th17 response. The induction of TReg cells by commensal microorganisms and the occurrence of intestinal inflammation in their absence indicate that TReg cells regulate the equilibrium between non-inflammatory homeostasis and intestinal inflammation. However, experimental and clinical findings have demonstrated that TReg cells, by suppressing the innate and adaptive immune responses, are a major factor contributing to the immunosuppressive tumor microenvironment, thus fostering tumor progression (20). Strategies that deplete or inhibit Treg cells and promote a competent immune response in the tumor microenvironment could be the goal in future immunotherapeutic studies in cancer patients.

#### Gut microbiota and colorectal cancer

In 1975 Reddy *et al.*, firstly linked the gut microbiota to CRC development. They found that only 20% of germfree rats develop chemically induced CRC; in contrast, the tumor incidence in conventional rats was 93% and the neoplasms were multiple (21). This data has been recently confirmed by Vannucci *et al.* who found that germ-free rats, compared to conventionally reared animals, develop fewer and smaller tumors both spontaneously and after chemically-induced carcinogenesis (22). In addition, germ-free mice has also shown less oncogenic mutations and a decreased tumor formation in both colitis-associated cancer and *Apc*-related CRC (23).The absence of the physiological inflammation caused by the commensal microbiota may explain the capability of the germ-free rats to develop a more efficacious anti-cancer immune response.

Many bacterial species have been found in CRC samples and in tissue adjacent to tumors, namely, *S. bovis, Bacteroides fragilis (B. fragilis), Escherichia coli (E. coli)*, etc (*Table 1*).

The best known association is that between *S. bovis* bacteremia and CRC, recognized since 1951, when McCoy

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Table T Bacteria and Telated pathogenetic incentanishis linked to colorectal cancer	
Pathogenetic mechanism	
Activation of STAT3	
Induction of Th-17 immune response	
Production of IL-1	
Cleavage of E-cadherin	
Activation of b-catenin signaling	
Activation of MyD88-dependent signalling	
NF-KB activation	
Increased bacterial presence	
-	
-	
Intracellular colonization	
ROS production and DNA damage	
Production of IL-8	
Aberrant crypt formation	
Increased proliferation	

ROS, reactive oxygen species; Stat, signal transducer and activator of transcription; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor κB.

and Mason first reported a case of enterococcal endocarditis, likely from S. bovis, associated with a carcinoma of the cecum. Since then, the connection between S. bovis septicemia and colonic neoplasia has been confirmed by several other case reports and case-control studies. About 25-80% of patients with S. bovis bacteremia exhibit a CRC; in addition, a significantly higher fecal carriage of S. bovis has been reported in patients with CRC compared with control subjects (24). The mechanisms underlying this association are not known. Ellmerich et al. reported that S. bovis enhanced the expression of the proliferation markers and polyamines, and induced the formation of colonic adenoma in 50% of rats, as well as a higher number of aberrant colonic crypts. The authors also found that S. bovis and its wall antigens are able to increase the production of IL-8 in the colonic mucosa (25). IL-8 induces the formation of NO and ROS that contribute to the neoplastic process by altering cell DNA. On the basis of these data, several authors have suggested that all patients with S. bovis bacteremia should undergo a complete endoscopic evaluation of the colon.

*B. fragilis* strains comprise approximately 0.1% of the normal colonic flora and are found in the colonic flora in up to 80% of children and adults. The "enterotoxigenic *B. fragilis*" (ETBF), producing *fragilisyn*, has been associated

with CRC. The toxin cleaves the extracellular domain of the E-cadherin, which is the principal structural component of the zonula adherens and is responsible for cell-tocell adhesion (26). Treatment of HT29/C1 cells with B. *fragilis* toxin triggered the nuclear localization of  $\beta$ -catenin, which in turn, after binding with T-cell factor-dependent transcriptional activators, induced c-myc and cyclin D1 transcription and translation, resulting in persistent cellular proliferation (27). Activation of  $\beta$ -catenin signaling via mutations in one or more of the APC complex proteins, contributes to the development of inherited and sporadic forms of CRC and possibly other cancers. Toprak et al., by investigating the prevalence of ETBF in stool specimens from 73 CRC patients and 59 controls found the enterotoxin gene in 38% of the isolates from CRC patients compared with 12% of the isolates from the control group (26). More recently Wu et al. (27) showed that ETBF strongly induces CRC in multiple intestinal neoplasia (Min) mice, by activating Stat3 and a selective TH17 response. The authors also demonstrated that the antibody-mediated blockade of IL-17 as well as that of the receptor for IL-23, a key cytokine amplifying TH17 responses, inhibits ETBFinduced tumor formation (28).

*E. coli* is a normal inhabitant of the human gut. The colonic mucosa of patients with adenomas and carcinomas

has shown an increased intracellular mucosal carriage of *E. coli* compared to healthy controls (29). Whether this increased carriage had a causal or incidental origin is currently not known. *E. coli* strains of the phylogenetic group B2 harbor a genomic island called "pks" that codes for the production of a polyketide-peptide genotoxin, colibactin. The *in vivo* infection with *E. coli* harboring the Pks Island, but not with a pks isogenic mutant, induced the formation of phosphorylated H2AX foci in mouse enterocytes, contributing to the development of sporadic CRC (30).

Until now the relation between gut microbiota and CRC was based on culture ex vivo methods. However, 60-80% of the gut bacteria are uncharacterized because they cannot be cultivated ex vivo. Recent advances in molecular methods, based on the highly conserved bacterial 16S ribosomal RNA (rRNA) gene have enhanced our ability to study and characterize both luminal and adherent bacteria communities in the gut. By using these approaches, only a few studies have investigated changes in the microbiota composition during CRC. Nevertheless, these studies indicate that the altered colonic environment in CRC could have implications for the composition of the microbiota in the lumen and on mucosal surfaces. Gueimonde et al., by qRT-PCR, analyzed samples of colonic mucosa from 34 patients (21 CRCs, 9 divertiulitis and 4 inflammatory bowel diseases) and found that patients with CRC had significantly lower levels of both Bifidobacterium longum and bifidum than patients with diveritulitis and inflammatory bowel disease (31). Similarly, Shen et al., by evaluating adherent bacteria in 21 adenoma and 23 non-adenoma subjects by a sophisticated molecular approach, sequenced and processed for phylogenetic and taxonomic analysis a total of 335 clones and found higher Proteobacteria and lower Bacteroidetes numbers in tumor cases compared with control subjects (32). Sobhani et al. using pyrosequencing of stool bacterial DNA and subsequent Principal Component Analysis (PCA) demonstrated a composition change in the microbiota of CRC patients; in particular Bacteroides/Prevotella species were more numerous in cancer patients (n.60) than in control subjects (n.119). In addition, IL-17 immunoreactive cells were expressed at significantly higher levels in cancer patients than in those with normal colonoscopy (33). Very recently Marchesi et al. compared differences in healthy and cancerous tissue within cancer patients and found that species of the genera Coriobacteridae, Roseburia, Fusobacterium and Faecalibacterium were over-represented in tumor tissue; these are generally regarded as gut commensals with

probiotic features. Further, this study found decreased colonization by members of *Enterobacteriaceae*, such as *Citrobacter*, *Shigella*, *Cronobacter*, and *Salmonella* in CRC tissue from the investigated patients (34). Finally, Scanlan *et al.* investigated the diversity and presence of methanogens in healthy, polyp and cancer patients and found significant differences in bacterial stability over time. Specifically, the diversity of the *Clostridium leptum* and coccoides subgroups was increased compared to healthy controls. Importantly, metabonomic faecal water analysis was able to distinguish CRC and polyp groups from healthy controls, indicative of an altered metabolic activity of the intestinal microbiota in these patients (35).

Taken together, these data show that the gut microbiota may play a major role in CRC development at both quantitative and qualitative level.

#### Probiotics and colorectal cancer

The emerging relationship between the gut microbiota and cancer opens the door to new ways of thinking about cancer prevention. Probiotics are defined as viable microorganisms that, when administered in adequate amounts, confer a health benefit to the host. They may positively affect the gut microbiota and have a beneficial effect in the prevention and treatment of specific pathological conditions. There are many mechanisms by means of which probiotics positively affect the gut microbiota and liver health, i.e., inhibition of intestinal bacterial enzymes, stimulation of host immunity, competition for limited nutrients, inhibition of bacteria mucosal adherence and epithelial invasion, protection of intestinal permeability and control of bacterial translocation from the gut to the bloodstream. The biological activity of probiotics depends prevalently on delivering anti-inflammatory mediators that downregulate pro-inflammatory cytokines, including IFN-y and TNF- $\alpha$ , via the NF- $\kappa$ B pathway. The mechanisms through which probiotics may exert beneficial effects include macrophage activation, cytocrome P450 blocking, reduction of carcinogen generation, down-regulation of Ras-p21 expression, increase of cell differentiation, inhibition of COX-2 up-regulation, inhibition of NO synthase, increase of short chain fatty acid production, and reduction of intestinal pH with lessening of putrefactive bacteria (36,37).

The anticarcinogenic effects of probiotic microorganisms *in vitro* and in animal studies are well documented. In a very recent study, Bassaganya-Riera *et al.* investigated the ability of VSL#3 bacteria to modulate mucosal immune

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responses and thereby ameliorate colonic carcinogenesis in mouse models of inflammation driven CRC. In mice treated with VSL#3, adenoma and adenocarcinoma formation was diminished by both treatments (38). Chang et al. demonstrated that the oral administration of Lactobacillus acidophilus (L. acidophilus) KFRI342 to rats with 1,2-Dimethylhydrazine (DMH)-induced CRC inhibited the development of preneoplastic lesions and lowered the microbiota populations of both E. coli and aerobic bacteria, which have been associated with carcinogenesis (39). The possibility that probiotics modulates immunity may inhibit colon carcinogenesis has been also investigated. Foo et al. by evaluating the effect of long term (24 weeks) treatment with B. longum and Lactobacillus gasseri (L. gasseri) on the development of DMH-induced colonic precancerous lesions and tumors in 70 male mice showed that both probiotics significantly inhibited DMH-induced aberrant crypt foci formation, as well as decreased tumor multiplicity and the size (40). Several studies have shown that the intake of probiotics can influence enzyme activities and can be linked with the risk of colon carcinogenesis. Lactobacillus casei (L. casei) treatment of mucosa samples from duodenum, jejunum, ileum, cecum, and colon of 45 male Wistar rats was able to monitor the expression of selected cytochromes P450, testing the hypothesis that the L. casei probiotic might contribute to preventing CRC by decreasing levels of certain forms of xenobiotic-metabolizing enzymes (41). Finally probiotics may retard colon carcinogenesis by stimulating tumor cell apoptosis. Preinoculation with the probiotic L. acidophilus NCFM for 14 days in BALB/cByJ mice in which orthotopic CRCs were implanted, reduced the severity of colonic carcinogenesis caused by CT-26 cells (42), such as the level of colonic involvement and structural abnormality of epithelial/crypt damage (43). A significant down-regulation of the CXCR4 mRNA expression, associated with reduced apoptosis, was observed (44).

Data from human studies are still controversial. An epidemiological study performed in Finland demonstrated that, despite a high fat intake, CRC incidence is lower than in other countries because of the high consumption of milk, yoghurt and other dairy products (44). In two population-based case-control studies of CRC, an inverse association was observed for yoghurt and cultured milk, adjusted for potential confounding factors (45,46). An inverse relationship has been demonstrated between the frequency of consumption of yoghurt and other fermented milk products and breast cancer in women. On the other hand, two American prospective studies, the Nurses' Health Study and the Health Professionals study, did not provide evidence that intake of dairy products is associated with a decreased risk of CRC (47). In a cohort study in the Netherlands, it was shown that the intake of fermented dairy products was not significantly associated with CRC risk in an elderly population with a relatively wide variation in dairy product consumption, although a weak nonsignificant inverse association with CRC was observed (48). The contrasting results may be related to study designs, population examined, follow-up, bacterial strains used, endpoints, dietary habit and so on. An intervention study in humans in which both probiotics and prebiotics were used was recently performed among 17 patients with FAP. In this single-center human study on patients with FAP, a 4-week intervention with (I) sulindac; (II) inulin/VSL#3; and (III) sulindac/inulin/VSL#3 was performed. Cell proliferation was lower after treatment with sulindac or VSL#3/ inulin; the combination of sulindac/inulin/VSL#3 showed the opposite effect. Glutathione S-transferase activity increased after treatment with sulindac or VSL#3/inulin; the combination treatment showed the opposite effect (49). However, FAP is a rare disorder, so the main weakness of this study is the small number of patients included in a single-center fashion.

In 2006 Capurso *et al.* produced a systematic review of data from basic science (animal and *in vitro* models) and human (epidemiological and interventional) studies, addressing the risk of CRC and the use of probiotics (50). The *in vitro* studies, confirm the ability of probiotics to dialogue with intestinal cells. Overall, 26/29 animal model studies suggested that probiotics had a protective anticancer effect; however, given the different study designs and treatments, the results are difficult to compare. Finally, the epidemiological human studies are difficult to interpret given their extreme heterogeneity (50). Further experimental studies in animal models and clinical trials in humans are needed to quantify the effect and elucidate the mode of action of probiotics in prophylaxis and treatment of CRC.

#### Conclusions

Over the years, it has become apparent that the gut microbiota is not a bystander in the complex biological events regulating intestinal homeostasis, but it may lead to beneficial or detrimental effects to the host. Multiple lines of evidence support the notion that gut microbiota can contribute to colorectal carcinogenesis. Various bacteria

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have been linked with experimental carcinogenesis in animal models or correlated with CRC in human observational studies and multiple microbiota-based studies suggest differences in mucosa associated and luminal bacteria in subjects with CRC.

Therefore, a beneficial modulation of the composition and metabolic activity of the gut microbiota might represent an interesting approach to reducing the risk of CRC development. Even though the mechanisms by which probiotics may inhibit CRC are not fully elucidated, certain potential mechanisms have been disclosed, such as the alteration of the composition and the metabolic activities of the intestinal microbiota, the changing physicochemical conditions in the colon, the binding of dietary carcinogens, the production of short chain fatty acids, the protection of the colonic mucosa and enhancement the immune system. In the near future, high quality mechanicistic experimental studies and interventional human studies might provide the scientific premises for the clinical use of probiotic in the prevention of CRC.

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# Risk of colorectal cancer after detection and removal of adenomas at colonoscopy

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In the United States, a large proportion of endoscopists are conducting surveillance examinations after polypectomy along the American Gastroenterological Association guidelines (1).

In the guideline, patients can be stratified more definitely at their baseline colonoscopy into those at lower risk or increased risk for a subsequent advanced neoplasia. People at increased risk have either 3 or more adenomas, or advanced adenomas which is an adenoma with high-grade dysplasia, or with villous features, or an adenoma 1 cm or larger in size. It is recommended that they have a 3-year follow-up colonoscopy. People at lower risk who have 1 or 2 small (<1 cm) tubular adenomas with no high-grade dysplasia can have a follow-up evaluation in 5-10 years. People with hyperplastic polyps only should have a 10-year follow-up evaluation, as for average-risk people. After this guideline published, several studies have examined the risk of advanced colorectal neoplasia in patients with previously endoscopically resected colorectal adenomas to quantify their risk of developing a subsequent advanced adenoma or cancer. A pooled analysis of eight prospective studies (with a total of 9,167 subjects) estimated that the risk of advanced colorectal neoplasia was 12 percent during a median followup of four years; 58 patients (0.6 percent) developed invasive cancer (2). The strongest risk factors were advanced neoplasia in the initial polypectomy, older age, and the number and size of prior adenomas.

However, in most of studies, evidence for surveillance intervals continues to be based primarily on adenoma recurrence rather than on Colorectal Cancer (CRC) incidence. In this study, authors aimed to assess risk of CRC rather than adenoma recurrence. They showed that patients with a history of detection and removal of at least one adenoma had a strongly and significantly reduced risk of CRC up to 5 years after colonoscopy compared with people who had never undergone large-bowel endoscopy. They concluded that extension of surveillance intervals to 5 years should be considered, even after detection and removal of high-risk polyps, whereas it is the common understanding that a surveillance interval of 3 years is needed after detection and removal of high-risk adenomas, which is mainly based on studies that focused on risk of advanced adenomas following colonoscopic polypectomy (3-7).

This study was conducted retrospectively. However, the authors sought to raise evidence level. This is multicenter study with 22 hospitals, and they could recruit 6,422 persons, and this is five fold samples of their previous report (8). Personal interviews were conducted by trained interviewers who visited the patients during hospitalization or, if they had already left the hospital, at their homes. The standardized interviews lasted for about 1 hour. Furthermore, they sought to validate the obtained information by medical records from the participants' physicians.

There is evidence of substantial overuse of surveillance colonoscopies, especially after detection and removal of low-risk adenomas (9-12). So, it is important to evolve the adequate time interval to surveillance colonoscopy after adenoma removal.

Recently, several new risk factors have suggested in many studies. An increased body mass index (BMI) is associated with an increased risk of colorectal adenomas (13). COX-2 agents demonstrated significant reductions in advanced and metachronous adenomas (14-16). Aspirin also reduces the incidence of metachronous adenomas and probably cancer (17). Ursodeoxycholic acid reduces the risk of adenomas with high-grade dysplasia (18).

Further and even larger studies are needed to more precisely define surveillance intervals with enhanced risk stratification.

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#### Footnote

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# Colorectal cancer screening: are stool and blood based tests good enough?

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**Abstract:** Colorectal cancer (CRC) is the third commonest cancer worldwide. As many CRC patients were identified at advanced stages, screening asymptomatic individuals has substantial clinical benefit. Most CRC arises through recognizable early stage. With the improved understanding of the biology of CRC and precancerous lesion, testing molecular aberrations in stool and blood promises novel screening approaches that are noninvasive, sensitive, and more affordable compared with traditional structural examinations.

Keywords: Colorectal cancer; screening; biomarkers; stool

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#### **Colorectal cancer**

#### Epidemiology

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females. Over 1.2 million new cancer cases and 600,000 deaths were estimated to have occurred in 2008 (1). The lifetime risk of CRC is approximately 6%. Risk factors for CRC include family history, male gender, smoking, alcohol consumption, physical inactivity, obesity, and red and processed meat consumption. The risk of CRC increases with age, particularly after 50. Death rates of CRC have been decreasing in several Western countries largely because of improved treatment, increased awareness and early detection (2-4). However, both the incidence and death rates of CRC are increasing in Asia because of the lack of guideline for screening and public awareness (5).

Around 15% of CRCs are inherited. The most common forms are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). HNPCC arises because of mutations in mismatch-repair genes, including MLH1, MSH2, MSH3, MSH6, PMS1 and PMS2 (6), leading to DNA instability, such as in the length of microsatellite sequences, and results in microsatellite instability (MSI) (7). HNPCC is characterized by the early onset of colorectal tumors, particularly in proximal colon.

Around 85% of CRCs are sporadic. Based on pathological data, most sporadic CRCs are developed from adenomas (8-10). Adenomas are masses that protrude into the gut lumen, which can either be pedunculated or sessile. Adenomas can be flat or even depressed. The epithelium of adenomas can form glands (tubular adenomas), fingerlike structures (villous adenomas), or a combination of both (tubulovillous adenoma). Adenomas that are larger than 1 cm, or those with severe dysplasia or a villous architecture are referred to as advanced adenomas. The development of CRC from adenoma is estimated to require 5 to 10 years, as referred to the adenoma-carcinoma sequence.

#### Screening

Patients with early stage CRC or precancerous lesion are mostly asymptomatic. By the time patients present with symptoms such as anemia, abdominal pain, weight loss, change in bowel habit, and rectal bleeding, the disease is likely to have reached an advanced stage. The survival from CRC is closely related to the stage of cancer when diagnosed, with late CRC having the worst outcome (11). Since most CRC develops from precancerous lesions, screening has substantial clinical benefits to patients. Based on the guidelines from the United States, there are several options for CRC screening (12-14). Flexible sigmoidoscopy and colonoscopy are more invasive but offer the opportunity for removal of detected lesions. Stool based test represents a noninvasive approach; the most widely used is fecal occult blood test (FOBT) that tests the presence of blood in stool. With the progress in the understanding of the biology of CRC, tests based on detecting molecular abnormalities in stool offer new strategies for screening.

Using a flexible fibre-optic instrument inserted through the anus, colonoscopy allows direct visual examination of the entire colorectum, and is regarded as the gold standard for detecting colorectal lesions. It allows the option of removal and treatment of screen-detected lesions. However, colonoscopy imposes a risk of bowel perforation and bleeding, and a very low mortality risk of 1-3 death per 10,000 (14). Many patients find the procedure and the bowel preparation unpleasant. Due to its invasive nature, the cost of equipment and the demand for skilled operators, colonoscopy is not widely used as a first-line screening tool.

Stool based and blood based tests are the mainstream platforms for noninvasive CRC test. Compared to colonoscopy, both means are less sensitive and do not offer the option of immediate removal and treatment of the lesion. However, with the increased understanding in CRC biology, improved methods in stabilizing and purifying biomolecules from biological samples, these tests provide an excellent platform for testing various molecular abnormalities for CRC screening.

#### **Stool based tests**

Neoplastic features of intestinal lumen can be consistently detected in stool. Theoretically, stool based tests enable screening of the entire length of the colorectum, require no bowel preparation, and the specimens are easily transportable, which means that these tests can be obtained without the need to visit their doctors. These properties are likely to increase patient acceptability.

#### Fecal occult blood

The most widely used stool based test is the fecal occult blood test (FOBT). It detects blood in the stool that has leaked from disrupted vessels on the tumor or adenoma surface. FOBT has a low sensitivity as not all colorectal adenomas and tumors bleed, and those that do bleed do so intermittently (15). There is evidence that large adenomas and tumors bleed more frequently than smaller lesions (16). Asymptomatic tumors, which are the intended target of screening, also bleed less than symptomatic tumors (17). The classical FOBT involves a guaiac test for the peroxidaselike activity of heme in haemoglobin. Since heme is present in red meat, and peroxidase activity is present in fresh fruits and vegetables, false positive rate is high using this test. A diet or medication restriction is needed to optimize test performance. Sensitivity of FOBTs is typically around 50% for CRC and lower than 20% for adenomas. Despite its low sensitivity, FOBT is the only form of noninvasive test with proven efficacy in reducing CRC mortality. In three randomized controlled trials from the United States (18,19), Denmark (20,21), and the United Kingdom (22) using FOBT with annual or biennial testing has demonstrated a moderate (15-33%) reduction in CRC mortality after 10-14 years of follow-up.

A more advanced version of FOBT is the fecal immunochemical tests (FITs). FITs use antibodies specific to human hemoglobin or other blood components independent of peroxidase activity. They could be more specific in detecting blood of human origin and can eliminate the need of diet and medication restriction. Furthermore, FITs enable automated analysis for reading the test results, removing human error associated with interpretation. FITs have demonstrated a higher sensitivity towards CRC compared to guaiac based tests but its sensitivity remains low for precancerous lesions (23). In a study consisting of more than 20,000 subjects, FIT showed a sensitivity of 27% for advanced neoplasms and 66% for invasive cancer (24).

#### Stool DNA

Molecular alterations found in tumors can be detected in the stool because colonocytes exfoliate consistently into the lumen. The stool DNA test represents the most established noninvasive test for CRC. Various DNA mutation and methylation have been reported to be useful in discriminating CRC patients from healthy individuals. A study in an averagerisk population showed that the individual marker of APC, TP53, KRAS, MSI and DNA integrity has a sensitivity ranging from 3.2% to 25.8% for the detection of CRC; a combined panel of these DNA markers has a sensitivity and specificity of 52% and 94%, respectively, for the detection of CRC (15). Technology used to detect DNA mutation continues to improve and the DNA panels continue to refine. Pilot studies have demonstrated the use of more sensitive approaches in testing stool based DNA mutation, such as BEAMing (which derives its name from its principal components: beads, emulsion, amplification, and magnetics) (25) and digital melt curve (26).

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Better stool based DNA recovery was achieved by using EDTAcontaining buffer to stabilize the stool sample (27). The addition of vimentin into the marker panel had also greatly improved the panel's performance (28). A new generation of stool DNA panel was described recently (29). It combined 4 methylation markers (*BMP3*, *NDRG4*, *vimentin*, and *TFPI2*), 7 reference mutations in *KRAS*,  $\beta$ -*actin* and a hemoglobin assay, achieved a sensitivity of 85% for CRC, and 54% for adenoma  $\geq$ 1 cm. Each component marker typically yielded an area under the curve (AUC) value ranging from 0.61 to 0.75 towards CRC. This version of DNA test is currently seeking approval from the U.S. Food and Drug Administration.

#### Stool messenger RNA and protein

Stool based messenger RNA (mRNA) is another frequently exploited analyte. Several reports have shown that detecting stool based mRNA such as cyclin (30), cyclo-oxygenase 2 (COX-2) (31-34), or matrix metalloproteinase 7 (MMP-7) was able to discriminate CRC patients from healthy individuals. Notably, COX-2 mRNA was reported to be able to detect 26 out of 29 CRC cases (90% sensitivity) with 100% specificity in a Japanese study (32). Although some mRNA markers could achieve high sensitivities, the lack of stability of mRNA in stool samples has limited its application. In addition, neoplasm-derived proteins such as minichromosome maintenance proteins (35), carcinoembryonic antigen (32,36), M2 pyruvate kinase (37) and secreted clusterin isoform (38) in stool samples were also reported to be able to discriminate CRC patients from controls. Among them, stool carcinoembryonic antigen showed a sensitivity of 86% and a specificity of 93% for CRC (36). Compared with the stool DNA test, testing for RNA or protein in stool is less established. Validations in larger numbers of patients, including patients with adenomas, are warranted.

#### Stool microRNA

microRNA (miRNA) is a relatively new class of biomolecules being exploited as disease markers. They are 18- to 25-nucleotide non-coding RNA molecules that regulate the gene translation (39). Binding of a miRNAloaded RNA induced silencing complex (RISC) to a complementary sequence will lead to either translational repression or decay of the targeted mRNA (40). Through this, miRNAs regulate a variety of cellular processes including apoptosis (41-43), differentiation (44) and cell proliferation (45). Altered miRNA expression profiles were found in most tumor types including CRC (46-49).

In colorectal tumors, miRNA expression profile tends to show a typical signature aberration (50). Since in 2009, several pilot studies based on small cohorts have reported the feasibility of using stool based miRNAs as biomarkers for CRC screening (51,52). In a cohort of 197 CRC patients and 119 healthy controls, Koga et al. investigated the sensitivities of stool based miR-17-92 cluster members, miR-21 and miR-135 in discriminating CRC patients from healthy individual (53). They reported a combined sensitivity of 74% and a specificity of 79% towards CRC; however, sensitivity towards adenoma was not investigated in this study. Wu et al. demonstrated stool miRNAs were relatively stable in stool and the detection by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was highly reproducible (54). Notably, miR-92a showed a sensitivity of 72% for CRC and 56% for polyps (including hyperplastic polyps and adenomas), with a specificity of 73%. The level of stool miR-92a dropped significantly after the removal of tumor or advanced adenoma. miR-92a also had a higher sensitivity towards advanced adenoma than minor polyps, and a high sensitivity in detecting distal CRC than proximal CRC.

#### **Blood based tests**

For the markers released by the tumor to be detected in blood, the mechanism of vascular invasion is required. In precancerous lesions of which vascular invasion has not yet been involved, it is expected that the amount of blood entering bloodstream is negligible. But as the staging of the cancer advances, the amount of marker detected in blood will increase as the degree of vascular invasion progresses. Compared to stool based test, blood test could be less sensitive in detecting early stage lesions but easier to implement and comply with.

#### **Blood** protein

Carcinoembryonic antigen (CEA) is a glycoprotein involved in the process of cell adhesion. It was first described as a specific CRC marker in 1969 (55). Kuusela *et al.* demonstrated its value as a diagnostic marker, in a cohort of 111 CRC patients, serum CEA showed a sensitivity of 69% and specificity of 70%. In the same cohort, cancer antigen 19-9 (CA 19-9), a cancer marker more commonly used to detect pancreatic cancer, showed a sensitivity of 36% and a
specificity of 97% for CRC (56). Until now, serum CEA level is still frequently used as a marker to monitor recurrence after surgery, but rarely as a marker in predicting the disease. Colon cancer-specific antigen (CCSA)-3 and CCSA-4 are nuclear matrix proteins. They were found to detect all 28 CRC patients (sensitivity =100%) in a study, with test specificities of 96% for CCSA-3 and 98% for CCSA-4 (57). Galectin-3 is a beta-galactoside binding protein relevant to tumor progression and metastasis. Bresalier *et al.* showed serum Galectin-3 level was able to discriminate patients with CRC from those with other colorectal diseases (hyperplastic polyps, adenomas, and inflammatory bowel disease). However, no sensitivity or specificity of Galectin-3 was reported in this study (58).

#### Blood messenger RNA and microRNA

Few studies had exploited blood based mRNA as CRC biomarkers. Identified by oligonucleotide microarray analysis on colorectal tissues, KIAA1199 was described as a CRC biomarker, however its function remains not clearly understood (59). Serum KIAA1199 mRNA level demonstrated a sensitivity of 74% for CRC and adenoma, and a specificity of 66%, based on a cohort of 20 CRC, 20 adenoma and 20 normal subjects. More studies had focused on plasma miRNAs, largely because they remained very stable in plasma and could be robustly quantified (60,61). Plasma based miRNA was first demonstrated to be useful as CRC biomarkers by Ng et al. (62). They reported plasma miR-92a, a candidate identified by miRNA array profiling, had a sensitivity of 89% and a specificity of 70% in discriminating CRC from control subjects. Notably, plasma miR-92a level dropped significantly upon the removal of tumor, showing the marker was likely to be derived from the colorectal lesions. Since then, more miRNA candidates were reported, including miR-29a (63), miR-221 (64), miR-21 (65), U2 small nuclear RNA (RNU2-1) (66), miR-601 and miR-760 (67). Among them, RNU2-1, a marker for both CRC and pancreatic ductal adenocarcinoma (PDAC), was found to have a sensitivity of 97.7% in detecting CRC and/or PDAC, at a specificity of 90.6%. But this has not yet been tested in another independent study.

#### Blood DNA

Because of the established mutation and methylation characterized in adenoma-carcinoma sequence, plasma DNA has been more robustly evaluated than other plasma based markers. Diehl *et al.* showed that mutant APC fragment has a 100% sensitivity in detecting Dukes D stage patients (n=6) and a sensitivity of 63% in detecting Dukes A and B stage (n=16). The test remained poor in detecting advanced adenoma (68). Hypermethylated Septin-9 is the most studied plasma DNA marker. Multiple studies had reported its sensitivity towards CRC, ranging from 52% to 73% at specificities ranging from 84% to 91%, while sensitivity towards advanced adenoma was less than 20% (69-72). Currently, Septin-9 test is the only commercially available plasma DNA test intended for CRC detection.

#### Blood fatty acid

Gastrointestinal tract acid-446 (GTA-446) is a long-chain polyunsaturated fatty acid. Its serum level can be detected by mass spectrometry. Serum GTA-446 level was found to be reduced in CRC patients. Ritchie *et al.* showed that among 4923 subjects who had undergone colonoscopy, 84 out of the 98 CRC cases were detected to have a low serum GTA-446 level (as defined by the lowest tenth percentile), with a test specificity of 90% (73). The reduction of serum GTA-446 level was proposed to represent a compromised ability to protect against abnormal cell growth and chronic inflammation.

#### Stool test vs. blood test

Tumor markers enter the stool and blood stream through different mechanisms. Theoretically, exfoliation of colonocytes into the lumen occurs earlier than vascular invasion. Stool based test should be more effective in detecting precancerous lesions. Ahlquist et al. compared two commercially available tests: the stool DNA panel test (Exact Sciences Corporation, Madison, Wisconsin) and plasma Septin-9 test (ARUP Laboratories, Salt Lake City, Utah) in the same cohort of CRC and adenoma samples (n=42) but using separate sets of normal controls (stool, n=46; plasma, n=49). They found that the stool test had a higher sensitivity in detecting CRC (87% vs. 60%) and large adenomas (82% vs. 14%) compared to the plasma Septin-9 test. The specificity for the stool test and plasma test was 93% and 73% respectively. Based on this study, the stool DNA panel test is more effective in detecting early stage lesion that the plasma Septin-9 test.

#### Conclusions

Colonoscopy remains to be the gold standard in detecting CRC. Stool and blood based tests could serve as first line screening tests for the screening of asymptomatic

individuals, in which only those tested positive will proceed to perform colonoscopy. Among the reported studies, many stool or blood markers had demonstrated very high sensitivity and specificity. And new biomarkers will also continue to emerge as we improve our understanding of CRC biology. However, it is always more important to validate the markers in multi-centered studies with large cohorts of samples. With vigorous testing and validation, it is foreseeable in the near future that highly sensitive noninvasive test could be achieved through combining markers of different classes of molecule (e.g., DNA, RNA, protein) sourced from different biological samples (stool, blood). Population-based CRC screening will become more common and effectively conducted.

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#### Footnote

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### Improved colorectal cancer screening: a new option and opportunity

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**Abstract:** An important new test for colorectal cancer screening was evaluated by Imperiale *et al.* and reported in the April 4, 2014 *New England Journal of Medicine* entitled "Multitarget stool DNA testing for colorectal-cancer screening". This editorial notes the favorable trend in the reduction of colorectal cancer incidence and mortality, and explores the significant issue of suboptimal patient uptake of existing colorectal cancer screening examinations. The findings of the multitarget stool DNA test study are summarized, put into perspective, and the potential interest in this examination is considered. By expanding colorectal cancer screening uptake, the multitarget stool DNA test may further reduce the burden of colorectal cancer.

**Keywords:** Colon cancer; rectal cancer; colorectal cancer; colorectal neoplasia; cancer screening; cancer screening; stool DNA; multi-target stool DNA test; cancer testing; colonoscopy; fecal immunochemical test (FIT); stool occult blood; KRAS; NDRG4; BMP3; colon polyp; rectal polyp; colon adenoma; sessile serrated adenoma

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The distinctly encouraging journey toward prevention and early detection of colorectal neoplasia took another major step forward with the publication by Imperiale and colleagues of Multitarget Stool DNA Testing for Colorectal-Cancer Screening (1). The good news is that substantial progress is being made in the multi-faceted struggle with colorectal cancer. The annual update of data from the American Cancer Society published in January 2014 indicates that the incidence of colorectal cancer has been declining steadily between 2006 and 2010 by about 3.3% for men and 3.0% for women (2). Similarly, colorectal cancer mortality rates have decreased by 2.5% and 3.9%, respectively, over the same time period, and are down by 46% from their maximum (2). Long term reduction in incidence is thought to be due to reduction of risk factors and introduction of screening programs. The precipitous decline in incidence from 2008-2010, 4% per year, is thought to be due to the utilization of colonoscopy that has the ability to remove precancerous polyps (2).

Worldwide, at least 25 countries have implemented programs to screen for colorectal cancer (3). Most of these extensively use stool testing for occult blood or fecal immunochemical testing, but the United States, Germany, and Poland place a major emphasis on structural screening examinations of the colon (3,4). Several organizations in the United States publish colorectal cancer screening guidelines that are supported by virtually all healthcare insurance programs. In general, the guidelines suggest beginning of screening for average risk individuals at age 50, and include the options of colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, or fecal immunochemical test (FIT) every year (5,6).

A significant problem with the current US screening recommendations is that the uptake by the population offered them is suboptimal. Quite simply, many patients who should be screened for colorectal cancer do not participate in screening programs. In the United States, the Center for Disease Control (CDC) conducts a regular national telephone survey of a representative sample of the population known as the Behavioral Risk Factor Surveillance System (BRFSS), and posts robust information about the health of the US population on its website (7). The latest results [2012] show that nationally, of those surveyed over age 50, 66.8% report having ever undergone a flexible sigmoidoscopy or colonoscopy. The greatest uptake was in Massachusetts at 76.7% and the lowest in Alaska at 60.6%. Comparison to reports of mammogram uptake in women age 50 and above

within the last two years over the very same period may shed light on an achievable public health opportunity. The Behavioral Risk Factor Surveillance System reports that nationwide, in women 50 and above, 77% have undergone mammograms in the last 2 years. The greatest uptake of breast cancer screening was in Massachusetts at 87.1%, and the lowest was in Wyoming at 64.5% (8). Although the CDC BRFSS data examines different diseases with different health optimization behaviors, an opportunity for increased colorectal screening examination uptake may exist if factors surrounding this screening, including characteristics of the examinations themselves, were enhanced.

Similar issues in colorectal neoplasia screening test uptake have been shown in other populations. When a cohort of 53,309 asymptomatic individuals aged 50-69 in Spain were offered colonoscopy or biennial FIT by a pre invitation letter, invitation letter, and two follow up letters, only 24.6% opted for colonoscopy while 34.3% selected the FIT screening program, (P<0.001) (9). Although cultural and social factors make comparisons of health optimization behaviors among different populations across the globe difficult, opportunities for improvement in colorectal cancer screening uptake may exist. The importance of the screening uptake issue is highlighted by The United States National Colorectal Cancer Roundtable. This organization, consisting of The CDC, American Cancer Society and other like-minded groups, is sponsoring a major initiative to get colorectal cancer screening rates up to 80% by 2018 (10).

When the population uptake gap of structural colorectal screening studies and the suboptimal performance characteristics of existing stool based screening strategies are considered, significant interest in development of an accurate noninvasive colorectal screening test emerged. Imperiale and colleagues used a novel multitarget stool DNA test and compared this to a commercial fecal immunochemical test (1). The new test quantitates mutant KRAS, aberrantly methylated BMP3 and NDRG4 promoter regions, controls for human DNA with beta-actin, also includes a built in immunochemical assay for human hemoglobin, and utilizes a logistic regression algorithm to provide a result. The authors studied a cohort of 9,989 asymptomatic average risk participants at 90 sites (private practice and academic) across North America having a screening colonoscopy. Of the cohort, 65 subjects (0.7%) were found to have colorectal cancer, and 757 (7.6%) had advanced lesions (adenomas or sessile serrated polyps >1 cm) on colonoscopy. The key finding was that the sensitivity of detecting colorectal cancer was 92.3% with the multitarget stool DNA testing and only

73.8% with FIT (P=0.002). Notable findings included the sensitivity of detecting advanced precancerous lesions at 42.4% with DNA testing and just 23.8% with FIT (P<0.001). The rate of detection polyps with high grade dysplasia was 69.2% with DNA testing and only 46.2% with FIT (P=0.004). The detection rate of sessile serrated polyps measuring 1cm or more was 42.4% for the DNA testing versus just 5.1% for the FIT (P<0.001). FIT had a higher specificity rate and had less subject samples rejected for technical reasons. The specificity with DNA testing and FIT were 86.6% and 94.9% (P<0.001), respectively, when subjects had no advanced or negative findings on colonoscopy, and 89.8% and 96.4% (P<0.001), among those with negative results on colonoscopy. The authors conclude that the multitarget stool DNA test detected significantly more cancers than FIT but had more false positive results.

It is clear that the multitarget stool DNA test significantly outperforms FIT on all the sensitivity based metrics evaluated: colorectal cancer detection, detection of advanced precancerous lesions, detection of polyps with high grade dysplasia, and detection of sessile serrated adenomas. As a cautionary note, the multitarget DNA stool test had lower specificity than the FIT test. The specificity of the multitarget stool DNA test correlated inversely with age. Potential reasons for declining specificity with age include lesions not detected by the index colonoscopy procedure or age related change in DNA methylation (11). Technical analytic problems resulting in subject exclusion were encountered more frequently in the DNA group than in the FIT group, both from insufficient material for analysis (213 vs. 34, respectively) and logistic issues with specimen shipping.

A large unanswered question is how the multitarget stool DNA test will be used in clinical practice. As the many currently unknown factors become clarified, the clinical role will be defined. On March 27, 2014 the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Panel to the US Food and Drug Administration (FDA) unanimously recommended (10-0) the test for approval (12). It is quite likely the FDA will ultimately approve a more sensitive noninvasive way to screen for colorectal neoplasia than is currently available. Unknown is what the manufacturer will charge for the test in each nation that it is offered. Also unknown is what comprehensive analytic modeling studies of projected use-alone, coupled with other tests, performed at varying intervals, including sensitivity analyses of charges for each test-might show.

Guideline promulgating groups have yet to make a clinical recommendation for use of the new test, an important point

as many published clinical guidelines ultimately become health insurance payment policy. In spite of the large amount of uncertainty that exists now, it seems quite likely that many patients who currently will not accept a structural screening test of the colorectum may want this exam. Patients who are at above average procedural risk for a structural exam of the colorectum are also likely to be keenly interested in this exam. Furthermore, patients looking for the most sensitive way to screen their colorectum with a nonstructural exam are likely to be asking about this test. Even without the eventual modeling studies and forthcoming guidelines, the most important stakeholder in the colorectal cancer screening decision matrix is the patient, and the current suboptimal screening uptake suggests that an improved examination option may be welcomed.

Since the initial experience in 1969, and the reports by Wolf and Shinya of successful colonoscopic polypectomy in 1973, it has been widely recognized that colorectal cancer may be prevented by removing premalignant polyps (13,14). Until better dietary advice, more research supported physical activity regimens, and effective chemoprevention strategies emerge, the main way colorectal cancer will be prevented is by colonoscopic polypectomy. Although several colorectal lesion detection strategies exist, patient adoption has been suboptimal. By development of a more accurate examination that may enable additional patients to be willing to undergo colorectal cancer screening, the multitarget stool DNA test described by Imperiale is an important step in the journey toward reduction of the burden of colorectal neoplasia. Technological refinements and advancements in colorectal cancer screening will undoubtedly continue beyond this particular significant contribution (15). Once available, this new test offers the opportunity to expand colorectal cancer screening uptake and further reduce the burden of colorectal cancer.

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#### Footnote

*Conflicts of Interest*: Dr. Heigh participated in the Multitarget Stool DNA Testing for Colorectal-Cancer Screening study at Mayo Clinic Arizona as the site Principal Investigator. Mayo Clinic has licensed technology to Exact Sciences related to stool DNA testing.

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## What is the optimal interval for screening colonoscopy after diagnosis of a colorectal adenoma?

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Colorectal cancer (CRC) remains one of the most common causes of death in industrialized countries. The incidence rates vary among different populations, but are higher in males than females and increase with age. Obesity, diabetes, cigarette smoking, high alcohol consumption, eating red meat (particularly processed meat), and lack of physical activity are all recognised risk factors. Colorectal cancer is potentially amenable to secondary prevention by screening, because the detection and removal of an adenomatous polyp can prevent colorectal cancer from subsequently developing. In addition, when CRC is diagnosed while still localized (i.e., confined to the wall of the bowel), 5-year survival is likely to be extremely favourable in the region of 90%, but falls to 66% for stage II (i.e. disease with lymph node involvement). Hence, the principle of the benefit of colonsocopic screening is widely accepted. Yet the large numbers of colonoscopies required demands considerable resources, and existing guidelines tend not to provide estimates of resource implications.

Brenner *et al.*'s recent article in the *Journal of Clinical* Oncology (1) goes against European guidelines (2) and recommends that current colonoscopy surveillance intervals can be extended to a minimum of 5 years. In this population-based case-control study from Germany, the risk of CRC among participants with detection of at least one adenoma at a preceding colonoscopy was compared with participants without previous large-bowel endoscopy among 2,582 cases with CRC and 1,798 matched controls. Their recommendations are based on results which showed a significant risk reduction of colorectal cancer within 5 years for both men and women, younger and older participants, with and without high-risk polyps (defined as three or more polyps, at least one polyp  $\geq 1$  cm, at least one polyp with villous components), and those with and without polypectomy in the right colon.

This policy negates the need for a colonoscopy at 3 years for both low and high risk adenomas, which is recommended in recent European Guidelines (2) (Atkin 2012). This policy would therefore be welcomed by those who control the financial purse-strings as this reduction in the number of surveillance colonoscopies required would lead to financial savings and a likely reduction in adverse events risk by lowering the number of what might be considered 'unnecessary' endoscopies.

Up to 10% of adenomatous polyps will develop into invasive bowel cancer, with the result that the majority of adenomas removed may not ever progress to a colorectal cancer. However, when we analyse all the evidence, the conclusions are not that clear. In the study by Brenner (1), there was a significant CRC risk reduction by 60% in those who underwent a surveillance colonoscopy in less than 3 years and 50% risk reduction in the 3-5 surveillance interval after polypectomy for high-risk polyps. The risk reduction is therefore marginally higher in the shorter surveillance interval, and patients might choose any further chance in risk reduction, which would go against the recommendation for lengthening the surveillance interval for high-risk adenomas.

European age standardised incidence rates of CRC have increased by 27% between 1975-1977 and 2007-2009, with the most marked increase between the mid-1970s and late 1990s. This rise in incidence has been observed despite widespread colonoscopy surveillance, suggesting that although we have reduced the incidence of adenoma in patients who have undergone colonoscopy, there remains a large number of the population who will not have had this endoscopic protection. This is shown in the present study where only 160 cancers arose in patients having undergone a colonoscopy and polypectomy compared with the overall large number of cancers [2,582].

This problem has been addressed by the introduction of colorectal cancer screening. Pilot studies showed reduction in CRC mortality by about 25% for either the use of faecal occult blood testing (3,4) or flexible sigmoidoscopy (5). In the UK, the cost of Bowel Cancer Screening is £77.3 million. The majority of patients who undergo colonoscopy following a positive initial test will have colorectal adenomas which will continue to increase the costs of screening. However, screening has the greatest potential to reduce the incidence of and mortality from colorectal cancer which is why Brenner *et al.* commented that 'colonoscopy resources could be used more efficiently by increasing the number of people who undergo a first colonoscopy and by extending surveillance intervals to 5 after colonoscopic detection and removal of polyps, even in the case of high-risk adenomas'.

Quality assurance is vitally important. The historical evidence suggests that following the initial colonoscopy where an adenoma is detected and removed, 30-50% of patients will have further adenomas detected within 3 years, but less than 1% will be found to have cancers. Some of these further adenomas and cancers have simply been missed at the baseline colonocopy. Clearly both education and training and the quality of the endoscopist in addition to the inherent characteristics of the polyps removed are crucial, since all will impact on the number of polyps/ cancers found subsequently.

A population screening programme in the UK (The UK Flexible Sigmoidoscopy Screening Trial) reported longlasting reduction of colorectal cancer (CRC) incidence and mortality by 33% and 43% respectively from CRC among those screened with a single flexible sigmoidoscopy (5). Only subjects with large distal polyps ( $\geq 10$  mm) or with smaller advanced adenomas (<10 mm) were referred for total colonoscopy. In this study the few endoscopists were very highly trained surgeons with a very high throughput, and were in competition to remove the highest number of polyps.

However, there is a considerable variation in the recommendations for surveillance intervals after detection and removal of adenomas at colonoscopy (both within and between individual countries) (6). Once an adenoma has been removed, the optimal time interval to the next surveillance colonoscopy remains controversial. Adenomatous polyps are common with increasing age particularly over 55, but the majority do not mature into adenocarcinoma. The evidence regarding both recurrence of the adenoma and the development of a cancer is patchy, empirical and mostly based on observations of adenoma recurrence. Adenomas have been defined as both high and low risk. One or two small adenomas with no high-grade dysplasia are considered low risk, and recommended to undergo colonoscopy every 5 years. In contrast, surveillance intervals of 3 years are often recommended for patients with high-risk adenomas - defined as a polyp  $\geq 10$  mm in size or high-grade dysplasia or those with polyps showing significant villous components. A family history of CRC or adenomas, and a history inflammatory bowel disease are also considered high risk, along with the recognised genetic syndromes predisposing to CRC.

Another observational study at a veterans hospital in California comprising 1,819 patients undergoing elective colonoscopy showed that 15% of individuals (who did not have Lynch Syndrome) had small nonpolypoid colorectal neoplasms seen with chromoendoscopy and these "flat" lesions were 10 times more likely to contain advanced dysplasia than polypoid lesions (7). More advanced histology may be present in 10% of small (5-10 mm) colorectal adenomas (8). Since carcinogenesis may be accelerated in Lynch Syndrome, improved detection of small lesions may be especially important in this patient population. Chromoendoscopy, performed by spraying dye on the colorectal mucosa during colonoscopy, has been reported to improve visualization of mucosal lesions.

British Society of Gastroenterology (BSG) guidelines are inherently logical but advocate screening for adenoma more frequently than screening for patients who have had cancer. Recent European guidelines for colonoscopic surveillance following adenoma removal (2) have been published by the European Commission. These new EU Guidelines provide 24 graded recommendations which aim to improve the quality and effectiveness of surveillance. These guidelines are based on the principle that "Patients can be divided into low, intermediate and high risk groups with respect to their risk of developing advanced adenomas and cancer based on findings at baseline colonoscopy" High risk (defined as >5 small adenomas or at least one >20 mm, intermediate risk as 3-4 adenomas and at least one 11-19 mm, and low risk as 1-2 adenomas and both small (<10 mm). The recommendation

for intermediate risk is a further colonoscopy within 3 years, and for high risk within 1 year (2). Clearly age, family history, the believed completeness of the procedure, all need to be known to assess the risk.

Advice offered on healthy lifestyle and how to avoid cancer at the time of cancer screening may also provide an unique opportunity to improve dietary behaviours as this may offer a "teachable moment" (9).

#### Conclusions

Ultimately, the decision on the optimal interval will be made by health organisations, because the definite increase in CRC incidence, the increase in colonoscopy numbers and the uptake of bowel cancer screening with recommendations to an increased age extension (as in the UK) may sway some to choose to intensify colonoscopic surveillance, rather than to increase the interval and concentrate resources saved on screening and educating the wider population.

Education, training and the quality assurance of endoscopy is the key to success. But large well conducted collaborative multicentre randomized trials are still needed with sufficient statistical power to clarify how to improve cancer prevention for individuals at high risk of developing CRC. For low risk adenomas adopting a healthy lifestyle is as likely to prevent bowel cancer as surveillance colonoscopy. The opportunity to utilise the teachable moment should not be missed.

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#### Footnote

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

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### Current surgical considerations for colorectal cancer

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#### Background

Colorectal cancer is the second leading cause of cancerrelated deaths in the United States each year. Among men and women, it is the third most common cancer following lung cancer, prostate and breast cancers, respectively. In recent years, It has been estimated that in 2012 there were more than 100,000 new cases of colon cancer and more than 40,000 cases of rectal cancer (1,2). Fortunately, both the incidence and mortality of colorectal cancer have declined steadily in the past three decades. This has been largely attributed to more effective screening programs and improvements in treatment modalities (1,2). Surgical resection offers the best chance of achieving cure, but the management of colorectal cancer often requires a multidisciplinary approach, which has been pivotal in achieving better patient satisfaction and outcomes.

#### Surgery for colon cancer

#### Overview

The diagnosis of an invasive colon cancer requires a complete staging work up that includes endoscopic evaluation of the entire colon, baseline imaging of the abdomen and chest to rule out distant spread, and routine labs including a baseline carcinoembryonic antigen (CEA) level (1). Colectomy should be offered to those patients with resectable tumors that have no evidence of distant metastasis. The extent of the colectomy is primarily determined by the location of the tumor and the blood supply to that segment of bowel. Adequate margins ( $\geq 5$  cm) should be gained proximal and distal to the primary tumor and should include the associated mesentery containing regional lymph nodes. Tumors that are adherent to adjacent

structures should be resected *en bloc* to ensure complete removal of the cancer. Adjuvant chemotherapy is offered to patients with evidence of lymph node metastasis.

#### Laparoscopy for colon cancer resections

Traditionally, colectomies have been approached via a laparotomy with good clinical outcomes. However, the advent of laparoscopy has revolutionized surgery and, in appropriate patients, is now a popular alternative for the surgical management of colorectal disorders. This has been primarily due to the substantial short-term benefits, which include less postoperative pain, earlier return of bowel function, and shorter hospital stays (3,4). While laparoscopy has been shown to be consistently safe and feasible for a variety of gastrointestinal pathology, initial enthusiasm about employing a minimally invasive approach for colorectal cancer was tempered by a steep learning curve as well as reports of wound and trocar site recurrences (4). Therefore, the steady implementation of this approach has required balance of the potential short-terms benefits with preservation of oncologic outcomes. These criticisms were addressed with initial data reported in retrospective studies and later confirmed by larger, randomized clinical trials, which demonstrated that laparoscopy does not compromise oncologic outcomes or increase perioperative complications (3, 5-8).

The Barcelona trial was among the first randomized, prospective, single-institution trials, which compared laparoscopic colectomy to the conventional open approach. From 1993 to 1998, 206 patients were enrolled (105 patients in the laparoscopic arm) with cancer-related survival as the primary endpoint. The authors found that laparoscopy was more effective than open surgery with respect to morbidity,

hospital stay, tumor recurrence, and cancer-related survival. A follow up to this study with longer follow up data (median 95 months) comparing laparoscopic and open colectomies demonstrated that the overall survival and recurrence rates favored the laparoscopic group, but did not reach statistical significance (5,6).

A larger prospective, randomized, multicenter trial by the Clinical Outcomes of Surgical Therapy (COST) Study Group showed similar long-term results. Between 1994 and 2001, 872 patients (435 patients in the laparoscopic arm) were randomized. The median follow-up time was 52 months and the primary endpoint was time to tumor recurrence. Analysis at three years demonstrated similar recurrence rates in the laparoscopic and open groups, 16% and 18%, respectively. Additionally, there was no difference in overall survival (86% in the laparoscopic group vs. 85% in the open group). The authors have also recently published 5-year data from this original cohort demonstrating that overall and disease-free survival were similar between the two treatment groups. Additionally, overall recurrence rates remain similar (19.4% laparoscopic group; 21.8% open group) (7,9). These survival data have been confirmed in the slightly larger European multicenter Colon cancer Laparoscopic or Open Resection (COLOR) trial that was designed to evaluate disease-free survival and overall survival 3 years after laparoscopic or open resection for colon cancer. For all stages, the 3-year overall and disease-free survival rates were not significantly different between groups. Local and distant recurrence rates were also similar (8). It should be noted that lymph node harvest is also similar between open and laparoscopic groups. The main criticisms of these trials center on the probability of selection bias when offering a laparoscopic approach to those with cancer.

In fact, those with smaller tumors (amenable to smaller incisions) and those with tumors that involve only the colon (T3 and below) are most likely still the best candidates for laparoscopy.

#### Postoperative complications and quality of life (QOL)

While the short-term benefits of laparoscopy have been well documented and reproducible across practices, many also postulate that laparoscopy also facilitates fewer complications than traditional open surgery. While the primary endpoints of the aforementioned clinical trials were tumor recurrence and survival, these initial data also offer some information on intraoperative and perioperative complications. The Barcelona Trial found that the patients in the laparoscopic group had significantly less intraoperative blood loss and postoperative morbidity (5). However, the COST study and the COLOR trial did not demonstrate any significant difference in postoperative morbidity or 30-day mortality. The rates of intraoperative complications, rates or severity of postoperative complications, rates of readmission, and the rates of reoperation were similar between groups (7,8). Tjandra *et al.* recently published a systematic review of 17 randomized trails of laparoscopic resections for colon cancer, which analyzed 4,013 patients. The authors found that there were no significant differences in the overall complication rate. However, laparoscopic surgery had significantly lower perioperative mortality as well as lower wound complications (infection and dehiscence) (10).

Overall quality of life parameters after colorectal cancer resection have also been fertile ground for study and there is significant data to suggest that patients undergoing laparoscopic colectomies have modest improvements in these parameters. Analysis of the responders from the COST study (428 patients) showed short-term benefits according to the global rating scale score at 2 weeks after surgery. No difference was found between the groups using the other instruments or at other time points (2 days and 2 months) (11). Long-term follow up of the patients in this study found that at 18 months after surgery, patients who underwent laparoscopic resections had significantly greater improvement from baseline in the global QOL rating and total QOL index (QLI) (12).

#### The role of surgery in metastatic colon cancer

Up to 25% of patients with colon cancer will present with synchronous colorectal cancer metastasis and of these, only approximately 10-20% will have lesions that are ultimately resectable (1,13). More commonly, patients will develop metastasis in the interval after resection of the primary colon tumor with the liver being the most commonly involved organ.

Patients with colorectal liver metastasis (CLM) should have a complete evaluation with the coordinated care of a multidisciplinary team—including oncologists, radiologists, colorectal and hepatobiliary surgeons in order to assess resectability. Surgical resection of these metastatic lesions should only be considered in medically fit patients with good performance status, if obtaining negative margins is feasible and adequate functional liver reserve (>20%) can be maintained. While surgery is the gold standard for resectable disease, other potential treatment adjuncts, including radiofrequency ablation (RFA) and hepatic artery infusion (HAI) of chemotherapy, have been employed. Neither of these other modalities alone has been shown to be as effective as chemotherapy and surgical resection, which have reported 5-year survival rates up to 40% (1,14-16).

While the benefit of surgery and chemotherapy are clear, considerable controversy still remains in the optimal sequence of these treatments. Proponents for a surgery-first approach cite the potential for progression of disease and chemotherapy-associated liver injury as reasons to forego neoadjuvant chemotherapy; however, there is limited data that supports that this approach confers an advantage in overall survival (17). Contradictory data has been presented in the EORTC 40983 trial, which compared perioperative chemotherapy (pre- and postoperative) with surgery alone. The authors found that there was an 8.1% improvement in the 3-year progression-free survival with perioperative chemotherapy. However, postoperative complications were more frequent in the chemotherapy group (18).

The management of patients with synchronous, resectable CLM has also been subject to controversy. The traditional approach has been resection of the primary colon tumor followed by adjuvant chemotherapy and staged hepatic resection; however, more recent studies have shown that simultaneous colon and liver resections are safe in specialized centers and appropriately selected patients (19). This combined approach is advantageous in sparing the patient the morbidity of additional surgery and eliminating potential progression of liver disease during recovery from primary colorectal surgery. More recently, a reverse strategy, or liver-first approach, has been proposed for early management of metastatic liver disease, which proponents assert optimizes the potential for cure (20). While the data related to this approach is not as robust, the greater body of study on the management of synchronous CLM suggests that the approach should be individualized. The patient's functional status and burden of disease must be assessed in order to balance surgical risk and oncological benefit (21).

In patients with asymptomatic primary colon tumors and unresectable minimally symptomatic metastatic disease, chemotherapy is the mainstay of treatment. The available data supports that there is little benefit in resection of the primary tumor. Doing so risks delaying necessary chemotherapy and offers no survival advantage. In 2009, Poultsides *et al.* reported a series of 233 patients with unresected primary tumors and synchronous metastasis receiving chemotherapy. They found that 93% of patients did not require any surgical palliation of their primary tumor (22). Clearly, if the patient is exhibiting signs and symptoms of obstruction, which cannot be controlled with dietary changes alone, then palliation with resection is required. This seems to be the minority of cases.

#### **Surgery for rectal cancer**

#### Overview

The surgical decision-making process for rectal cancer is complex and often requires a multidisciplinary approach. While the pathophysiology of rectal cancers is believed to be identical to that of colon cancers, the anatomic location within the bony pelvis offers unique surgical challenges. Over the past century, an improved understanding of the histopathology as well as patterns of recurrence has afforded significant strides in the treatment of rectal cancer (23).

The initial management of rectal cancer requires complete evaluation of the local extension as well as distant spread. Unlike colon cancers, rectal tumors are more easily accessible by physical examination, which can provide added information on size, the degree of fixation, and location (2). Ultimately, the choice of treatment hinges primarily on the location of the tumor in the rectum and the depth of local invasion. Therefore, modalities such as endorectal ultrasound (ERUS) and pelvic MRI are often used for local staging of tumor depth and nodal involvement (24,25). Patients with evidence of locally advanced cancers in the distal and mid rectum (defined as Stage IIA and beyond) are now routinely referred for neoadjuvant chemoradiation, which has been shown to decrease rates of local recurrence (23,26). This paradigm has been challenged and the Alliance for Clinical Trials in Oncology is currently accruing patients for a phase II/III trial of neoadjuvant chemotherapy with the selective use of radiation in locally advanced rectal cancer. Treatment of upper rectal cancers (those above the peritoneal reflection or at the rectosigmoid junction are more controversial. Data suggests that a more individualized approach may be needed for these patients, with bulky large tumors getting neoadjuvant and smaller ones getting treated primarily with surgery.

#### Total mesorectal excision

Historically, local and radical resections for rectal cancers have been plagued by significant patient morbidity and high local failure rates (25). In 1982, Heald *et al.* named the concept of total mesorectal excision (TME), which has

drastically changed the surgical approach to proctectomy. An appropriate TME requires sharp dissection in the areolar, presacral plane between the mesorectal envelope (fascia propria) and the adjacent pelvic structures (27). For distal rectal cancers, TME is performed circumferentially down to the pelvic floor muscles incorporating the entire mesorectum. This allows complete removal of the rectal tumor and the regional lymph nodes while ensuring a negative radial margin and preserving the autonomic nerves (23,24,27). This has been shown to be an integral part of achieving lower local recurrence. A prospective, randomized trial, organized by the Dutch Colorectal Cancer Group, which was among the first to include surgical quality control for TME, reported a local recurrence rate of 8.2% at 2 years (10.9% at 6-year follow-up) in patients who underwent complete rectal cancer resection alone (28,29). Proximal rectal tumors, as mentioned, often do not require a total mesorectal excision since lymphatic spread is generally limited to within a few centimeters of the tumor. In these cases a partial mesorectal excision can be performed after ensuring an adequate distal margin. Bulky large proximal tumors may, however, benefit from preoperative chemotherapy and radiation in selected patients.

#### Radial and distal margins

Achieving the appropriate distal and radial margins is often not problematic in segmental colon cancer resection, but these are critical concepts in the surgical management of rectal cancer. A high-quality TME has improved our ability to achieve negative radial or circumferential resection margins (CRM), which has been shown to be an important predictor of local recurrence, distant metastasis, and survival (27,30,31). A positive CRM is defined as tumor extension to within 1 mm of the radial tissue edge and can occur due to direct tumor extension, mesorectal tumor deposits, involved mesorectal lymph nodes, or inadequate surgical dissection. In 2002, Wibe et al. reported a series of 686 patients who underwent proctectomy without adjuvant radiation, which underscored the significance of the circumferential margin. After a median follow up of 29 months, they found that the overall local recurrence rate for those with a positive CRM was 22% as compared to 5% for those with a negative margin (>1 mm). The CRM was also an independent risk factor for distant metastasis (hazard ratio 4.7) and mortality (hazard ratio 3.7) (32).

The ideal distal margin in rectal cancer surgery remains relatively controversial, especially in this era of sphincterpreserving procedures. A 5-cm distal margin had been previously advocated; however, this has been largely refuted based on pathology data demonstrating limited intramural spread of low rectal cancers (33,34). The degree of intramural and extramural spread is crucial in determining the ideal distal resection margin. In one of the larger retrospective review on the subject, Shirouzu et al. reported a series of 610 patients who underwent rectal cancer resections and found that only 10% had distal intramural spread. Moreover, the majority of these cases were within 2 cm of the distal border of the primary tumor. As a result, the authors postulated that a distal margin of 1 cm would be appropriate for most rectal cancers (34). Based on the available data, current recommendations suggest that a 2-cm distal margin is adequate for most rectal cancers. Smaller tumors that are low in the rectum may be resected with an acceptable margin of 1 cm (35,36).

#### Sphincter-preserving surgical procedures for rectal cancer

The extent of surgical resection for rectal cancer largely depends on the location of the mass in the rectum, the degree of local invasion, and the patient's baseline sphincter function and medical co-morbidities (23,26,35). For tumors in the mid and upper rectum a low anterior resection (LAR) is generally the ideal approach. During the procedure, a TME dissection is carried out after the sigmoid colon and upper rectum are dissected free from the peritoneal attachments. The inferior mesenteric artery, which is the principal feeding vessel, is ligated and divided proximally. The distal rectum is left in place after ensuring a margin 4-5 cm distal to the inferior edge of the tumor. A colorectal anastomosis is then created using a circular stapler; however, a hand-sewn anastomosis is also possible. Tumors in the lower rectum can also be considered for LAR as long as a 1-2 cm distal margin can be obtained adequately. Intestinal continuity is then restored with a stapled or hand-sewn coloanal anastomosis. The potential for pelvic sepsis due to anastomosis leak can be mitigated by a temporary loop ileostomy in those patients with low pelvic anastomoses and those that have required preoperative radiation.

Many patients experience disordered bowel function after LAR, typically characterized by increased stool frequency, bowel fragmentation, fecal urgency, and incontinence, which has been termed "low anterior resection syndrome" (37). The incidence is variable, as there are no validated tools for diagnosis, and the etiology is likely multifactorial. Reported rates range from 20-50% and possible causes include sphincter

injury, decreased rectal compliance, or neuropathy (37). Alternative reconstructive techniques to the straight end-toend anastomosis following TME with coloanal anastomosis including colonic J-pouch and transverse coloplasty have been explored in attempt to improve postoperative function. In these cases, randomized trials have shown that the colonic J-pouch results in superior postoperative bowel function for at least 18 months after surgery, after which function becomes similar to the end-to-end anastomosis (38). The ability to do this from a technical standpoint, however, is quite dependent upon the patient's body habitus with a narrow pelvis often precluding the safe formation of a colonic pouch.

#### Abdominoperineal resection

Patients with pre-existing fecal incontinence or with very low rectal cancers will ultimately require an abdominoperineal resection (APR). During the abdominal phase of the procedure, the TME dissection is carried out down to the pelvic floor muscles and a permanent colostomy is created using the descending colon. During the perineal dissection, the anus and the sphincter complex are excised widely in continuity with the proximal specimen. High rates of bowel perforation, positive circumferential margins, and subsequently local recurrence have been reported with conventional APR (39-41). Therefore, much emphasis has been placed recently on achieving a cylindrical resection, which avoids narrowing of the resected specimen at the level of the levator ani muscles. This approach has been shown to reduce the risk of local recurrence without increasing local complications (42).

The primary closure of the perineal wound has been plagued with significant complications, especially in the setting of preoperative radiation. Infection and wound dehiscence are among the most frequent complications with incidences that range from 10-40% in the existing literature (43). As a result, efforts to mitigate these complications with the routine use of rotational myocutaneous flaps have been proposed with variable success (43,44). Currently, there is no standard recommendation for the use of myocutaneous flaps in the reconstruction of the perineal wound. Individualizing treatment is required—those at higher risk of perineal wound complications (obese, diabetic, malnourished) may be selective candidates for flap closure.

#### Minimally invasive surgery for rectal cancer resections

Laparoscopy for rectal cancer resection has been approached with as much enthusiasm as initial studies for

colon cancer; however, the available data is not as mature. While a minimally invasive approach to proctectomy with laparoscopy, or even robotically, is more challenging and costly, the available technology offers the added benefit of better visualization and more precision than traditional open surgery. Initial nonrandomized studies demonstrated that laparoscopic proctectomy was safe and feasible with similar short-term benefits and oncologic outcomes (45). This has been confirmed in subsequent small, randomized trials; however, sufficient long-term data is lacking. The American College of Surgeons Oncology Group (ACOSOG) is nearing completion of a large phase III prospective randomized trial comparing laparoscopic-assisted resection versus open resection for rectal cancer which should further illuminate this subject. However, recent meta-analyses of the available randomized clinical trials comparing laparoscopic to open rectal cancer resections conclude that laparoscopy is associated with significantly lower rates of intraoperative bleeding and postoperative blood transfusion, quicker return of bowel function and shorter hospital admission (46,47). Additionally, when compared with open TME, there is no difference in the number of lymph nodes harvested, involvement of CRM, local recurrence, 3-year overall survival, and disease-free survival for rectal cancer (48). The results of larger multicenter, randomized clinical trials are pending. Complicating adoption of this technology is the large learning curve needed to implement these techniques in practice. Often "hybrid" open/laparoscopic approaches are utilized with some success to keep incision sizes small and mimic the advantages of a total laparoscopic approach in less time.

#### Local excision for early rectal cancers

In carefully selected patients, local excision has generally been considered as an acceptable treatment option for small, early (T1 and T2) cancers in the mid to distal rectum that have favorable histologic features (well-differentiated, absence of lymphovascular invasion, superficial submucosal invasion) (49,50). It has also been proposed in patients that are unsuitable for radical surgery as the resection of these lesions with traditional transanal surgery, or transanal endoscopic microsurgery (TEM) for more proximal tumors, is associated with lower patient morbidity.

Traditional transanal excision (TAE) is reserved for small tumors within 8 cm of the anal verge that are readily accessible. A full-thickness resection through the bowel wall into the perirectal fat is carried out with a minimum of

1-cm margins. In some cases, prominent lymph nodes can be resected but generally a thorough lymphadenectomy is not feasible, which is a major concern in more advanced tumors; therefore, preoperative patient selection and accurate staging is critical. The mucosal defect is then closed primarily. More proximal tumors can be accessed using TEM, which was introduced in the early 1980s as a minimally invasive alternative. The operating platform consists of an operating proctoscope and specialized microsurgical instruments that allow dissection in the upper rectum for lesions that previously could only managed with abdominal surgery (50).

The initial studies of local excision for early rectal cancers demonstrated that this procedure was associated with high local failure rates (17% for T1 tumors and up to 46% for T2 tumors) (51,52). In 2000, Mellgren et al. reported a retrospective study comparing 108 patients T1 and T2 rectal cancers excised locally with 153 patients who underwent radical resection. They found that local recurrence was significantly higher after local excision for both T1 and T2 cancers as compared with standard resection (T1: 18% vs. 0%, T2: 47% vs. 6%). Additionally, overall 5-year survival decreased significantly after local excision of T2 cancers as compared with standard resection (81% vs. 65%) (51). These findings were confirmed in a larger, retrospective study using the National Cancer Database. In this report, local recurrence after local excision was 12.5% for T1 cancers and 22.1% for T2 cancers. These were both statistically higher than rates for standard resection. Interestingly, despite these data, the authors also found that the use of local excision had increased significantly from 1989 to 2003 (53).

Salvage surgery may be possible for local recurrence after local excision but often not without significant morbidity. It often involves multimodality treatment including preoperative chemoradiation and extensive surgery (multivisceral resection or pelvic exenteration). Sphincter preservation is not always possible and overall 5-year survival is relatively poor (54).

These data suggest that in appropriately selected patients with T1 rectal cancers, local excision has similar acceptable overall survival rates as compared with standard resection. However, patients should be counseled that the reduced short-term morbidity of local excision is also associated with significantly higher rates of local and overall recurrence. Local excision of T2 rectal cancers has not been routinely recommended outside of clinical trials. The preliminary results of the ACOSOG Z6041 trial of neoadjuvant chemoradiation followed by local excision of T2 cancers have just been reported. The authors found that this strategy resulted in high rates of complete response (44%) and 64% of patients had their tumors downstaged. Negative resection margins were achieved in 99% of the included patients; however, the chemoradiation toxicity and postoperative complications were not insignificant. Sixty-two patients (72%) were able to complete chemoradiation per protocol and 39% of patients developed grade 3 adverse events or higher. Perioperative complications occurred in 58% of study patients and the most common grade 3 adverse events included rectal pain, bleeding, infection, urinary retention, and anal incontinence (55).

#### Management of locally recurrent rectal cancer

Despite the advances in chemoradiation therapy and surgical technique, local recurrence occurs in up to 10% of cases (56,57). The prognosis is generally poor and is only slightly improved with additional adjuvant treatment alone; therefore, radical surgical resection offers the only possibility for cure. The patterns of local recurrence are variable but may occur at the anastomosis or within the pelvis with attachments to the pelvic sidewall(s), bony structures, or adjacent pelvic organs. There is currently no accepted universal classification to define local rectal cancer recurrence; however, important features include patient symptoms, anatomic location, and the degree of fixation (57).

Patients who are suspected to have locally recurrent disease require a thorough endoscopic and radiographic evaluation to rule out distant metastasis and to define the degree of local involvement. Suspicious lesions should be biopsied with the help of useful diagnostic modalities including pelvic MRI, CT scan, or PET scan. Urologic and gynecologic exams should be performed as indicated.

Surgical resection is often complex and requires careful preoperative planning incorporating a multidisciplinary team (colorectal surgery, urology, gynecology, orthopaedics, and oncology). Patients that have not previously received chemoradiation should have neoadjuvant treatment followed by the anticipated resection, while those that have had previous radiation should proceed to surgery, if medically fit. Intraoperative radiation therapy (IORT) or brachytherapy may be indicated based on the degree of residual disease after resection. Extended resection should be performed *en bloc* with any contiguous organ to ensure no residual disease remains (57).

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A recent series of 304 patients with locally recurrent rectal cancer undergoing subsequent curative resection found an overall 5-year survival rate of 25%. Preoperative external beam radiation was given in 244 patients (80%) and IORT in 131 patients (43%). Negative resection margins were achieved in only 138 patients and 5-year survival was significantly improved in these patients as compared with those that had residual gross or microscopic disease (32% vs. 16%). Extended resections (involving at least one surrounding organ) were performed in 130 patients and were associated with a higher complication rate; however, survival was not significantly different from those that underwent limited resections. Symptomatic pain and fixation in more than one location were associated with a poor prognosis (58).

#### Conclusions

Colorectal cancer remains a significant cause of morbidity and mortality worldwide. Surgery is the mainstay of treatment for cure in these patients but the overall management of these cancers often requires a multidisciplinary approach. The advent of laparoscopy, robotic and other surgical technology, as well as an increased awareness of the importance of operative technique, have revolutionized the surgical management of this disease. Likewise, innovation in newer chemotherapy regimens and radiation therapy have increased median survival and decreased local recurrence in advanced disease. Despite these advances, there is ample room for further improvement.

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#### Footnote

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# Surgical management of colorectal cancer: the Fudan University Shanghai Cancer Center experience

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**Abstract:** The incidence and mortality of colorectal cancer (CRC) are increasing in China. Although surgery is the initially preferred intervention, systematic and individualized treatment has become far more important, on account of the considerable developments in radiotherapy and chemotherapy. Nowadays, treatment decisions are usually made following multidisciplinary team (MDT) meetings, especially in Fudan University Shanghai Cancer Center (FUSCC). With precise and specific imaging examinations, effective pre-operative staging and restaging after neoadjuvant therapy have been the routine, resulting in individualized treatments guided by MDT. These advantages also result in less invasive and function-preserving surgery. Based on clinical evidence of targeted therapy compared with traditional chemotherapy, effective treatment of CRC with metastasis, especially liver and peritoneal metastasis (PM), became more effective. Screening of patients with hereditary CRC, special consultant for surgical procedure and surveillance of hereditary CRC families are routinely performed.

Keywords: Colorectal cancer (CRC); surgical management; Fudan University Cancer Center

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#### Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. In China, it is the fifth most common cancer and also the fifth most common cause of cancer-related death. Notably, the incidence and mortality has been constantly decreasing in most developed countries, like the United States, because of early screening and multiple treatment strategies (1,2). However, this trend has not been observed in Chinese patients. The most probable reason for this is the disparity in economic levels between urban and rural areas of China, which leads to unbalanced medical care. Furthermore, public health education requires improvement (3). Therefore, patients with local advanced colorectal cancer or metastasis (mCRC) are still prevalent in China, which presents a great challenge to Chinese oncologists. Surgery plays the most important role in CRC treatment. In the recent 5 years, Colorectal Surgery of Fudan University Shanghai Cancer Center (FUSCC) conducted the highest number of CRC surgeries in Shanghai, which reached over 2,000 cases per year. *Figure 1A* summarizes the number of cases operated in our department. Five-year overall survival rate of patients with localized stage is comparable to most top centers in the world (*Table 1*).

#### Multidisciplinary team (MDT): the cornerstone of CRC treatment

The MDT, including surgeons, physicians, radiologists, radiation therapists, pathologists, and interventional therapists has proved to be very efficient and useful in the management of CRC (4,5). The CRC MDT of FUSCC,



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**Figure 1** Constantly increased patients underwent surgeries (A) and MDT discussion (B). MDT, multidisciplinary team.

established in 2005, is one of the earliest CRC MDTs in China. Difficult cases or late staged cases are recommended for discussion in the MDT meeting each week. Besides, new clinical trials or research should always be presented for suggestion of the MDT members. *Figure 1B* illustrates the trend of MDT development in the last decade. Because of the excellent job done by the MDT, our center has been selected as one of the five demonstration centers by Ministry of Health of China. Each month, at least 20 doctors visit our center to learn how to run the MDT.

#### Treatment of precancerous lesion or early staged cancer: role of endoscopic resection

CRC is the second most common cancer in Shanghai. So FOBT with optional colonoscopy is adopted as part of annual physical examination for Shanghai residents, which is financially supported by the Shanghai government. With this change, more and more asymptomatic polyps and early stage cancer be detected.

Once a polyps or neoplasm is detected, biopsy will be performed for pathological diagnosis. Small polyps <1 cm with low grade intraepithelial neoplasia will recommend for loop resection or coagulation. Polyps >1 cm with low grade intraepithelial neoplasia will recommend for endoscopic mucosal resection (EMR). Polyps with high-grade intraepithelial neoplasia and small cancerous lesion <2 cm 
 Table 1 Five-year overall survival in FUSCC compared to America

 SEER database

Store	Five-year overall survival (%)		
Slage	FUSCC	SEER database	
II	94.0	93.2	
IIA	84.0	84.7	
IIB	78.0	72.2	
IIIA	86.0	83.4	
IIIB	73.0	64.1	
IIIC	53.0	44.3	

FUSCC, Fudan University Shanghai Cancer Center.

will firstly underwent endoscopic ultrasound and systematic CT scan, to determine invaded layer, lymph node and distant metastasis. If the lesion is confirmed as locally or early stage, ESD or TEM will be recommended.

Any sample resected by EMR, ESD or TEM will be pin on a wood board and send to pathology for final diagnosis and staging. If a patient was finally diagnosed as early stage CRC, and considered to have unfavorable characteristics, a radical surgery will be recommended. For localization of the resected lesion, titanium clips with abdominal X-ray and methylene blue injection is routinely used pre-operation. The unfavorable features of an early staged cancer include: positive margin, invaded over SM1, neural-vascular invasion, poor differentiation, diameter large than 2 cm. After endoscopic resection, all patients are recommended for endoscopic re-examination at 6 months.

## Treatment of locally advanced CRC: precise staging and standardized treatment

#### Pre-treatment staging

When a patient is diagnosed as CRC, a systematic radiological examination will be arranged. Chest, abdominal, pelvic CT or magnetic resonance imaging (MRI) are routinely recommended for all patients. PET-CT is mostly used in patients with metastasis. However, organspecific imaging, such as rectum-specific MRI and Pumei (gadoxetic acid disodium injection) liver-specific MRI, are powerful tools for precise staging. It can offer critical information for decision making especially for surgery.

In our center, rectum-specific MRI with diffusion weighted images (DWI) is routinely conducted in all patients with



Figure 2 MRI images of rectal cancer from one patient. (A) T2WI image showed invasion across bowel wall with suspicious lymph nodes in mesenterium. Arrow indicated another suspicious lymph node beside iliac vessels; (B) DWI image showed enhanced lymph nodes. MRI, magnetic resonance imaging; T2WI, T2 weighted image; DWI, diffusion weighted images.

rectum cancer for assessment. Tumor invasion depth (T stage), lymph node status (N stage), extramural vascular invasion (EMVI) and mesorectal fasciae invasion (MRF) and distance from the anal verge should be reported. Coincidence of diagnosis between radiology and pathology in our center is 79.3%. *Figure 2* shows different MRI slices of the rectum of one patient before and after neoadjuvant chemoradiation.

Although neoadjuvant chemoradiation is widely accepted as part of the standard treatment for locally advanced rectal cancer and resulted in significant improved local control. Neoadjuvant chemotherapy has not been adopted for locally advanced colon cancer. However, some promising results revealed its role in the future (6,7). Based on contrast-enhanced CT, we define T3–T4 and/or N+ disease as locally advanced colon cancer. A single-arm phase II trial has recently been accomplished in our center. Response rate of neoadjuvant chemotherapy with XELOX was 66% (8). A multicenter randomized Phase III trial lead by our department is now recruiting.

## Update of surgical concepts: minimal invasion and function preservation

Minimal invasion and function preservation are two trend of colorectal surgery. There are two ways to make these two trends possible: (I) less resection area. With the use of effective preoperative treatment, tumor shrinkage or down stage is possible. Thus make it a little bit easier for surgeons to achieve satisfied resection margin without resect the adjacent organ; (II) less abdominal wall incision. One of the advantages of laparoscopic surgery is radical resection with minimal incision of the abdominal wall, which would make patient experience less postoperative pain and ileus, and thus accelerate patients recovery. With the development of laparoscopic surgery, more and more clinical trials conclude that laparoscopic surgery is as oncologically safe as open surgery.

In our center, the proportion of cases operated with laparoscopic approach increased constantly in the latest 5 years. Laparoscopic right/left hemi colectomy, laparoscopic anteria resection, laparoscopic abdominal perineal resection, and laparoscopic total colectomy/ colo-rectomy are all our routine surgical procedure. For example, In 2015, altogether 851 patients with rectal cancer underwent resection, in which almost 40% had successfully laparoscopic surgeries (*Figure 3A,B*). According to the pathological reports, laparoscopic surgery has the same quality of CRF (99.6% vs. 99.6%, laparoscopic vs. open, P=0.920), and lymph node collection (15.9 vs. 15.6, laparoscopic vs. open, P=0.271) compared with open surgery.

Especially for rectal cancer, advantages of laparoscopic surgery were optimized local views and flexible surgery in the narrow pelvis, which greatly facilitate surgeon to perform better nerve preservation, anal preservation. Development of low sphincter preservation surgeries was summarized in *Figure 4A-C*. In 2015, 35% of patients with low rectal center underwent laparoscopic sphincter preservation surgeries. The R0 resection rate is 100%.

Although surgical duration was longer in laparoscopic approach (P=0.001), hospitalization days are shorter (P=0.013).

#### Treatment of synchronous mCRC: comprehensive analysis and combined treatment is gradually increasing

#### Patients with synchronous liver metastasis

Although there have been remarkable improvements in the management of CRC, outcomes remain poor, with approximately 40-50% of patients who undergo curative surgery dving from distant metastases. Liver metastasis is the most common reason for mortality (9-11). The incidence of synchronous liver metastasis, according to Manfredi's analysis of 13,463 patients with CRC, reached about 14% (12). In patients with colorectal liver metastasis (CLM), radical resection is the only curative therapy (13), which can increase 5-year survival to 50% (14). Patients

P value

0.001

0.013

www.amegroups.com

Figure 4 Development of low sphincter preservation surgery in FUSCC center. Increased patients underwent low sphincter preservation surgeries (A,C). Surgical duration and hospitalization days were compared in patients underwent laparoscopic low sphincter preservation or not (B).

2013

2012



2010

2011

0

2015

2014





Figure 3 Constantly increased patients underwent rectal surgeries

(A) and laparoscopy proportion (B).

Variable	Group A (N=80) (N/%)	Group B (N=57) (N/%)	P value
Sex, male	43 (53.8)	31 (54.4)	0.941
Media age, years [range]	59 [29–80]	60 [32–73]	0.892
Surgical approach			0.143
Totally laparoscopic	17 (21.3)	6 (10.5)	
Partly laparoscopic	12 (15.0)	14 (24.6)	
Open	51 (63.7)	37 (64.9)	
Type of colorectal resection			0.344
Right	35 (43.4)	19 (33.3)	
Left	9 (11.3)	4 (7.0)	
LAR	33 (41.3)	31 (54.4)	
APR	3 (4.0)	3 (5.3)	
Type of hepatectomy			0.024
Wedge	39 (48.8)	15 (26.3)	
Segment	15 (18.8)	18 (31.6)	
Major (≥3)	26 (32.4)	24 (42.1)	
Medium Hospital stay, days, [range]	10 [5–55]	10 [7–58]	0.722
90-days mortality	0	0	
Morbidity	11 (13.8)	10 (17.5)	0.543

**Table 2** Comparison of basic characteristics from patients withsynchronous resection of primary lesion and CRLM

Group A, synchronous resection of primary lesion and CRLM; Group B, synchronous resection after neoadjuvant therapy. CRLM, colorectal liver metastases; LAR, low anterior resection; APR, abdominal-perineal resection.

presenting in our center with synchronous CLM are generally be divided into three groups: those with initially resectable disease; those with potentially resectable disease; and those whose liver metastasis is unresectable.

In the first situation, the question is (I) if we should give neoadjuvant chemotherapy to those with resectable tumors; (II) how to perform the resection, simultaneous or staged? Because the rational for neoadjuvant chemotherapy is to decrease the possibility of recurrence, we routinely use CRS score, which is created by Fong *et al.* in MSKCC, to evaluate the risk of recurrence. If the score is over 2, then the patient will grouped into high recurrence. Two to three cycle neoadjuvant chemotherapy, usually XELOX will be given to the patient before surgery. We prefer simultaneous resection of primary lesion and CLM as the first treatment choice. Because it could remarkably reduce the number of hospitalization days without increase post-operative complications and influence long-term survival (15,16).

In the second situation, the main question is (I) which regimen we should use for chemotherapy and how to combine with targeted therapy; (II) when to stop chemotherapy and give surgery. All this group of patients will be referred to MDT for discussion, then re-imaging and re-evaluate every 2–3 cycles. If a negative margin and future liver volume rate (FLVR) could be accomplished, surgery, mainly sychronous resection will be performed.

Patients with unresectable liver metastases will be discussed in MDT. Chemotherapy  $\pm$  target therapy, transarterial chemoembolization (TACE), radiofrequency ablation (RFA) were usually given to the patient (17,18). Resection of the primary tumor in mCRC will not be performed if only patients have life-threatening complications, including perforation, bowel obstruction, and severe bleeding.

*Table 2* demonstrated the safety of simultaneous resection of primary and liver metastases in patients with synchronous CLM in the latest 3 years. Preoperative chemotherapy did not affect the postoperative recovery of patients.

#### Patients with peritoneal metastasis (PM)

It had been reported that the incidence of isolated PM ranged from 15% to 25% in patients with stage IV CRC. Patients with PM mostly die from widespread abdominal complications, like bowel obstruction, fistula, or malnutrition. In patients with PM who received no treatment, the median and mean survival was less than 6 months (19). There is increasing evidence supports the surgical management of PM with cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Survival rates could approach 30–45% at 5 years in carefully selected patients, which is similar to the outcomes seen in resected patients with liver metastases (20).

Considering that the sensitivity of imaging examinations remain low, diagnostic laparoscopy with histological confirmation remains the gold standard for evaluating colorectal PM. The peritoneal cancer index (PCI) score is used for measuring the disease burden, while the margin evaluation is used for evaluating the completeness of cytoreduction. Patients with PM in our center, who have a PCI score of less than 20 with good physical status and operable condition, are considered suitable for the Table 3 The Fudan criteria for testing HNPCC in CRC

Patients should be tested for MSI in the following situations

At least three relatives with colorectal cancer or with an extracolonic cancer: cancer of endometrium, stomach, small bowel, ureter or renal pelvis. One relative should be a first-degree relative of the other two

At least two successive generations should be affected

At least one tumour should be diagnosed before age 50

FAP should be excluded

Tumours should be verified by histopathological examination

HNPCC, hereditary nonpolyposis colorectal; CRC, colorectal cancer; MSI, microsatellite instability.

cytoreduction with HIPEC. When the intent is curative, HIPEC is applied twice a week.

A clinical trial is now recruiting for patients with tumors at risk of dissemination, like perforation, T4 CRC, or tumor with poor differentiation. The purpose of this trial is to evaluate the usage of HIPEC as a prevention of PM. By now, more than 100 patients have been recruited in this trial.

#### Extension of routine medical care: management of hereditary CRC

Hereditary CRC, including hereditary nonpolyposis colorectal (HNPCC) and hereditary colorectal polyposis (HCP), comprise about 5–10% of CRC in Chinese patients. Patients with hereditary CRC need individualized treatment strategy. Families with hereditary CRC need genetic counseling for cancer screening and prevention. In 2000, our center developed a diagnostic criterion for HNPCC, which is called the Fudan criteria, based on family history. However, with the decreasing size of Chinese families, diagnostic depending on family history became difficult. Herein, we developed a new routine for the detection and management of hereditary CRC.

HNPCC is the most common hereditary CRC. Most of the HNPCCs are caused by germline mutations in MMR genes, which is also called the Lynch Syndrome (21). Because of inherited MMR gene deficiency, tumors from patients with Lynch syndrome show microsatellite instability (MSI) or loss of expression in one of the MMR gene in immunohistochemistry. In our center, family history should be recorded in all patients. And after surgery, tumor samples of patients should be tested by immunohistochemistry to detect deficiency of MMR. Patients with positive family history or lost express of any of the *MMR* genes will be suggested for further counseling. Mutation detection of *MMR* gene should be offered if patient is highly suspected. Fudan Criteria for screening patients with high risks was summarized in *Table 3*.

Another comparatively common type of hereditary CRC is familial adenomatous polyposis (FAP). The basic clinical feature of FAP is the numerous polyps spread all over the colorectal, which tend to develop into cancer before age 45. Thus, prophylactic surgery should be considered in all of the FAP patients.

In most cases of hereditary CRC, prophylactic total colectomy proctocolectomy should be considered. After comprehensive analysis of the prognosis of the syndrome and the life quality of the patient, preferred surgical procedure will be discussed with the patient. After surgical resection, intensive surveillance for metachronous cancer should be offered. Colonoscopy will be performed at least once in every 2 years post-surgery. Other organs at high risk should also be assessed during follow-up. First degree relatives should also be included in routine screening.

#### Conclusions

Precise and individualized standard treatment has become the objective and principle for treatment of CRC MDT in FUSCC. Early detection of precancerous lesions and early cancer call out a challenge for proper selection of patients for endoscopic resection. In CRC, precise diagnosis and staging helps surgeons to make informed decisions. Neoadjuvant therapy and laparoscopic procedure make colorectal surgery less invasive but more possibility for functional preservation. With regard to metastatic CRC, especially liver metastasis, a reasonable therapeutic strategy is the key. Simultaneous resection of synchronous liver metastases is safe. Cytoreduction with HIPEC is a promising treatment for patient with PM. Screening for hereditary CRC is important for affected patient and family. Proper clinical routines are helpful for detection of hereditary CRC.

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#### Footnote

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### Considering value in rectal cancer surgery

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*Comment on:* Silva-Velazco J, Dietz DW, Stocchi L, *et al.* Considering Value in Rectal Cancer Surgery: An Analysis of Costs and Outcomes Based on the Open, Laparoscopic, and Robotic Approach for Proctectomy. Ann Surg 2016. [Epub ahead of print].

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As new surgical technologies are introduced into the market, their cost and overall efficacy must be critically evaluated. One area of ongoing debate is the role of robotic surgery in rectal cancer resection. As it is clear that robotic surgery is becoming increasingly utilized for proctectomy in the US, a better understanding of the potential benefits and limitations is needed. Particularly three areas need to be addressed: (I) short-term oncologic outcomes: quality of TME resection, margin status, lymph node harvest; (II) cost; and (III) long-term oncologic outcomes. In the May 2016 issue of Annals of Surgery (Epub ahead of print), Silva-Velazco et al. have introduced an interesting and unique article titled "Considering value in rectal cancer surgery: an analysis of costs and outcomes based on the open, laparoscopic, and robotic approach for proctectomy" comparing value in open versus laparoscopic versus robotic rectal cancer surgery.

To compare the different approaches to rectal cancer surgery, the authors used a single center prospective database spanning from January 2010 to December 2014. An intent to treat analysis was used: if a minimally invasive surgery was converted to open, the patient remained in the original minimally invasive cohort. A total of 488 patients were included. Demographics between the three groups were similar with the exception of female sex (significantly higher in laparoscopic group) and body mass index (significantly lower in the laparoscopic group). Major comorbidities amongst the groups were similar. Tumor characteristics (pathological and clinical TNM staging, tumor grade, use of neoadjuvant chemoradiotherapy) were similar except for a significantly higher rate of positive lymph nodes on final pathology in the open surgery group. The endpoints evaluated were direct costs of hospitalization for the primary resection, 30-day readmissions, and ileostomy closure. Secondary endpoints were short-term oncologic results, postoperative outcomes, and 30-day perioperative morbidity. To compare cost data, total technical direct cost was collected for all hospitalizations. This cost data includes all costs accrued by the patient from admission to discharge: imaging, anesthesia, medications, OR time, consumable supplies, nursing, diagnostic procedures, laboratory tests, pathology assessment, and all other ancillary services needed during the admission. It does not included surgeon or other physician salaries. Of note, a portion of the total cost of the robot itself was applied evenly to all three patient groups, and no additional fees for robotic surgery were captured.

The first issue addressed when comparing the three groups is short-term oncologic outcomes. To characterize this variable, the authors used four criteria: (I) number of lymph nodes examined; (II) involvement of the distal margin; (III) involvement of the circumferential resection margin (CRM); (IV) mesorectal grading. If the distance between the tumor and the circumferential margin was less than or equal to 1 mm, the margin was considered involved. The authors defined a successful resection as one with a negative CRM, a negative distal margin, and completeness of the total mesorectal excision. When comparing the three groups, there were no significant differences between

any of the short-term oncologic outcome parameters. A successful resection was achieved in 83.9% to 89.5% of all cases. This data is compared to a recent national study examining the effects of surgical approach on short-term oncologic outcomes in rectal cancer. Utilizing the 2010 National Cancer Database, Midura et al. analyzed outcomes of 8,712 patients undergoing open, laparoscopic, and robotic resections (1). The short-term oncologic outcomes measured were resection margin status and lymph node harvest. Overall, 7% of cases had positive margins, and one-third of cases had an inadequate number of lymph nodes harvested (<12). After propensity score matching analysis, a minimally invasive approach was associated with an improved R0 resection rate, though despite matching, these patients were not randomized, and the distinct possibility of selection bias, where more difficult tumors received open surgery exists. The paper by Silva-Velazco et al. suggests overall higher success in regards to short term surgical outcomes than national data; however, a relatively small sample size and a single-center study can skew these results. Recent randomized clinical trials investigating laparoscopic approach versus open approach in rectal surgery have been published. ACOSOG Z-6051 failed to show non-inferiority of laparoscopic surgery when compared to open surgery regarding a composite oncologic outcome specified as a distal margin without tumor (greater than >1 mm), a circumferential radial margin greater than 1 mm, and the total mesorectal excision quality (complete: smooth surface of mesorectal fascia with all fat contained in the enveloping fascia to a level 5 cm below the tumor for upper rectal cancer or the entire mesorectal envelope for low rectal cancer; nearly complete: the mesorectal envelop was intact except for defects no more than 5 mm deep) (2). Additionally, in the COREAN trial, there was no statistically significant difference in short-term oncologic outcomes between laparoscopic and open surgical approaches following neoadjuvant therapy (3). While there are no large randomized controlled trials published evaluating laparoscopic versus robotic rectal surgery, the ROLARR trial currently underway aims to compare the two. Preliminary data shows no statistically significant difference in conversion to open surgery or completeness of the CRM, though long-term oncologic data have yet to be seen.

The second issue addressed in the paper by Silva-Velazco *et al.* is cost. The authors showed that the overall cost was

31% higher for patients undergoing robotic proctectomy when compared to open surgery. The cost of laparoscopic surgery was only 4% higher when compared to open surgery. This was despite shorter hospital stays and lower rates of complications. Recent literature supports this finding as well. Other studies demonstrate a 32% higher cost associated with robotic surgery when compared to laparoscopic surgery (4) and a 59% increase with robotic surgery compared to open surgery (5).

One issue not addressed in this study is long-term oncologic outcomes for rectal surgery. The COREAN study found that there was no significant difference in long term oncologic outcomes (3-year disease free survival) between laparoscopic and open rectal surgery following neoadjuvant therapy (3). Unfortunately, there is no data looking at long term oncologic outcomes following robotic rectal surgery.

Though robotic surgery is being utilized increasingly for rectal cancer, current data shows longer operative times, higher cost and unclear short-term oncologic benefit. The ultimate utility of this technology will be better understood when long-term oncologic outcomes are available.

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of clinical and economic outcomes between robotic, laparoscopic, and open rectal cancer surgery: early experience at a tertiary care center. Surg Endosc 2016;30:1337-1343.

# Indocyanine green fluorescence angiography during laparoscopic rectal surgery

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Advances in medical equipment and surgical techniques have enabled surgeons to offer patients better oncological and clinical outcomes after colorectal resections. However, anastomotic leakage remains one of the most serious postoperative complications in rectal surgery. The rate of anastomotic leakage after rectal surgery has been reported at 6% to 14% (1-4). In particular, low anastomoses have a considerably higher risk of leakage compared to intraperitoneal ones (1,2). Anastomotic leakage results in increased length of hospital stay, health care cost, morbidity, and mortality rates (3,4). In addition, anastomotic leakage has been found to negatively impact prognosis on local recurrence and cancer specific survival (5).

There are many risk factors related to anastomotic leakage. Risk factors can be categorized as patient-related, disease-related, and intraoperative-related. Patientrelated risk factors include gender, body mass index (BMI), nutrition, and American Society of Anesthesiologists (ASA) score (1-3,6). Disease-related factors include level of anastomosis, neoadjuvant therapy, and tumor size (1,2,6). These risk factors may be beyond the influence of the surgeons. Conversely, intraoperative-related factors including blood perfusion to the anastomotic tissue, tension on the anastomosis, operative time, blood loss, and number of stapler firings (2,6-8), can be controlled by the surgeons. Among these factors, blood perfusion is thought to be an important factor for avoiding anastomotic leakage. Adequate blood supply is crucial for successful healing, and avoidance of intestinal ischemia and necrosis (6-8). Anastomotic leakage and stricture may be attributed to inadequate perfusion of anastomotic tissue.

Accurate determination of the resection margin of the viable bowel may help to reduce anastomotic leakage. The selection of an optimal site for anastomosis has been dependent on the surgeons' gross inspection. Intestinal microperfusion and viability is usually estimated intraoperatively from clinical parameters, such as color of the bowel wall, presence of bowel peristalsis, bleeding from the edges of the bowel, and palpable pulsations of mesenteric arteries. However, this assessment is subjective and based on the surgeons' experience. Karliczek et al. (9) evaluated the accuracy of the surgeons' gross inspection for anastomotic leakage occurrence in a prospective clinical study. The surgeons' ability to predict anastomotic leakage appeared to be low in gastrointestinal surgery, with a sensitivity of 61.3% and a specificity of 88.5%. Thus, objective and reliable intraoperative methods to assess bowel viability are required.

There are several different intraoperative assessment of anastomotic microperfusion, such as Doppler technology, tissue oxygen tension, and oxygen spectroscopy (10,11). However, due to equipment cost, complex maneuvers, lack of reproducibility, and the need for a specialist, these techniques have thus far been experimental and have not achieved widespread clinical acceptance. In recent years, indocyanine green fluorescence angiography (ICG-FA) has proved useful in assessing real-time microperfusion intraoperatively and can apply to open, laparoscopic, and robotic surgery.

ICG is a sterile, anionic, water-soluble, tricarbocyanine compound dye that serves as an optical contrast agent. It absorbs near-infrared (NIR) light at 800-810 nm and emits it at a slightly longer wavelength of 830 nm. Following intravenous injection, ICG rapidly and extensively binds to plasma proteins, and is confined to the intravascular compartment. It is cleared by the liver in 3 to 5 minutes and excreted via the bile within 10-15 minutes. ICG has been safely used clinically in many countries for over 30 years. ICG exhibits a low toxicity with few adverse events (12,13). However, ICG contains sodium iodide and therefore should be used with care in patients with an iodine allergy. Special camera filters are necessary to visualize the ICG fluorescence. The light needed for the excitation of the fluorescence is generated by a near infrared light source which is attached directly to a camera. This camera allows the absorption of the ICG fluorescence to be recorded in real time. ICG-FA is suitable for use as an intraoperative imaging tool, and has been associated with improved outcomes in coronary, transplant, plastic surgery, and a number of other surgical procedures (14). ICG-FA was validated for assessing bowel microperfusion in a pig ischemia model (15). The fluorescence intensity was directly correlated with tissue perfusion, and ICG-FA could effectively detect the demarcation between ischemic and vascular areas.

There are several recent articles which describe the usefulness of ICG-FA for colorectal surgery with first report published by Kudszus et al. (16). They reported that ICG-FA led to a change of the initially planned proximal transection line in 13.9% (28/201) of cases. ICG-FA significantly reduced anastomotic leakage rate in colorectal surgery by 4% compared to a historical control group (3.5% vs. 7.5%). ICG-FA during colorectal surgery has also been described in other non-randomized studies (17-22). Jafari et al. (17) reported the results of a multiinstitutional prospective single armed study, PILLAR-II that assessed the feasibility and utility of ICG-FA in leftsided colorectal resections. In this study, ICG-FA obtained successful imaging in 98.6% (137/139) of cases. The overall anastomotic leakage rate was 1.4% (2/139). ICG-FA led to change in the surgical plan in 8% (11/139) of cases, with most changes occurring at the time of transection of the proximal margin due to hypoperfusion, and no anastomotic leakage occurred in these patients. However, the height of anastomosis from the anal verge was higher than or equal to 8 cm in 74.1% (103/139) of cases and this study did not focus on total mesorectal excision (TME).

There are very few articles focused on the use of ICG-FA during rectal surgery with TME, which has a higher risk of leakage compared to colon surgery, and the rate of diverting stoma is higher (18,19). Boni *et al.* focused on rectal surgery with TME and reported that ICG-FA was safe and effective. ICG-FA influenced the surgical strategy in 4.7% (2/42) of cases and there was no anastomotic leakage (0/42) in low rectal cancer resection. Gröne *et al.* (18) also reported that the overall anastomotic leakage rate was 5.6 % (1/18) in low rectal and anorectal anastomoses.

Most of the studies were focused on the change in surgical decision making, however there are a few studies that have reported on the reduction in anastomotic leakage rate (16,20,21). Boni et al. reported that the anastomotic leakage rate was 0% and 5.2% in the ICG-FA group and historical control group, respectively. A recent systematic review showed that ICG-FA of colorectal anastomosis was associated with a significantly lower risk of anastomotic leakage compared with a control group without ICG-FA (3.8% vs. 7.6%; P=0.0055) (20). Only one retrospective case-matched study by Kin et al. (21) revealed that there was no difference in anastomotic leakage rate in colorectal resection between the ICG-FA group and control group. The authors acknowledged several limitations of their study such as the retrospective nature of the study, selection bias and the small sample size.

There are several limitations of ICG-FA. First, the surgeons' assessment of the intensity of perfusion is subjective. One study attempted to evaluate the fluorescence intensity by a five step score ("1" indicating no uptake and "5" indicating maximal uptake) but this assessment did not clearly show any conclusion regarding the predictive value of an abnormal ICG-FA (19). Another study aimed to quantify the fluorescence intensity level by using specially designed software that calculated the steepness of the light emission curve (pixel intensity per second) in order to achieve a more objective perfusion assessment (16). Unfortunately, this study did not lead to a cut-off value to quantify the fluorescence intensity, which is needed to minimize observational variability between surgeons. The ideal time to perfusion after injection of ICG is unknown. Kawada et al. (22) reported that the median time to perfusion was 35 seconds. However, the association between the time and poor perfusion is unclear. Therefore, ICG-FA remains subjective until more objective cut-off levels for

sufficient perfusion are established.

Secondly, ICG-FA can be influenced by various conditions, such as distance, surrounding lighting, the dose of ICG injection and the effect of repeated ICG injections. The distance between the tip of the camera and subject, and the operating room lighting may affect the fluorescence intensity (23). The optimal dose of ICG injection prior to assessment is unknown. The fluorescence intensity of ICG is almost linearly increased with concentration within a low concentration range, while the fluorescence intensity peaks and subsequently decreases at a higher concentration, a phenomenon known as the 'quenching effect', and is an important consideration (23). This effect cannot be controlled by the surgeon and lower concentrations are recommended to avoid this problem. However, the dose of ICG varies according to the studies. The effect of repeated injections of ICG is unknown and has not been investigated (24).

In conclusion, ICG-FA enables the surgeon to ensure sufficient blood supply to the anastomosis. ICG-FA is easily reproducible, cost effective, incurs little additional time, and has limited adverse effects. ICG-FA may prevent anastomotic leakage in patients undergoing colorectal surgery. However, no randomized controlled trials have been published and the present studies lack a high level of evidence therefore the clinical benefit of ICG-FA is inconclusive. A large, randomized, controlled trial, PILLAR-III, could determine if ICG-FA would have a positive impact on anastomotic leakage rate in rectal surgery.

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# Contrast-enhanced CT colonography for colorectal cancer localization in laparoscopic surgery

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I have read the paper published in *The American Journal of Surgery* by Yap *et al.* (1) entitled "Colonoscopy localization accuracy for colorectal resections in the laparoscopic era", focused on the preoperative evaluation of patients with CRC with great interest. This topic is now subject of a relevant debate considering the laparoscopic-assisted colonic surgery era we are facing, and also the interest related to the large trial (2) that is currently investigating potential benefits of neoadjuvant chemotherapy for patient with colon cancer.

The authors have discussed the accuracy of colonoscopy in describing the site of colonic cancer, and useful methods to reduce the risk of an incorrect localization; by investigating alternative methods for this critical evaluation, they have highlighted the limitations of conventional CT, the importance of endoscopic tattooing, and they have suggested the potential use of a metal endoscopic clip.

Among these alternative methods, we believe that computed tomography colonography (CTC) should not only be included, but could probably be the most suitable method for a series of reasons.

There are different reports in literature describing how accurate CTC is in diagnosing the precise site of colonic cancer; in particular this test has precisely judged the site of colonic lesions in almost all reported cases, correcting the colonoscopy reports in percentages ranging between 4% and 21%.

Moreover, CTC can be easily added to the conventional abdominal CT normally prescribed by clinicians to know about local and distant cancer staging. Performing a combined contrast-enhanced CTC instead of the conventional contrast-enhanced abdominal CT doesn't significantly impact on costs or on the time span, nor is it dangerous for the patient.

In one of our previous reports (3), we observed that information given by CE-CTC concerning colorectal cancer location and synchronous colonic cancers and polyps changed the laparoscopic surgical strategy for almost 14% of patients.

Among the advantages of CE-CTC, optimal patient acceptability, synchronous CRC and/or polyps diagnosis, and information on the mesenteric vessels should also be mentioned.

Moreover, CE-CTC permits high accuracy in preoperative T staging (4); a recent meta-analysis (5) in particular has shown that conventional CT and CTC are able to detect tumor invasion beyond the bowel wall (T1–T2 vs. T3–T4), with summary estimates for sensitivity and specificity of 90% and 69% for CT, and of 97% and 81% for CTC.

For all of these reasons, we propose contrast-enhanced CTC as first line test in patients with colonic cancer, and

in particular in those patients with cancer preventing a complete colonoscopy.

As described above, the use of CE-CTC offers several advantages, but some limitations should be mentioned. First of all, CTC is not such a well-known test by general practitioners, clinicians and even some radiologists, and this is not a negligible factor limitating its diffusion worldwide. Secondly, there is a need for radiologists' training in CTC; to be ready to report about CE-CTC radiologists should be as familiar as possible with standard CTC.

Considering that CTC is about to become a screening procedure in Europe after being accepted as such in the United States, we believe that both limitations can be rapidly overcome.

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### New competency assessment tool for laparoscopic colorectal surgery

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Due to an increasing awareness of the complications of medical and surgical treatment, the public has a growing distrust of the medical system and of their physicians. Patients have become more demanding when it comes to knowing the qualifications of those who are treating them. The expectations of physician training are increasing and the tools we use to assess that training must also improve. Historically, there has been little to no formal assessment of technical skill for board certification or credentialing in the United States. The assumption has been that if you have completed residency training, you are proficient. Board certification in surgery requires completion of a training program and passing written and oral exams, but no technical exam. Compounding the problem of assessment after residency and fellowship, many of the procedures performed by practicing surgeons were not taught in their training because they did not exist and are learned on the job. There is, therefore, a pressing need for formation and adoption of assessment tools such as the one presented in the recent Annals of Surgery article by Miskovic et al. (1).

Miskovic *et al.*, present their competency assessment tool (CAT) which they have been using to assess apprentices following training in the National Training Programme in Laparoscopic Colorectal Surgery in England. The CAT was designed to assess surgeons who were already certified to be independent practitioners but were receiving specialized further training in laparoscopic colorectal surgery. The authors used complex statistical methods to validate the tool. Briefly, the authors used the Delphi method to have expert colorectal surgeons list and rate characteristics of competent performance in laparoscopic colorectal surgery.

This was used to make an assessment tool for task-specific assessment in 4 areas: access and exposure, identification and dissection of the vascular pedicle, mobilization of the colon and rectum, and resection/anastomosis of the bowel. These tasks are rated in 4 domains on the assessment tool: use of instruments, tissue handling, errors, and the quality of the end product. Statistical assessment of validity and reliability were performed. The average CAT score of the experts was significantly better than those of the apprentices and the tool was able to distinguish between passing and failing apprentices.

The CAT is the first study of assessment of this type of tool for specialty practice. The authors should be applauded along with the National Training Programme in Laparoscopic Colorectal Surgery. More programs such as this one and validated skills assessment for those who complete them should be used to ensure that surgeons who are adopting these complex surgical procedures are going to be able to perform them safely.

One critique of the study is that the apprentices were asked to self-select videos of cases for assessment. Another is the lack of proven improvement in clinical outcome which is the gold standard. The score that predicts a low complication rate in patients is unknown. The authors argue that tools like this should be used to identify those who lack competence before waiting for poor outcomes to accumulate but did not link those to their tool in this study. More study is needed to prove this tool can be used to prevent problems.

As surgeons, we must have the confidence to operate on patients. We open their bodies and attempt to repair their
pathophysiology. We complete a long and arduous training in order to be able to do so. Considering this, there is often reluctance to question the competency of the surgeon. The consequences of incompetence in the operating room can be devastating to our patients. This was seen when laparoscopic cholecystectomy became popular and the rates of common bile duct injuries increased substantially (2). This increase in the rate of complications exposed the need for credentialing when new techniques become available.

Colon resections are commonly performed for a variety of problems, most commonly for colorectal cancer and diverticulitis. Laparoscopic colon resections are increasingly being performed in lieu of open procedures (3) but laparoscopy has a steep learning curve (4). Between 25 and 38 laparoscopic resections are needed to reach proficiency in studies of the learning curve for laparoscopic colectomy (5,6) but improvements in operative time, conversion rate, leak rate, and node harvest were found even after 200 laparoscopic resection (7). Thus, the outcome for the patient may be different depending on the number, type, and complexity of cases previously performed by the operating surgeon. In the case of colorectal cancer, proper resection can improve long term survival. Many practicing surgeons learn to perform complex laparoscopic procedures at short courses. A study by Lewis et al., showed that after only a short training program on laparoscopic colorectal surgery, up to 80% of the surgeons then incorporate these new procedures into their practices (8). Improved assessment of surgeon competency to perform these complex laparoscopic procedures is needed.

Several studies of complex disease have shown that patients treated by specialists or in specialty centers have improved outcomes. This has been shown in colorectal and pancreatic cancers (9,10). There is no way to parse out whether this is due to the medical care they receive or if the technical prowess of their surgeons is the reason for their improvement. Surgeons who have a specialized practice and those who have performed an increased number of laparoscopic colon resections have improved surgical outcomes (11).

While the assessment tool presented by Miskovic *et al.*, is a move in the right direction, much work is left to determine how this type of tool should be used. It has great potential for use in certifying and credentialing. The next step in the validation of these types of tools is to assess for a correlation between performance on them and clinical

outcomes. Ensuring the safe and effective practice of new techniques is a concern in surgery worldwide and using assessment tools may be one way to do so.

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### Single-port laparoscopic surgery for colorectal cancer: how can we move forward?

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The successful introduction of laparoscopic colorectal surgery results in remarkable improvement of short-term outcomes, such as less postoperative pain, early return of gastrointestinal function, hence shorter length of hospital stay (LOS) and less estimated blood loss. In recent years, improvements in surgical instrumentation has dramatically impacted the surgical approach to gastrointestinal surgery and single-port laparoscopic surgery (SPLS) has been developed as a new alternative to conventional laparoscopy surgery (CLS). The potential benefits of SPLS are to help decrease morbidity, optimize the cosmetic outcomes of CLS and minimize the surgical trauma, when compared to CLS. Each incision in CLS carries potential morbidity risks of bleeding, visceral organ damage, pain and formation of incisional hernia. Moreover the small incisions performed for trocar placement may result in multiple scar formation and compromised cosmetic outcome. SPLS performed through a vertical trans-umbilical incision can have a wound hidden within the umbilicus or a patient with a rectal cancer can be virtually scarless without any incision after operation by operating through a planned stoma site. On the other hand, SPLS is more difficult and requires high surgical skills to overcome the problems. Technical difficulties of single-access as the lack of triangulation and exposure, the in-axis view and conflicts between instruments are the most important challenges. The handling of both a grasper and an energy-based device in parallel with the laparoscope through the single port decreases the possibility of the surgeons manoeuvre and result in inadequate exposure and difficult dissection in the surgical field

The feasibility and safety of SPLS for colorectal cancer is demonstrated by many case series, comparatives studies, and some randomized trials. Two randomized controlled trials, one measured postoperative pain as primary outcome proved that SPLS is associated with less pain and earlier discharge after operation and the other study showed that SPLS for rectal cancer may reduce postoperative pain and it may have a similar trauma-induced inflammatory response compared to CLS (1,2). In contrary to the common belief, most reports showed that the procedure time of SPLS is not significantly longer than CLS. Other short term operative outcomes of the two procedures are also similar. However, a few drawbacks hamper still the further implementation of the SPLS approach in colorectal surgery. Procedure times are sometimes longer, patient applicability may be limited, the current technology remains inadequate and difficulties with training result in a significant learning curve (LC). The SPLS approach inevitably is a one-operating-surgeon technique, which may impose a negative impact on surgical education and training (3).

Many studies reported similar operating time between SPLC and CLS. These studies may reflect that the SPLS approach is not difficult in hands of experienced laparoscopic surgeons. However, there is also little is known about how many conventional laparoscopic colectomies one has to do before attempting SPLS. The steepness of the

LC for SPLS is another big concern if this procedure will be practiced widely and subsequently by trainees. Kim *et al.* reported in his single surgeon series that the operating time for SPLS reduced significantly after 48 cases and became comparable to that required for CLS (4).

Recently, Kim et al. published multicenter observational study using multidimensional statistical methods about LC of SPLS for colon cancer concluded that the LC of SPLS for anterior resection and right colectomy performed by more than 200 CLS-experienced surgeons were 13-36 and 6-15 cases, respectively. For surgeons experienced in conventional laparoscopic colorectal surgery, the LCs of SPLS for colon cancer ranged from 6 to 36 cases, which is shorter than the LCs reported for conventional laparoscopic surgery. Data were collected from two studies; one from a retrospective pooled analysis and the other one from a multicenter controlled trial. The achievements of each participating surgeon were analysed using multidimensional statistic methods. The main factors to overcome technical difficulties during the SPLS procedures were different baseline characteristics of Asian patients, such as lower BMI and shorter abdominal circumference, or particularly greater experienced surgeons in CLS. Despite these advantages the LC could be longer for new surgeons (5). It is obvious that SPLS requires substantial skills in two-handed laparoscopy. To optimize clinical outcome specialized training in advanced laparoscopy, e.g., computer-based and clinical training is recommended before this technically demanding procedure is introduced in a general clinical setting. Robotic technology may also contribute to overcome the restrictions of limited space and instrument collision inherent to SPLS. There are some similarities between SPLS and transanal endoscopic microsurgery (TEM). Experience from TEM training courses may be useful for educating future colorectal surgeons in SPLR.

At the present, there is still need some important information about SPLS. When introducing any new technology and surgical technique, associated costs need to be considered. SPLS requires purchase of proprietary access devices and maybe additional equipment in some cases and it can be difficult to demonstrate any economic benefit compared with CLS. Only a few conversions, a shorter LOS and less morbidity, will make SPLS more cost-efficient. The patient satisfaction related with body image perception after SPLS has also not been evaluated. If better cosmetic result in some patient groups remains to an important drive for performing SPLS, its impact to patient satisfaction should be studied. It is important to stress that most of published reports of SPLS for colorectal cancer were done in selected patients by highly experienced laparoscopic surgeon. Even when SPLS is performed safely in the competent hands, it seems that its benefits are likely to be modest. Continued acceptance of SPLS for colorectal cancer depends on benefits, improved patient outcomes, surgeon efficiency, and maybe decreased healthcare costs without compromising patient safety. It will only be widely recognized in surgical community, if they can be reproduced by more large prospective randomized trials. Eventually, patient preferences are more likely than physiological benefits to decide whether CLS or SPLS will become the method of choice for the minimally invasive treatment of colorectal cancer.

SPLS is a major step after CLS and represents the crossing link between robotic surgery and natural orifice surgery (NOTES). The huge developments in the fields of imaging, data processing, simulation and virtual reality in the future have the potential to help SPLS mature as computer-assisted single-access surgery through a single transabdominal incision or a natural orifice. It is believed that the future of minimally invasive surgery will be a hybrid form of SPLS, NOTES and robotic surgery.

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## Single port laparoscopic colorectal surgery: what did we learn from the ECSPECT prospective multicenter registry study?

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The development and growth of any new technology or operative procedure brings with it the need for careful scrutiny. First, the concept has to be developed. Then, individual experiences progress and are reported upon, followed by larger experiences and preferably multiinstitutional studies. Ultimately, if the question is important enough, a randomized clinical trial is carried out. While it goes without saying that a multi-institutional randomized controlled trial (RCT) represents the most scientifically rigorous approach to address questions in medicine and particularly in the surgical forum, not every question requires or deserves to proceed in this fashion. The ECSPECT trial goes a great distance in terms of addressing questions existing in the surgical community regarding single port (SP) laparoscopic surgery, short of a RCT.

The ECSPECT group must be congratulated for performing and conducting the analysis on such a large number of SP cases. In this *British Journal of Surgery* article, they present a wonderful experience in a tremendously well-done study. To put this study into perspective, one has to consider the questions that revolve around the innovative technique of SP surgery. Particularly, what serves as a barrier for wide spread adoption of SP colorectal surgery? Can SP surgery be performed safely and effectively? Does it make sense to perform laparoscopic surgery in a SP fashion if SP is harder? Are there benefits to SP surgery? Are there any drawbacks to this approach? Can SP colorectal surgery only be done for right colectomies in highly selected patients or can a variety of colorectal operations be done in a SP fashion? These are the essential and fundamental questions that need to be addressed for wider spread adoption of the SP technique.

With these questions in mind, let us explore what we can learn from the ECSPECT trial. First regarding SP's safety and efficacy, this study nicely demonstrated a low conversion rate to open surgery of 4.2%. This is better than the conversion rate of 16% in the COLOR II trial (1). Additionally, a low postoperative complication rate of 12.7% is significantly less in comparison to the current norm of 21% of laparoscopic and 20% of open colorectal surgery (2). In terms of predicting which patients might have problems with SP surgery, the study showed a higher complication rate and conversion rate for male sex, ASA grade > I and distal/rectal procedures. However, these findings come as no surprise. Stated differently, hard surgery is hard, especially in high risk patients. Deep pelvic surgery in men with a high ASA will predictably result in worse outcomes. We don't interpret this as a complication for SP surgery in these patients, but it may help the surgeon to phrase the conversation with the patient regarding expectations around SP surgery. Clearly from this experience, SP surgery has been shown to be safe and effective.

Does it make sense to do colorectal surgery in a SP fashion? If one can repeat the excellent results reported in

#### Marks and Nagatomo. Single port laparoscopic colorectal surgery



Figure 1 Postoperative incision of SILS colectomy in comparison to open appendectomy.

 Table 1 Morbidity and mortality for single port, multiport and open colorectal surgery

Variables	Morbidity	Mortality
Single port (ECSPECT)	12.7%	0.5%
Multiport (3)	13.1%	0.65%
Open (2)	20%	1%

the ECSPECT trial, the answer is clearly "yes". With 92% SP surgery completion rate without additional trocars, a low conversion rate and a low postoperative complication rate, SP colorectal surgery makes a lot of sense. Even if there are no clinical differences between SP and multiport (MP) surgery, with a similar safety profile, it is unquestionable that patients prefer to have the improved cosmesis of SP surgery (*Figure 1*). In terms of the length of hospital stay in this study, it is difficult to interpret the data since this is a European study and mean length of stay is longer in Europe than in the US.

In terms of potential drawbacks of SP surgery, I don't believe there were any demonstrated. The study shows no increase in morbidity and mortality over what one would expect from MP surgery (*Table 1*) (1-3). Previously, our research demonstrated that SP colorectal surgery is a safe alternative to MP surgery across an array of procedures in disease-equivalent patients in a case-matched study (N=190) using 7-criteria of age, gender, BMI, previous abdominal surgery, previous XRT, disease process, and procedure. In this study, we showed that SP conversion rates (0% SP versus 1.1% MP; P<0.05) and morbidity rates (10.2% SP versus 16.3% MP; P=0.52) are superior or equivalent to MP without compromising the quality of surgical techniques. We also reported lower EBL in SP surgery,

equivalent intraoperative complications, and shorter mean operative time in SP left colectomies compared to the MP approach, with a trend of shorter operating time in all SP procedures (4). All of these findings were similarly reported in the ECSPECT study.

Perhaps, most salient is whether or not this is just a special operation for right colon resections in thin patients. Clearly this does not seem to be the case as there were 1,769 total operations in the ECSPECT trial: 519 right colectomies, 868 left colectomies, 214 rectal resections, 48 APRs, 120 restorative proctocolectomies. Conversion rates as low as 4.2% and even in pelvic cases, a conversion rates of 8.1% is lower in comparison to 11.3% of ACOSOG Z6051, 16% of Color II and 9% of ALaCaRT (1-4). With regard to the patients in which SP surgery can be utilized, is this done in a variety of patients? In looking at the percentage of cases done in a SP fashion over this time, the largest accrual centers were doing between 50-65% cases in SP fashion. This is truly quite impressive and correlates well with our experience (4). Said differently this study shows excellent results for SP surgery over a wide variety of procedures with the approaches used quite well within general colorectal practice.

Of course, as with any study, there are things we would like clarified. One element would be oncologic outcomes of SP surgery. Although the authors mentioned that overall oncologic outcomes were not their targeted-questions, further data upon long-term clinical outcomes (>30 days) and oncologic outcomes of SP surgery would further add strength to this paper. In this regard, we previously demonstrated that SP surgery is not only equivalent in perioperative morbidity but also local recurrence, distant metastasis, and overall 5-year survival rate (4). This clinical evidence would further build the positive SP feasibility and safety profile.

Additionally, while this study shows high utilization of SP technique, there is no explanation of what the indicators were for selecting SP versus MP laparoscopy, which would be quite helpful. Another significant omission in this paper has to do with incision and hernia rates. There has been a large amount written regarding incisional hernia rate, which might be higher in SP cases. This is a significant question for SP cholecystectomy where the extraction site is enlarged to do the operation in SP versus MP fashion. For SP colon surgery, we believe this is not an issue, as there will always be an incision greater than 2.5 cm in order to exteriorize a specimen. Incisional hernia rates of 5% in SP colon surgery and 3–8% in SP cholecystectomy are the currently reported



**Figure 2** SP three trocar technique to minimize interference between hands. Operating surgeon: 1, right hand-ligature device (Covidien Ltd., Norwalk, CT, USA); 3, left hand-bariatric length grasper. Assisting surgeon: 2, 5-mm flexible tip Olympus EndoEye (Olympus America Inc., Center Valley, PA, USA); 4, Gelport SP device through a wound protector (Applied Medical, Rancho Santa Margarita, CA, USA). SP, single port.

norm in the literature (5). It also would be of interest to see the average size of incisions and number of incisions made. These all would add to the strength of the paper. Perhaps, in a subsequent publication the authors will explore these issues.

Lastly, from a technical standpoint, questions that were not addressed in this paper that would be very helpful to the surgical community have to do with how the operation was carried out. In particular, what optical systems were used? Was it a flexible tip camera or a straight rod lens system? Were the lenses 0/30/45 degree? Did they use normal length or bariatric length camera? What was the role of curved instrumentation? In our experience, we found either an instrument or camera is needed to be curved in order to get a hand away from operative field to allow two hands operate freely. In our opinion, the easiest most producible way to do this is with flexible tip camera. This will allow camera operators to have their hands well away from the hands of the surgeon. With a single bariatric length in one hand and normal length instrument in the other hand, the operation is able to be carried out through a small opening without a great deal of interference between the hands (Figure 2).

That being said, the authors should again be congratulated for this ECSPECT trial. Certainly, this paper adds justification and support for practitioners of SP surgery as to why and how this can be utilized. Hopefully it will excite others to enter into the field as this is a wonderful option for selected patients. Of course, no arguments have been made that this is for every patient and every surgeon. With proper patient selection and an experienced operative team, this trial shows, without questions, that the patients can be cared for in an effective and safe fashion with good results and argues for SP colorectal surgery to be within the toolbox of all minimal invasive colorectal surgeons.

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### Is previous abdominal surgery still a contraindication for laparoscopic surgery in colorectal cancer patients?

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Laparoscopy emerged as an alternative surgical approach after the introduction of laparoscopic cholecystectomy in 1987, although certain conditions such as previous abdominal surgery (PAS) were considered as absolute contraindications for this technique. Technical advances with development and improvement of instrumentation, growing surgical experience and increased laparoscopic skills over time made laparoscopic surgery the preferred method in certain centres for a range of complex and technically demanding procedures such as gastric, colorectal and even hepatic and pancreatic resections. In the same time, traditional absolute contraindications for laparoscopic surgery such as PAS have been reconsidered and largely resolved but still remain an issue of concern.

In a recent article by Dr. Lee and colleagues (1) published in the April 2016 online issue of *Surgical Endoscopy* the impact of PAS on short- and long-term outcomes of laparoscopic colorectal surgery was evaluated. The authors retrospectively reviewed a considerable number of patients (n=3,188) with primary colorectal cancer who underwent resectional laparoscopic colorectal surgery and compared patients with a history of PAS (n=593) to those without such history (n=2,595). They showed that overall PAS did not affect a range of intraoperative (conversion rate, operating time, number of harvested lymph nodes) or postoperative (time to flatus or defecation, length of hospital stay, and overall complication rate) parameters. However, when major PAS (defined as surgery involving more than one

abdominal quadrant) was considered, it became evident that patients with major PAS (n=165) had significantly higher rates of conversion to open surgery when compared to those without a history of previous intraabdominal surgery (4.2% vs. 1.7%) and a higher rate of overall postoperative complications (17.0% vs. 10.8%), mainly because of prolonged postoperative ileus and increased wound complications,. Major PAS was also found by logistic regression analysis to be an independent risk factor for conversion to open surgery (adjusted odds ratio =2.74; 95% confidence interval: 1.197–6.269).

Overall, findings from this study are in general agreement with previously published series (2,3) showing that laparoscopic colorectal surgery can be successfully and safely completed in most patients with PAS and has similar shortterm outcomes without oncologic clearance and radicality compromise compared to those without PAS. However, important details worth analyzing for better understanding of the true influence of previous intraabdominal surgery on laparoscopic surgery performance are missing, probably due to the retrospective nature of the study. The number of patients with PAS having adhesions significantly interfering with the procedure, the location, extent, severity and qualitative features of adhesions, the need for adhesiolysis, additional time necessary for adhesiolysis, inadvertent bowel injuries, other adhesion-related visceral injuries or intraand post-operative complications and adhesion-related conversions to open surgery are all important parameters

in this context. However, this can only be achieved in a prospective setting specifically designed to address these issues.

In a previous study using the same methodology, adhesion-related conversions were more common in patients with major or minor PAS when compared to no PAS patients for both colon (50%, 20%, and 9.1%, respectively) and rectal (50%, 25%, and 8%, respectively) cancer patients undergoing laparoscopic colorectal resection, mainly due to specific types (gastrectomy and colectomy) of previous surgery (2). The rate of intraoperative enterotomies was also relatively higher in the same groups (major, minor, and no PAS) of patients; 8.3%, 3%, and 2.6%, respectively for colonic, and 6.3%, 3.8%, and 2.1%, respectively for rectal cancer patients. Nevertheless, mean operative time and other intraoperative and postoperative outcomes such as blood loss, mortality, severity of complications, time to soft diet, hospital stay, did not differ among the groups.

Another retrospective cohort study, evaluated the influence of specific types of previous surgery or different types of incision used during previous surgery on the outcomes of laparoscopic colorectal surgery (3). Adhesionrelated conversion to open surgery was significantly more often among patients with PAS than among those without PAS (5.6% vs. 1.6%). Multivariate analysis identified previous median, upper median and lower median incisions as risk factors for conversion to open surgery. Inadvertent small-bowel enterotomies occurring either during initial access to the peritoneal cavity or during adhesiolysis were significantly more common in the PAS group than in the no PAS group (0.9% vs. 0.1%) with multiple PAS increasing the enterotomy risk. PAS was also associated with prolonged postoperative ileus and time to flatus, and delayed oral intake. When the authors looked at the type of procedure performed and the type of previous abdominal incision it became evident that laparoscopic transverse colectomy with previous median and upper median incision, laparoscopic left colectomy with previous upper median incision, and laparoscopic total colectomy with previous median incision were the combinations most likely associated with conversion to open surgery. These findings underline the impeding role of PAS on the operative field of future laparoscopic colorectal surgery when both correspond to the same anatomical area.

Both this study (1) and a previous report (3) included in their study population patients with previous laparoscopic surgery. This is an interesting issue as laparoscopic surgery has been widely spread and hundreds of thousands of different laparoscopic procedures have been performed around the world. Theoretically, laparoscopic surgery associates with less visceral injury and diminished inflammatory response than manual handling during open surgery and therefore results in less adhesion formation. Apparently, the small number of laparoscopic cases

Apparently, the small number of laparoscopic cases prevented the authors from specifically examining the impact of previous laparoscopic surgery on the outcomes of laparoscopic colorectal surgery. It wouldn't be surprising to see in the future studies evaluating the influence of previous laparoscopic or even robotic surgery (4) on following laparoscopic colorectal surgery.

Important information provided by this study relates to the impact of laparoscopic surgery for colorectal cancer on disease prognosis (1). There has been some scepticism regarding the oncologic safety of laparoscopy in patients with PAS as technical difficulties with extensive bowel and tumor manipulation during adhesiolysis may breach the "no-touch" principle resulting in tumor cell shedding and intraoperative cancer cell dissemination. Survival curve and multivariable survival analysis showed that PAS either minor or major did not adversely affect overall or disease-free survival. Although details on duration and completeness of patient follow-up, adjuvant treatment used and cancer-specific causes of death are not given, inspection of survival curves reveals an authentic five-year overall and disease-free survival rate of over 80%. These are impressive figures given that almost two thirds of the study population had advanced (T3 and T4) tumors and almost one third of all patients had metastatic disease (as seen in the second table). In fact, patients with a history of minor PAS showed significantly better disease-free survival compared to those without PAS. As commented by the authors, this unexpected finding was mainly related to significantly better diseasefree survival of patients with previous appendectomy. The relationship between appendectomy and tumor recurrence, if any, is unclear whereas the influence of unidentified confounding factors on this observation cannot be excluded.

Nowadays, when laparoscopy is establishing its pivotal role in the treatment of colorectal cancer patients, this report adds further information on the feasibility and safety of the laparoscopic approach when applied to patients with previous open abdominal surgery. Most importantly, laparoscopic surgery for colorectal cancer patients with PAS appears to be oncologically safe (1). It does not compromise the oncologic completeness of the surgery and has no detrimental effects on the long-term outcomes and disease prognosis. Furthermore, these effects appear to be valid even in cases of conversion to open surgery (5). Although some delay in postoperative intestinal function recovery may occur and despite the possibility of conversion to open surgery especially when specific operations or operations of certain location have been previously performed, patients with PAS have the right to benefit from the wellknown advantages of laparoscopic surgery. Previous open abdominal surgery itself should not be a contraindication for laparoscopic colorectal surgery and laparoscopy should be considered as the primary surgical approach even in these patients with open surgery being the alternative.

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## Comparison between laparoscopic and open surgery in stage II and III colorectal cancer using propensity score matching

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It is a great honor to comment on the article entitled "Propensity score-matched study of laparoscopic and open surgery for colorectal cancer in rural hospitals" by Nakao and his colleagues in the "Journal of Gastroenterology and Hepatology" (1).

This retrospective study compared the short- and longterm outcomes between laparoscopic surgery (LAP) and open surgery (OP) for stages II and III colorectal cancer, especially in middle-volume hospitals in rural areas of Japan. They defined a middle-volume hospital as a hospital that has more than 200 beds and less than 200 colorectal cancer operations per year. The study included patients who underwent colorectal surgery from January 2004 to April 2009. A propensity score-matched case-control study of colorectal cancer patients was conducted, and 261 patients were included in each cohort. Overall survival (OS), diseasefree survival (DFS), and postoperative complications of LAP and OP were compared, and they concluded that LAP may be a feasible option for stages II and III colorectal cancer.

In detail, as for short-term outcomes, the blood loss was significantly less in LAP than in OP (P<0.01), wound infection and ileus occurred less frequently (P<0.01, P=0.01) after LAP. Median postoperative hospital stay was 12 vs. 18 days, which was significantly shorter in the LAP group (P<0.01). There were no significant differences in the number of harvested lymph nodes, severity of postoperative complications, and mortality within 30 days postoperatively. As for long-term outcomes, the 5-year DFS was 81.8% and

77.8%, and the 5-year OS was 90.3% and 88.8% for LAP and OP, respectively, with no significant difference.

LAP for colon cancer has become common nowadays. Several randomized studies have reported not only its shortterm benefits (i.e., decreased pain, improved postoperative pulmonary function, reduced postoperative ileus, improved incidence of wound infection, faster recovery, and shorter hospital stay) (2-7), but also its noninferiority in terms of long-term outcomes (i.e., morbidity, DFS, and OS) (4,8-12). The results shown in the article followed these previously reported findings. In fact, in Japan, 38,992 of the total 54,169 patients with resected colorectal cancer underwent laparoscopic surgery in 2015. This accounted 72% of all resected cases (13).

According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines published in 2016 (14), it is recommended that careful consideration is necessary in adaption of LAP in stages II and III disease as it requires D3 lymphadenectomy. The concept of D3 lymphadenectomy in colorectal cancer is almost identical to that for mesocolic resection, which is widespread in the West. Many past randomized trials have excluded transverse colon cancer because of its anatomic complexity and difficulty (2,14,15). LAP for rectal cancer still is recommended to be performed as a "clinical trial" at this time (6,9), since it not only requires more advanced skills but also is unclear in oncologic safety (16,17). The guideline also refers to cases that need careful LAP adaption. High body mass index (BMI) and history of past laparotomy may lead to prolonged operation time, higher laparotomy conversion rate, and mortality (18-22). Therefore, the guideline recommends each hospital to determine their adaptation criteria by their learning level and individual surgeon's skill.

The latest article by the Japan Clinical Oncology Group (JCOG) reported that the survival outcomes following LAP verses OP D3 dissection for Stage II or III colon cancer (JCOG 0404) were similar (23). It is a phase 3, randomized controlled trial, accomplished under strict quality control. Also, uniform surgical procedure, including D3 lymph node dissection with intraoperative photographs assessed by the quality control committee, was demanded. Uniform adjuvant chemotherapy was given to patients with stage III disease with fluorouracil (500 mg/m<sup>2</sup> by bolus intravenous infusion on days 1, 8, 15, 22, 29, and 36) and leucovorin 250 mg/m<sup>2</sup> by 2-hour drip intravenous infusion on days 1, 8, 15, 22, 29, and 36).

In this study, 1,057 patients were assigned randomly to either OP (n=528) or LAP (n=529). Transverse colon cancer was excluded. The 5-year OS was 90.4% for OP and 91.8% for LAP, and noninferiority was not demanded because the number of events observed was insufficient. The group previously reported short-term outcomes of this study that showed LAP was more beneficial than OP (7). As a whole, they concluded that LAP D3 surgery could be an acceptable treatment option for patients with stage II or III colon cancer.

Nakao et al. (1) mentioned that the surgical procedure and postoperative chemotherapies were performed in accordance with the JSCCR guidelines (14) and the standards of the participating institutions. However, the detailed surgical procedure, especially the extent of lymphadenectomy, is not mentioned. There were 16 (6.1%)transverse colon cases in the LAP group and 15 (5.8%) in the OP group, and 37 cases (14.2%) of rectal cancer in both groups. These cases may require more advanced surgical skills, leading to higher morbidity rates. The conversion rate in LAP was 8.4%, higher compared to the JCOG 0404. Therefore, it may be better to exclude these cases when analyzing the data for comparison to previous randomized controlled trials (RCTs). On the other hand, the median numbers of harvested lymph nodes were 12 in LAP and 14 in OP, much less than 21 and 22, respectively, in the JCOG 0404 study. Still, the 5-year OS rate was 90.3% and 88.8% for LAP and OP, respectively, similar to that of 91.8% for LAP and 90.4 % for OP in the JCOG 0404.

The regimen of adjuvant chemotherapy is not introduced in this study by Nakao *et al.* (1). They have noted these points as limitations of this study and mentioned that further accurate investigation is required. I strongly agree with the authors because the level of lymphadenectomy and adjuvant chemotherapy regimen may have substantially influenced the long-term outcomes. Since the rectal cancer cases were included, the ratio of simultaneous covering stoma also is a point of interest.

This article has focused on the LAP for colorectal cancer cases in rural middle-volume hospitals in Japan. It may be the first article to assess the practical surgery performed in such hospitals, as no similar studies have been published previously in Japan as far as we searched. It is interesting to see and compare the practical clinical data between rural middle-volume hospitals and high volume– centered hospitals. The results of this study may be highly suggestive, but we always must have knowledge of the latest and standard guidelines to make a proper judgment.

In conclusion, the results of the present study were comparable to those of the JCOG 0404 study, demonstrating the safety of the laparoscopic approach in stages II and III colorectal cancer in middle-volume hospitals in Japan. As for rectal cancer, careful indication of laparoscopic surgery still is regarded.

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# Transversus abdominis plane block in laparoscopic colorectal surgery

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Beneficial outcomes of laparoscopic colorectal resection have been identified, including decreased postoperative pain, quicker functional recovery, and a shorter hospital stay. Acceptable oncologic outcomes for advanced malignancies have also been reported. Furthermore, such advances in surgical techniques may be associated with less postoperative complications. However, controlling postoperative pain, nausea and vomiting (PONV), and impaired bowel function remain major factors affecting the length of hospital stay and thus successful enhanced recovery after surgery (ERAS). Therefore, there has been a great deal of interest in analgesia for laparoscopic colorectal surgery.

Opioid analgesics, commonly used to control postoperative pain, are associated with an increased risk of PONV, impaired bowel function, urinary retention, sedation and respiratory depression. Thus, to facilitate recovery of patients who have undergone abdominal surgery, alternative analgesic modalities that utilize limited opioid use have been employed. The concept of multimodal analgesia, including some loco-regional anesthetic procedures, has also been introduced into postoperative recovery programs.

Laparoscopic procedures, with minimal trauma to the abdominal wall, can shorten intensive treatment for postoperative pain and can presumably reduce the inflammatory and neuroendocrine responses associated with surgical trauma. The optimum regimen or combination of analgesic modalities in laparoscopy may therefore be different from that required for open surgery.

Whilst epidural analgesia is considered a prerequisite in ERAS programs for open colorectal surgery, its role in laparoscopy has been questioned. Recently, undesirable effects of epidural analgesia during recovery from laparoscopic colorectal surgery have been reported in several randomized controlled trials (RCTs). These undesirable effects include increases in length of hospital stay, time to recovery of bowel function and duration of nausea (1).

The transversus abdominis plane (TAP) block, in which local anesthetic is injected into the neurovascular plane between the transversus abdominis and the internal oblique muscle to block the sensory nerves of the anterior abdominal wall, is an alternative form of postoperative pain control (2). Ultrasound-guided TAP blocks (3) are preferentially employed because of the accuracy afforded by clear visualization of the abdominal wall. This procedure is presumably effective for longer periods of time and offers better pain control when compared to local wound infiltration. The peripheral nerve blocks may help reduce the pain elicited by incising the abdominal wall whilst minimizing the adverse effects of analgesia. However, there is limited evidence for the efficacy of TAP blocks in laparoscopic colorectal surgery.

We read, with great interest, the manuscript published by Dr. Pedrazzani *et al.* in the November 2016 edition of Surgical Endoscopy (4). In a prospective non-randomized

study, the authors evaluated the efficacy of local wound infiltration plus TAP block, compared to local wound infiltration, in patients who underwent laparoscopic colorectal surgery under the ERAS program. The additional use of TAP block allowed pain control despite a reduced dose of opioid analgesics. Overall, this manuscript appears consistent with the previous double-blinded RCTs by Keller *et al.* (TAP *vs.* placebo) (5) and Walters *et al.* (TAP *vs.* no treatment) (6) Nonetheless, we should note that there were some discrepancies between these studies when each outcome measure is carefully analyzed.

Furthermore, the authors of the current manuscript report that adoption of a TAP block produced further beneficial results, i.e., prevention of PONV, facilitating recovery of bowel function and urinary catheter removal, plus acceptable tolerance of an oral diet. These remarkable effects can be explained, at least in part, by the reduced requirement for opioid analgesics. Thus the TAP block is capable of suppressing the intense pain produced by incising the abdominal wall for one or two days after surgery, and would appear to be a promising technique enabling quicker patient recovery after laparoscopic colorectal surgery.

However, two recent double blind RCT in patients undergoing elective laparoscopic colorectal resections failed to show any benefits of TAP block, including reduced pain scores or opioid consumption (7,8). The efficacy of ultrasound guided TAP block was evaluated in the management of postoperative pain compared to local wound infiltration or placebo control, and the authors report that the effects of TAP block were comparable to those of the controls both in terms of postoperative pain and analgesics dose.

Overall, a definitive answer is thus not readily available on the question of TAP block efficacy for postoperative care. These contradictory results may be due to the complexity of pain assessments or variability in background treatment for postoperative pain. The aforementioned clinical trials were conducted at a single center, and the sample size in each study appears to be too small to compensate for the inherent uncertainty in quantification of pain and other symptoms. Further studies are thus required to confirm the effectiveness and clinical relevance of TAP block in laparoscopic colorectal surgery. The concept of using TAP block in the postoperative period to suppress parietal pain is of significant interest, and, if repeated and consistently confirmed, may become the future standard moving forward towards improved surgical outcomes.

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### Post-operative outcomes in robotic and laparoscopic colorectal surgery

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I am pleased to comment the article entitled "Comparison of robotic and laparoscopic colorectal resections with respect to 30-day perioperative morbidity" by Feinberg and colleagues (1). This is a retrospective study about robotic and laparoscopic colorectal procedures based on the American College of Surgeons National Surgical Quality Improvement Program database (ACS-NSQIP), a validate program that prospectively collects perioperative data from North America hospitals and abroad (2,3). The authors have selected patients underwent to robotic or laparoscopic colorectal procedures, excluding open approaches and abdominoperineal resections. They also performed a subgroup analysis for rectal resections only. The main outcomes of the study included operative time, conversion rate, blood transfusions, post-operative complications, length of stay, readmissions, reoperations and 30-day mortality. A total of 472 robotic and 8,392 laparoscopic colorectal resections were included in the study. No differences were found respect to age, gender, body mass index, comorbidities, functional status, operative time, blood transfusions and postoperative complications between the two groups. In the robotic group there was slightly more incidence of cancer diagnosis compared to laparoscopy and lower incidence of open conversion rate. In the subgroup analysis of rectal resections a total of 79 robotic and 1,370 laparoscopic procedures were included. The two groups were comparable with respect to all the variables analyzed, except for postoperative ileus, which resulted with a lower incidence in the robotic group. The authors performed a multivariate analysis in order to identify independent variables associated with open conversion rate. Male sex, colon cancer, Crohn's disease and diverticular disease were all identified as risk factors for open conversion, whereas robotic surgery was found to be a protective factor for open conversion compared to laparoscopy.

Colorectal surgery has undergone a remarkable evolution in the recent decades with the introduction of minimally invasive techniques. This innovation was possible thanks to the continuous technologic evolutions in the medical and surgical fields. Several studies with different opinions about the best treatment options have been published over the years, in order to search a validation in terms of oncologic appropriateness. However, the world literature recently produced, appears unanimous on the appropriateness of the minimally invasive techniques, especially for procedures performed at referral centers and by experienced surgeons. Laparoscopic surgery has been demonstrated to be a safe and feasible technique, though it is affected by some limitations. To overcome its disadvantages, the robotic systems have been introduced in the surgical practice, with successfully application to several types of operations. The first use of the robotic approach in colorectal surgery was described in 2002 (4). Subsequently, several authors have reported their experiences, underlining the advantages and the drawbacks of this type of approach, with often conflicting results (5-7).

One of the most described advantages of robotic surgery is the minor incidence of conversions to open surgery, compared to laparoscopy (8). In the article by Feinberg et al. (1), the authors confirmed this result, with a significant decreased incidence of conversion in the robotic group (9.53% vs. 13.72% in laparoscopy, P=0.008). This result is similar to those reported in literature, with described values around 9-10% for robotics and 13% for laparoscopy (9). However, this finding has not been confirmed in the subgroup analysis of rectal resections. A similar result has been shown by the preliminary data of the RObotic Versus LAparoscopic Resection for Rectal Cancer (ROLARR) trial, with no significant advantage of the robotic system in terms of conversion rate (10). Furthermore, the authors performed a multivariate analysis in order to overcome the potential selection bias of the study. They evidenced that different factors could be independently associated with unplanned conversions, like male sex, malignancy and inflammatory bowel disease of the colon.

In the study by Feinberg et al. (1), no difference in operative time was found between the two groups. This is an interesting result, since one of the most important limitations of the robotic approach described in literature is the prolonged operative time compared to laparoscopy. This factor is explained by the need to dock and undock the robotic system during the procedures, in order to reach the correct position for every surgical step and, obviously, this is time consuming (6). Even in the rectal resections analysis no difference in terms of operative time was evidenced. This is a great result, showing that the standardization of the surgical procedures and the continuous training of the surgical staff with increasing experience in this field can improve the outcomes, leading to a progressive reduction of the operative time. In fact, the higher duration of operations for the robotic approach has been reported in literature especially in case of early experiences (11).

Another important reported result of the study by Feinberg *et al.* (1), is the low incidence of postoperative complications, with no statistical differences in the two groups. In particular, in the rectal resections analysis, a significant lower incidence of postoperative ileus was found (3.8% vs. 11.18\%, P=0.039). The unplanned reoperation, which reflects the major complications rate, were similar in the two groups (4.87% vs. 4.6%, P=0.74), even in the rectal resections (6.33% vs. 5.4%, P=0.62), showing the safety of the two approaches. These results are inferior to those published by other authors, which can reach 11.5% in robotic surgery and 12.4% in laparoscopy (12,13).

There are several limitations in the study, and the authors describe them carefully. First of all it is a nonrandomized retrospective analysis, with different selection biases. In particular, no selection of the patients was carried out, and they were treated in robotics or in laparoscopy without selection criteria, maybe on the basis of the experience of each surgeon or, most likely, on the basis of the difficulty of the cases individually. In particular the surgeon experience is an important factor to consider, because it can influence the surgical outcomes, especially in terms of open conversions and surgical complications. Moreover there is no description of the surgical technique used for each operation, and possible variations could be included in every procedure, in particular for some open steps. The authors attempted to minimize this bias excluding the procedures with a planned open phase, but inevitably the technical details of each operation could not be registered. Finally, the most important bias of this study is the inclusion of several types of procedures for different types of indications. The authors mixed benign and malignant diseases, and in some cases this is an important limitation because strong differences could be present among the procedures. For example, a colonic resection could be very different if it is carried out for benign disease, such as diverticulitis or inflammatory bowel disease, and for cancer. In the latter, an accurate oncologic resection should be performed, with complete mesocolic excision and lymphadenectomy and with proper margins. Moreover, in case of benign disease a large variety of procedures could be performed, like extended colonic resections in case of inflammatory bowel disease, or like the execution of a diverting stoma in case of diverticulitis. Even in the groups of rectal resections there is no mention about the ileostomy, which often is carried out in these cases and that could be an important bias, especially for the evaluation of the operative time and complications. Furthermore, important operative differences could exist among the procedures, even for the same indication. Indeed, a transverse colonic resection could be very different from a right or left resection, especially in terms of operative time. After all, for the malignant diseases, the inclusion of oncologic outcomes like the number of lymph nodes excised or the tumor stage, would have been more interesting.

In conclusion this is an interesting report comparing robotics and laparoscopy in colorectal surgery. The results of this study confirm some advantages of the robotic approach, especially in terms of postoperative complications. There is a significant report about the operative times, which resulted with no difference in the two groups. However, a proper selection of the cases and the need for a randomized trial could be advocated for a better study of the real benefits of the robotic system in colorectal surgery.

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#### Footnote

*Conflicts of Interest*: The author has no conflicts of interest to declare.

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### Laparoscopic vs. robotic colorectal resections: new insights from the American College of Surgeons National Surgical Quality Improvement Program

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We read with interest the article by Feinberg et al. (1) reporting the short-term results for colorectal resections performed by laparoscopy or Da Vinci System<sup>®</sup>. Data from of 8,864 colorectal resections performed in 2013 in hospitals participating at the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) were retrieved concerning preoperative, intraoperative, and 30-day outcome data. For each robotic colorectal procedure there were about 18 laparoscopic resections, 472 robotic (5.6%) vs. 8,392 laparoscopic overall. Rectal resections were 1,449, 79 robotic (5.4%). These preliminary findings show that the use of the Da Vinci System® was not dependent to rectal vs. colonic localizations and maybe is more related to the habits of each institution, where in some hospitals robotic surgery is employed both for colon and rectal resections and the same is true for laparoscopy.

Although there are not solid data from randomized trials, surgeons performing robotic rectal surgery are aware that it is easier than laparoscopy which is characterized by steep learning curve. It was recently calculated that the mean number of cases required for the surgeon to be classed as an expert in robotic rectal surgery was 39 patients (2). The study showed two main findings. The first one was that the robotic cohort had a lower incidence of unplanned intraoperative conversion (9.5% *vs.* 13.7%, P=0.008). The second was that in the subgroup of rectal resections the employment of the robot resulted in a lower incidence of postoperative ileus than laparoscopy (3.8% *vs.* 11.18%,

P=0.039). The only randomized control trial that was implemented [robotic versus laparoscopic resection for rectal cancer (ROLARR)] (3) had as primary end-point the conversion rate and after the completion of the enrolment failed to show a significant reduction rate of unplanned conversion in the robotic group overall. The subgroup analysis supported a benefit with the robotic approach for male patients, obese patients and those with lower tumors. The third interesting result is that there was no difference in duration of surgery between laparoscopic and robotic procedures. This is relatively new in the literature where robotic surgeries are reported to be more time consuming. There are two possible explanations. In the paper by Feinberg et al. a great amount of data were reported in a short time interval and in a recent year [2013], so that many institutions dealing with robotic surgery since early 2000s' have reached their plateau in the learning curve. Moreover, the same reason bringing a similar rate of robotic surgeries in colon and rectal cancer may account for a similar duration of surgery for laparoscopic and robotic procedures where institutions employing robotic surgery are committed to perform as many robotic procedures as possible, shortening the length of surgery. Focusing on colonic resections interesting data are coming out regarding the possible advantage of the Da Vinci system in performing right colectomies with a modified complete mesocolic excision technique (mCME). In a recent study (4), the authors confirmed the feasibility and safety of mCME for

the treatment of right-sided colon cancer. This technique provided satisfying short-term outcomes with promising 4-year oncologic results.

The problem of increased costs with robotic surgery is well known, however it was not a topic of the study by Feinberg *et al.* However the difference in costs per episode of care penalizing robotic surgery versus other conventional approaches widely ranges among studies (5). Moreover, an accurate analysis based on direct non-medical costs as well as indirect and social costs has never been conducted, and should be the aim for future studies.

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# Improving preoperative endoscopic localization of colon and rectal tumours

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We read with great interest the article published in *The American Journal of Surgery* by Yap *et al.* entitled *"Colonoscopic localization accuracy for colorectal resections in the laparoscopic era"* (1). The authors should be commended on their interesting study addressing an important aspect of preoperative planning in the increasingly established era of laparoscopic colorectal surgery.

The benefits of a laparoscopic approach to colon and rectal surgery have been well demonstrated, and this approach is used with escalating frequency with comparable oncologic results to open surgery (2). However, in contrast to open surgery which affords the surgeon the ability to palpate and confirm the location of masses intraoperatively, a laparoscopic approach is more dependent on accurate preoperative localization of the lesion. Efforts to understand and minimize errors in preoperative localization of colorectal lesions are therefore of relevance and importance to reduce the frequency of intraoperative changes to the surgical plan.

In their study, Yap *et al.* found that of the 221 colon and rectal masses retrospectively reviewed over a six-year period, only 175 (79.2%) had been accurately localized when intraoperative findings were compared with preoperative endoscopy reports. Of the 46 incorrectly localized lesions, 17 (37%) required an intraoperative change in the surgical plan, with three requiring ileostomy creation due to unexpected rectal lesions, and one requiring conversion from laparoscopy to open for palpation of the tumour (1).

Of the 46 lesions which were incorrectly localized

preoperatively, the correct location was ultimately determined intraoperatively by tumour visualization in 26.1%, by visualization of endoscopic tattoo in 26.1%, and by CT scan in another 21.7%. Of the remaining lesions, 19.6% were identified by means not specified in the operative report (1). In light of these findings, and given that all patients in this study underwent preoperative colonoscopy for diagnosis, it is notable that only 110 lesions (49.7%) were tattooed, and just 196 lesions (88.7%) had a documented staging CT to complete the patient's preoperative work up (1).

On univariate and multivariate analysis, Yap *et al.* (1) found that two factors influencing the likelihood of an incorrectly localized tumour remained statistically significant: (I) incomplete colonoscopy (P=0.026 on multivariate analysis); and (II) colonoscopy performed by an endoscopist with a gastroenterology (as opposed to surgical) background (P=0.028 on multivariate analysis).

Szura *et al.* (3) in their 2016 RCT found colonoscopic localization was accurate in 83.2% of the 129 patients in the study's endoscopy arm, although this number has been reported to be as high as 96–99% for studies examining single surgeon-endoscopists (4,5). While there has been recent discussion in the literature about endoscopy as the domain, preferentially, of the gastroenterologist, we feel that this study and the three referenced above (3-5) are reminders of the importance of a strong surgical presence within the endoscopy community. This ensures that the focus on preoperative planning and associated endoscopic considerations brought to bear by the operating surgeon can be shared and incorporated into future standards of practice to help minimize the risk of intraoperative localization errors, especially in the era of laparoscopy.

Yap et al. (1) also indirectly reinforce the importance of a complete diagnostic and staging work up for all colorectal tumours, as well as a multidisciplinary team review of a patient's management plan. It is important to note that approximately three-quarters of incorrectly localized tumours could be correctly identified intraoperatively by systematic examination of the colon, aided by the presence of an endoscopic tattoo and a staging CT scan (1). The interdisciplinary review of a patient's work up prior to finalization of the management plan serves to improve communication between the endoscopist, surgeon, and radiologist with regards to localization and evidence of nodal or metastatic disease. In addition, this provides an opportunity to discuss the timing and order of surgery with medical and radiation oncologists, whose roles are essential in the management of colorectal cancers.

Finally, and perhaps most fundamentally, our group is not aware of any standardized definitions for the endoscopically determined location of colonic lesions. This lack of a shared endoscopic nomenclature creates inherent ambiguity in the subjective assessment of tumours described as being located within the hepatic or splenic flexures, or within the descending, sigmoid, or rectosigmoid colon. Even the definition of a rectal cancer has been debated, with no agreed upon standard to guide reporting. Given the importance of clear communication about tumour location between the endoscopist and surgeon for accurate preoperative planning and informed consent, the establishment of a standardized set of definitions for localizing colorectal tumours is an essential starting point.

Yap *et al.* (1) highlight an important topic in the surgical management of colon and rectal cancers, and reinforce

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the importance of interdisciplinary communication and collaboration to improve patient outcomes. The establishment of a shared endoscopic nomenclature defining tumour location, as well as the adoption of complete diagnostic and staging work ups as institutionally prioritized quality indicators are crucial steps toward minimizing incorrect preoperative localization of colon and rectal cancers in the era of laparoscopic surgery.

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### Colorectal endoscopic submucosal dissection (ESD) could reduce the need for surgery of colonic polyps in the West

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This is an original article written by Gorgun *et al.* who are colorectal surgeons at a large tertiary referral hospital in USA. I read this paper with great interest because I thought most surgeons would believe that colectomy is simple and does not reduce QOL for patients except in rectal tumors.

#### A tincture of time

It is important to point out that the interval over which this study collected cases encompasses 16 years between 1997 and 2012. In our opinion, it is safe to assume that techniques such as wide-field endoscopic mucosal resection (WF-EMR) and endoscopic submucosal dissection (ESD) were not prevalent during this time and hence may have affected the referral patterns for surgery. Most academic centers now have faculty that perform WF-EMR and as such many of these polyps maybe now be managed endoscopically. It would be interesting with the current study design to determine the percentage of patients with large polyps that are now referred for surgical resection as a function of time.

#### **ESD** could reduce over-surgery

Colorectal ESD was developed in Japan and is now widely accepted there as first-line treatment for early colorectal cancers, large laterally spreading tumors (LSTs), and adenomatous polyps not amenable to complete resection by polypectomy or EMR (1,2). However, there is limited practice of colorectal ESD in the West, because of the technical challenge of performing the procedure, and as a result colectomy is commonly performed for large colorectal LSTs although there is no need for lymph-node dissection.

Before the introduction of ESD at the National Cancer Center Hospital, Tokyo, Japan, approximately 20% of surgeries for colonic polyps had only intramucosal neoplasia, however after introduction of ESD this number has dramatically decreased to 1%, and thus "over-surgery" was largely avoided (3). As we conduct challenging ESD on massive LSTs or submucosal cancer (T1a or T1b), about 10% of all ESD cases result in non-curative resections (3), but these patients could easily go on to have surgery with lymph node dissection without additional harm. In this way, patients are given the best opportunity to avoid surgery, and maintain their quality of life. The authors reported that "cancer was identified on the operative specimen in 37 patients (8.4%)", the other 402 patients (91.6%) could have potentially avoided surgery if ESD was an available option.

#### Clinical impact of pathological diagnosis of cancer by biopsy

The diagnostic criteria of cancer on biopsy samples should be discussed in this paper. The authors reported that "Of the 439 patients, 346 (79%) underwent preoperative colonoscopy in our institution for all polyps preoperative biopsy was benign." and "All patients who had cancer in the final pathology had preoperative biopsies and results were as follows: tubular (n=6, 16.2%), tubulovillous (n=22, 59.5%), villous (n=8, 21.6%) and SSA/P (n=1, 2.7%). Preoperative HGD rate was found to be significantly higher in patients who had cancer in the final pathology compared to benign polyps [n=18 (48.0%) vs. n=70 (17.4%) P<0.001]."

The consensus criteria for the pathologic diagnosis of intramucosal cancer in the West is only when dysplastic epithelial cells breach the basement membrane to invade the lamina propria or muscularis mucosae (MM); therefore, it might be difficult to diagnose a cancer by pre-operative biopsies.

In Japan, where there are consensus criteria for the pathologic diagnosis of intramucosal cancer without the invasion to lamina propria or MM, expert pathologists are able to diagnose intramucosal cancer on EMR, ESD and biopsy specimens. We believe it is important to establish the diagnosis of intramucosal cancer as we have had several cases of invasive and metastatic recurrence after piecemeal EMR of lesions with intramucosal cancer (4,5).

While small local adenomatous recurrences can easily be treated with follow up EMR, invasive and metastatic recurrences can have a much more devastating outcome (4). Due to these experiences, we no longer perform piecemeal EMR for LSTs-non-granular type >20 mm in diameter and LST-granular type >30 mm in diameter considering the risk of submucosal invasion and difficulty of predicting the area of SM invasion (6,7).

The differences of intramucosal cancer diagnosis between East and West, might help explain why the authors found that high grade dysplasia was associated with malignancy even if the endoscopic appearance of the polyp was benign. Within Japan many of these patient's biopsies might have been diagnosed with intramucosal cancer.

### Clinical importance of endoscopic diagnosis using pit pattern

The authors reported "An endoscopic diagnosis of a malignancy in a polyp is based on the appearance (irregular, ulcerated suggest cancer), feel (bard polyp suggests cancer), fragility (malignant polyps bleed easily) and fixity (a malignant polyp and surrounding colon wall move together)." But "None of the cancers in our series were like this. Preoperative biopsy may confirm or suggest cancer but did not here, reflecting an error rate of biopsies compared to examination of the entire lesion. Factors associated with malignancy among unresectable colonic polyps include left sided location, villous architecture, HGD, and advanced patient age. We found that polyp size and HGD were associated with malignancy. Our data establish the importance of high grade dysplasia as a clue that the polyp may be malignant even though it doesn't look it." In addition, 37.9% of patients believed to have a benign polyp endoscopically had stage IIa or higher colon cancer on resection.

In Japan, we routinely use magnified endoscopic evaluation to differentiate non-neoplastic from neoplastic lesions and estimate depth of invasion with a high degree of accuracy (8). While magnifying endoscopes are not commonly used in the West, near-focus systems are, that are able to deliver 50x magnification and similar results to optical zoom magnification (from 80x to 100x) may be obtained.

We do recommend, therefore, that use of pit pattern diagnosis with a near focus system be further explored and validated in the West. From our retrospective analysis, pit pattern diagnosis showed the highest accuracy and was an independent factor on multivariate analysis for estimation of early cancer depth of invasion (9).

#### Safety and QOL of ESD compared to surgery

The authors reported in this article that "The complication rate after colorectal surgery was nearly 20% in our series" and "Many of these complications could be avoided by using advanced endoscopic techniques. Based on the results of the current study we pushed advanced endoscopic techniques for the management of benign polyps not amenable to conventional colonoscopic removal. The algorithm we follow for the different colorectal lesions are summarized in Figure 3."

We have published several papers comparing clinical results and patient's QOL between ESD and surgery including laparoscopic colectomy (LAC) (10,11). LAC showed lower QOL and increased post-procedure

complications compared to ESD with similar clinical results (12). Accurate pre-operative diagnosis using pit pattern is essential for performing ESD technique for larger colorectal LSTs to ensure proper case selection (8,9). In addition, we do not perform any biopsies before endoscopic treatment because biopsies may cause fibrosis and that could cause non-lifting sign even for intramucosal neoplasm, and make subsequent resection more difficult. We believe that use of colonic pit pattern analysis (8,9) can help triage colonic polyps to the most appropriate treatment while avoiding the fibrosis that can be induced by endoscopic biopsies, and have adopted its use in all colonoscopies including screening.

#### Conclusions

In the West, patients with colonic polyps are not amenable to complete endoscopic resection with polypectomy or EMR traditionally undergo surgical resection. The article by Gorgun *et al.* suggests the majority of these lesions are benign and do not require lymph node dissection. Colorectal ESD would allow many of these patients to avoid the complications of surgery and maintain their quality of life, but due to the technical challenge of performing ESD there has been limited practice of ESD in the West. But that might be changing soon, there are now Western endoscopists who have been well trained in ESD under expert Japanese guidance that are performing ESD with high en-bloc resection and low complication rates, and we are optimistic they can move forward colorectal ESD in the West (12-15).

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#### Footnote

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### Is lymph node metastasis the only concern in high-risk submucosal colorectal cancer following endoscopic resection?

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Endoscopic resection represents a curative therapy for Tis colorectal cancer (carcinoma in situ; intraepithelial or invasion of the lamina propria) as it has no risk of lymph node metastasis (1-3). However, lymph node metastasis occurs in 7-15% of T1 colorectal cancers (invasion of submucosa) (4-10). In order to achieve curative resection of submucosal colorectal cancer, predictors for lymph node metastasis have been evaluated in many studies (7,9-14) and found to be depth of submucosal invasion (1,000 and 3,000 µm for nonpedunculated and pedunculated submucosal colorectal cancers, respectively), lymphovascular invasion, and poorly-differentiated adenocarcinoma (11,15,16). In cases of submucosal colorectal cancer with no risk factors for lymph node metastasis, no further treatments such as surgical resection appear to be necessary following complete endoscopic resection. Conversely, additional surgery has been recommended for high-risk submucosal colorectal cancer (11).

Some patients with high-risk submucosal colorectal cancer, however, hesitate to undergo surgery due to surgeryassociated morbidity and mortality. In certain circumstances, endoscopists also struggle with whether to offer surgery as the majority of patients with risk-factors for lymph node metastasis actually have no metastatic spread. Such scenarios seem to be more frequent in rectal cancers compared to colon cancers. Abdominoperineal resection—the standard treatment for low rectal cancer—can leave some patients with permanent stomas (17). Therefore, when taken together with the rate of lymph node metastasis of approximately 10%, careful observation can also be an alternative treatment option in select patients.

Until now, risk of lymph node metastasis has only been a concern in patients with high-risk submucosal colorectal cancer following endoscopic resection. Because rates of lymph node metastasis do not differ between submucosal colon cancer and submucosal rectal cancer (8,11,15), tumor location does not appear to be an important variable in evaluating highrisk submucosal colorectal cancer. However, Ikematsu et al.'s recent study (18) in the Gastroenterology demonstrated that the risk for local cancer recurrence was significantly higher in patients with high-risk submucosal rectal cancer than in patients with high-risk submucosal colon cancer when treated with endoscopic resection alone. That study reviewed data from 573 patients with submucosal colon cancer and 214 patients with submucosal rectal cancer and who underwent endoscopic or surgical resection at six institutions. This dataset constituted the largest retrospective study population for patients with submucosal colorectal cancer. In total, the number of patients treated with endoscopic resection was 327 and 101 for submucosal colon cancer and submucosal rectal cancer, respectively. Of those patients, 218 and 84 were high-risk for lymph node metastasis, respectively. Patients that refused additional surgery, designated as group B, were 31.7% of high-risk submucosal colon cancer (69 of 218) and 44.0% of high-risk submucosal rectal cancer (37 of 84). The results from this study suggest that patients with high-risk submucosal rectal cancer decline additional surgery more frequently than patients with high-risk submucosal colon cancer (P=0.043, Chi-square test). In group B, rate of local recurrence was higher in submucosal rectal cancer than in submucosal colon cancer (10.8% vs. 1.4%, respectively, P<0.01). This serves as an interesting finding as there was no difference in local recurrence rates for patients who underwent surgery or in patients with low-risk submucosal colorectal cancer treated with endoscopic resection alone. This study further demonstrated that disease-free survival for patients with high-risk submucosal rectal cancer was inferior to patients

with high-risk submucosal colon cancer (5-year disease-free survival rates: 77.7% vs. 96.5%, respectively, P<0.01). The authors proposed that recurrence rates greater than 10% might be expected when no additional surgery was pursued due to the increased possibility for micrometastasis. Based on these collective findings, it appears important to consider not only risk of lymph node metastasis but also risk of local recurrence when evaluating treatment options for patients with high-risk submucosal rectal cancer following endoscopic resection.

In this study, long-term disease-free survival of patients with low-risk submucosal colorectal cancer following endoscopic resection alone was excellent. All 104 patients with low-risk submucosal colon cancer did not exhibit recurrence during the defined follow-up period (mean: 55.2 months). In the low-risk submucosal rectal cancer group, only one patient (6.3%) had distant metastases—this patient had originally been classed as low-risk for lymph node metastasis, but upon reexamination of the original pathology specimen, additional slices exhibited lymphovascular invasion. Therefore, this patient was actually high-risk for lymph node metastasis, and additional surgery should have been recommended. Evaluation of this patient raises important considerations including: (I) further demonstration that long-term outcomes of low-risk submucosal colorectal cancer are excellent, and (II) presence and impact of pathologic error. A prior retrospective study demonstrated that pathologic errors in cancer diagnosis occur in up to 11.8% of cases (19). Such data underscore the importance of careful evaluation of cancer recurrence following endoscopic resection even in patients with lowrisk of lymph node metastasis. In addition, other reports have proposed further risk factors for lymph node metastasis including tumor budding and background adenoma beyond the classic criteria mentioned earlier (7,13,20). Although further research may be necessary, we believe that additional pathologic assessment for tumor budding and background adenoma in patients with low-risk submucosal colorectal cancers may help to better assess risk for lymph node metastasis. In contrast to patients with low-risk submucosal colorectal cancer, seven patients (6.6%) with high-risk submucosal colorectal cancer who underwent endoscopic treatment had recurrence. In addition, 14 patients with highrisk submucosal colorectal cancer (2.6%) had recurrence despite undergoing surgery. Lymph node metastasis was identified in 12.4% of patients (66 of 532) with high-risk submucosal colorectal cancer and who underwent surgery, findings consistent with previous reports (11,15).

In spite of extraordinary conclusion, results of the study should be interpreted with caution given study limitations.

#### Park and Lee. High-risk submucosal colorectal cancer

First, the en-bloc resection rate was not reported despite including of patients who underwent endoscopic piecemeal mucosal resection. Local recurrence of colorectal tumor occurs more frequently after piecemeal resection than with en-bloc resection (21,22). Second, multivariate analysis for disease-free survival may not have been appropriate, although univariate analysis showed that disease-free survival rate was lower in patients with high-risk submucosal rectal cancer than in patients with high-risk submucosal colon cancer. Tumor location was an independent risk factor for disease-free survival according to the proposed Cox regression hazard model (HR of rectum =6.73, 95% CI, 1.04-43.43). This model included tumor depth ( $\geq 2,000$ or <2,000 µm), lymphatic invasion, vascular invasion, and tumor differentiation (well-differentiated or moderatelydifferentiated). However, based on the established risk factors for disease-free survival, tumor depth ( $\geq 1,000$ or <1,000 µm) and tumor differentiation (well- to moderatelydifferentiated or poorly-differentiated) should be included in the model. We speculate that the differences in proposed models might be due to fewer patients having either poorlydifferentiated adenocarcinoma or submucosal cancer within 1,000 µm of tumor invasion. Third, disease-free survival in this study appears to be analyzed incorrectly. The 3rd table of the article demonstrated no recurrence in patients with low-risk submucosal colon cancer-however, Kaplan-Meier curves for disease-free survival showed that some lesions (perhaps three) had recurrence. In addition, Kaplan-Meier curves for disease-free survival were similar to overall survival curves. It seems, then, that disease-free survival of patients without recurrence of colorectal cancer and who died from other causes were considered as uncensored data. However, in disease-free survival analyses, such patients should be classified as censored data. Therefore, upon reclassification of the data, 5-year disease-free survival of patients with lowrisk submucosal colon cancer was 100.0% and not 95.9%. A similar error was also found in Kaplan-Meier curves for disease-free survival in patients from the high-risk endoscopic resection group. Although such errors may not alter the ultimate conclusions, they do question study reliability.

Despite these limitations, this was a strong study that revealed that risk of local recurrence following endoscopic resection was significantly higher in patients with highrisk submucosal rectal cancer than in patients with highrisk submucosal colon cancer. Why local recurrence occurs more frequently in high-risk submucosal rectal cancer as compared to high-risk submucosal colon cancer remains unanswered, although micrometastasis was suggested as a

plausible theory. Whether more extensive cancer excision with sufficient lateral margins improves disease-free survival in high-risk submucosal rectal cancer also remains unclear. Future studies should address these questions. At present, if an endoscopically-resected submucosal rectal cancer has been proven to be a high-risk lesion for lymph node metastasis, additional surgery should be considered to reduce not only distant metastasis but also local recurrence.

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#### Footnote

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# Commentary on transanal minimally invasive surgery for rectal lesions

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We read the article of Quaresima *et al.* (1) entitled "Transanal minimally invasive surgery for rectal lesions", published in *The Journal of the Society of Laparoendoscopic Surgeons*, with great interest.

The authors present a series of 31 consecutive patients, with mid and high rectal tumors, who were treated with TAMIS, between 2011 and 2016. The indications for the procedure were: T1 adenocarcinoma (54.8%), large adenomas (32.2%), GIST (6.5%), and carcinoid (6.5%). The mean distance of the lesions from the anal verge was 9.5 cm (range: 6-15 cm) and the mean tumor diameter was 2.4 cm (range: 1-5 cm). From the technical point of view, all patients had been placed in Lloyd-Davis position, two types of platforms (SILS and GelPath) were used and a full thickness rectal wall resection was the preferable surgical choice, while the rectal wall defect was sutured in all cases. In five patients intraperitoneal entry occurred, but in all of them, transanal suture of the defect was achieved without consequences. Although no conversion to laparotomy or laparoscopy was necessary, the method failed in two patients (6.5%) but even so, they were treated with the classic transanal technique. The postoperative complication rate was 9.6% and resection margins negativity was achieved in 96.8%. Within a mean follow up of 30 months, only one recurrence in a large adenoma, treated endoscopically, was observed.

The results of Quaresima's study (1) are in consistency with other published reports. The only systematic review (2) of 390 TAMIS resections, disclosed: a 3.0 cm average size of lesions resected, located within a mean distance of 7.6 cm from the anal verge (range: 3–15 cm), an overall margin positivity rate of 4.36%, a tumor fragmentation rate of 4.1% and an overall complication rate of 7.4%.

The largest single-center review of TAMIS outcomes (3) disclosed: a mean lesion size of 3.2 cm, located within a median distance of 10 cm from the anal verge, while malignant lesions represented the 22.7% of the study population. The platform used was either GelPath or SILS. In three patients there was intraperitoneal entry; that were closed transanally, postoperative complication rate was 4%, one patient had a fragmented lesion (1.3%), while five patients had positive resection margins. Within a median follow up of 39.5 months, recurrence was present in only one patient.

TAMIS is a fairly new technique and surgical community has not yet decided if it is a technique that is going to last in time. The results of TAMIS are mainly based on retrospective studies and case reports (4).

Current knowledge addresses that: TAMIS is defined as the use of any multichannel single-port which can be placed transanally, combined with the use of ordinary laparoscopic instruments, such as a laparoscopic camera (preferably a 5-mm, 30° or 45° lens) and a standard laparoscopic carbon dioxide insufflator for performing endoluminal and more recently, extraluminal surgery (5). There are approximately eight different platforms described in the literature, which has led to the creation of what is known as the TAMIS device or GelPOINT Path (3). Moreover, a "glove TEM port" has been (5) described and successfully used (6).

According to the NCCN guidelines (7), local excision of rectal tumors by using the TAMIS technique is clearly recommend for: (I) mobile/nonfixed rectal tumors; (II) less than 3 cm in size; (III) occupying less than 1/3 of the circumference of the bowel; (IV) not extending beyond the submucosa (T1); which are (V) well to moderately differentiated; and (VI) with low-risk histopathological features. On the other hand, local excision should be avoided in cases of lymphovascular invasion, perineural invasion and mucinous components which are considered as high-risk characteristics, with high lymph node metastatic potential.

The feasibility of the method is supported by all studies. The technique has a great adoption among the vast majority of colorectal surgeons, while surgeons are reluctant to adopt TEMS, mainly because of its cost and the steep learning curve (8). As pointed in the current study (1), none of the surgeons had previous experience with TEM technique, but all had substantial laparoscopic single-port device experience. Moreover, the TAMIS platform allows surgeons to translate familiar laparoscopic skills to transanal surgery, which is expected to result in rapid acquisition of the skills necessary for competency (9).

The results of TAMIS are mainly gathered retrospectively. Although the conversion rate to laparotomy or laparoscopy has been reported as 0% in Quaresima's *et al.* study, literature addresses a mean conversion rate of 3.1% (1). In the largest (n=75) multicenter series on TAMIS (10), intraoperative complications occurred in 8% and postoperative morbidity rate was 19%, with only one patient requiring re-intervention. In the only systematic review (2), overall complication rate was 7.4%. However, in the two most recent published reports (1,3) the complication rate has decreased to 4%.

The main intraoperative complication of the technique is the intraperitoneal entry, which occur more frequent in upper (more than 10 cm from the anal verge) and anterior (more than 8 cm from the anal verge) lesions (1). A recent report from Molina *et al.* (11), concludes that TAMIS has a higher risk of intraperitoneal entry in upper rectum tumors, mainly because of the shorter length of the platform. Thus, the authors advice the use of a longer or a rigid platform when approaching anterior and upper rectal lesions. Literature addresses that most of the defects can be sutured transanally (1,3).

The best method for the rectal wall defect closure after a full-thickness excision is still debated. Hahnloser *et al.* (10)

reported no difference in the incidence of postoperative complications whether the rectal defect was closed or left open. Our opinion is that if peritoneum is entered, the defect should be always closed, while a defect below the peritoneal reflection, may be left open (4).

The oncologic outcomes of TAMIS are based in short term results. Tumor fragmentation rate of 4.1% has been reported in the systematic review (2), while in the Quaresma *et al.* (1) study this rate dropped to 1.3%.

En block resection of the tumor is mandatory for R0 resection achievement, something not feasible with the endoscopic approach. R1 resection rate has been reported as 4.36% in the systematic review (2), as 3.2% in Quaresima *et al.* (1) study, while Keller *et al.* (3) reported 5 out of 75 patients with positive margins, 3 of whom were diagnosed with T2 tumors. Thus, patient selection is crucial for a favorable oncological outcome.

TAMIS has no impact to anorectal function, since the overall QoL was improved after the procedure, probably due to the removal of the tumor (12).

Finally, taking under consideration that the initial capital investment cost for TEM equipment is estimated at up to \$60,000 on average, while the TAMIS approach, carries a per procedure equipment cost of about \$500–650 over traditional laparoscopic surgery, makes the TAMIS procedure obviously cost-effective compare to TEMs technique (8,9).

In conclusion, as stated by Atallah *et al.* (13), TAMIS is giant leap forward. Its application in selected patients and under absolute indications can change the treatment for rectal cancer tumors.

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#### Footnote

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# Transanal minimally invasive surgery (TAMIS): validating short and long-term benefits for excision of benign and early stage rectal cancers

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It is with great pleasure that we provide commentary upon the manuscript entitled "Transanal Minimally Invasive Surgery for Rectal Lesions" by Quaresima *et al.* (1). This is a single-center case series of 31 patients undergoing local excision of mid- and upper-rectal tumors using a transanal minimally invasive surgery (TAMIS) platform. By translating their substantial prior expertise with single incision laparoscopic surgery to the use of the TAMIS transanal platform for the treatment of high rectal tumors, the authors demonstrate excellent results from their preliminary experience.

Though proctectomy with total mesorectal excision (TME) is the gold standard for curative resection of rectal cancers at any stage, such radical surgery has been associated with significant morbidity, mortality and impact on the patient's quality of life. Local recurrence rates for this procedure ranges 5–10% based on tumor stage, but because of the high morbidity and mortality, TME has been difficult to justify in the management of benign rectal lesions and early-stage rectal cancers (2,3). Therefore, transanal surgery has been in the arsenal of colorectal surgeons for the local excision of benign and early-stage rectal lesions for quite some time.

Conventional transanal excision (TAE), first described in 1963 by Parks, provides a direct approach via the natural anal orifice allowing avoidance of a stoma and the morbidity associated with abdominal surgery (4). The limitations of exposure within the anorectal lumen, however, pose a significant challenge to achieving a high-quality R0 resection. This is demonstrated by the high rates of margin positivity, tumor fragmentation, and local recurrence after TAE which have been reported as 29%, 35%, and 32% respectively (5). According to NCCN guidelines, successful TAE is thus limited to T1 lesions encompassing <30% of the rectal circumference,  $\leq$ 3 cm in size, and located within -8 cm from the anal verge (6). Additionally, these lesions should be mobile, non-fixed, well to moderately differentiated, and with clear margins >3 mm and no evidence of lymphovascular or perineural invasion (6).

In response to the challenges inherent with conventional TAE, Professor Buess *et al.* introduced transanal endoscopic microsurgery (TEM) in 1983 for the local excision of sessile polyps in the mid- and upper-rectum (7). Using a rigid TEM platform, better visualization and more precise dissection can be performed. This has provided improved outcomes relative to TAE, with rates of margin positivity, tumor fragmentation, and local recurrence at 10%, 6%, and 5%, respectively (5,8). A similar reusable, rigid transanal endoscopic operations (TEO) system has also been made commercially available, but unfortunately, TEM and TEO were never widely adopted due to the significant upfront cost of the rigid endoscopic platform and the specialized

instrumentation and the complex skill set it mandated from surgeons. Reimbursement in the United States was also problematic due to the lack of a category 1 CPT code.

It was not until 2010 when TAMIS was first reported by Atallah *et al.* as an alternative to TEM that the interest for transanal endoscopic surgery (TES) truly sparked (9). TAMIS is a hybrid between TEM and single-port laparoscopy, employing an alternative disposable platform compatible with standard laparoscopic equipment. The low upfront cost and availability of laparoscopic equipment in most operating rooms enabled surgeons in a variety of settings to apply their proficiency in laparoscopy towards TES. Currently, a number of case series describing TAMIS for the local excision of rectal lesions have demonstrated its safety and feasibility.

Review of all published TAMIS case series with  $N \ge 15$  highlight that among a total of 460 TAMIS procedures, indications for local excision using TAMIS include rectal adenoma with and without high grade dysplasia, neuroendocrine and carcinoid tumors, as well as incompletely resected benign and malignant polyps (Table 1) (10-21). Malignant indications predominantly include carefully selected T1 adenocarcinoma along with a minority of T2 and more advanced rectal tumors in patients deemed to be poor surgical candidates for radical resection and/or chemoradiation. The average size of the lesions and distance from the anal verge are 2.78 and 7.03 cm, respectively. TAMIS procedures were complicated by peritoneal entry in 10/460 cases (2.2%). Among the 10 incidences of peritoneal entry, 6 required laparoscopic assistance to close the rectal defect, and 1 required conversion to open laparotomy. The remaining 3 incidences of peritoneal entry were closed primarily with sutures placed transanally.

Regarding conversions from TAMIS to TAE, laparoscopic, or open surgery, one TAMIS case was converted to conventional TAE due to fibrosis secondary to prior radiation therapy for prostate cancer. A total of 5 cases were converted to laparoscopic low anterior resection (LAR) for reasons that included peritoneal entry, location of tumor above the recto-sigmoid junction, large size of the rectal defect after excision, large size of the tumor itself to where it could not be fully resected transanally. Two cases were converted to open LAR because of peritoneal entry and palliative debulking of a recurrent rectal cancer. There were 4 patients that required laparoscopic LAR after their TAMIS procedures due to upstage to pT2 on final pathology.

The overall average morbidity rate was 18.8% with the most common complications consisting of bleeding, urinary retention, and urinary tract infection (*Table 2*) (10-21). Among the 5 studies that reported length of stay (LOS), the average LOS was 2.2 days. The average follow-up ranged from 3 to 36 months, with most studies describing their results with a follow-up of less than one year. Overall rates of margin positivity, tumor fragmentation, and local recurrence were 6.4%, 5.6%, and 3.7% respectively.

The results by Quaresima et al. corroborate these findings and are slightly better. Indications for TAMIS included benign rectal lesions in 14 patients and T1 rectal cancer in 17 patients. Average tumor size was equivalent to that seen in other TAMIS series, i.e., 2.4 versus 2.8 cm. The average distance from the anal verge was higher, 9.5 vs. 7.0 cm, which may explain their higher rate of peritoneal entry (16.1% vs. 2.2%). That being said, there were no conversions to laparoscopic or open abdominal surgery, and all cases of peritoneal entry could be closed transanally. Complications occurred in 3 (9.6%) patients and included urinary tract infection, subcutaneous emphysema, and hemorrhoid thrombosis. In this series, R0 resection was achieved with TAMIS in 96.7%, with a 100% rate of en bloc resection and a 3.7% local recurrence rate at a mean follow-up of 30 months. The authors must be commended for the low margin positivity rates and low recurrence rates achieved at a relatively longer follow-up interval relative to other published TAMIS series, which suggests careful patient selection and excellent surgical technique, despite the fact that the sample size of this series is relatively small.

The limitations of this manuscript include the fact that the operating time was not described, nor was the final pathology of the resected specimens. This would have been of interest to evaluate whether any of the resected lesions were upstaged based on final pathologic assessment. Finally, functional outcomes, which only 5 out the 12 largest TAMIS series have reported on, are not described in this report. This would have been of particular interest given the current series' relatively long mean follow-up of 30 months. One of the proposed main advantages of TAMIS, relative to TEM and TEO, is the shorter set up and operative time, as well as possibly reduced trauma to the anal sphincters by using softer and more pliable platforms. Unfortunately,

Table 1 Patient characteristics and	d intraoperative data	from published clip	nical series of TAM	AIS with N>15
<b>TADIC I</b> I AUCHI CHAIACICHISUCS and	a muaupurative uata	moni published en	incar series or rrus	$/110$ with $1\sqrt{-1}$ .

Author	Ν	Indications (B:M)	s Mean tumor size (cm)	Mean distance from AV (cm)	Transanal platform	Operative time (min)	Peritoneal entry	Conversion
Lim <i>et al.</i> , 2012 (10)	16	5:11	0.84 (0.2–1.5)	6.9	SILS	91	NR	0
Albert <i>et al.</i> , 2013 (11)	50	23:27	2.75 (0.7–6.0)	8.2	SIIS, GelPOINT	75	1	1 Iaparoscopic LAR
Lee <i>et al.</i> , 2014 (12)	25	21:4	2.4 (0.5–6.0)	9.2	SILS	52	0	2 Iaparoscopic LAR
McLemore <i>et al.</i> , 2014 (13)	32	16:16	3 (1.0–5.0)	4	SIIS, GelPOINT	123	NR	1 TAE
Maglio <i>et al.</i> , 2014 (14)	15	5:10	3.5 (2.5–5.0)	7	GelPOINT	86	NR	NR
Hahnloser <i>et al.</i> , 2014 (15)	75	37:38	NR	6.4	SILS	77	3	2 laparoscopic LAR, 1 open LAR
Schiphorst <i>et al.</i> , 2014 (16)	37	NR	18.0 (4.5–56.0) (cm <sup>2</sup> median)	7 (median)	SILS, SSL	64	2	1 Iaparoscopic LAR
Gill <i>et al.</i> , 2015 (17)	32	11:21	2.1 (0.3–5.0)	7.5	GelPOINT	131	0	0
Sumrien <i>et al.</i> , 2016 (18)	28	17:11	4.4 (0–11.5)	NR	SIIS, GelPOINT	<60	1	2 laparoscopic LAR, 1 open LAR
Haugvik <i>et al.</i> , 2016 (19)	51	26:22	3.2 (0.4–6.0) (median)	8.0 (median)	SIIS, GelPOINT	40 (median)	NR	NR
Verseveld <i>et al.</i> , 2016 (20)	24	20:4	6 (0.25–51.0) (cm <sup>2</sup> median)	8.0 (median)	SSL	32 (median)	NR	NR
Keller <i>et al.</i> , 2016 (21)	75	57:17	3.2 (SD 3.1)	10 (median)	SIIS, GelPOINT	76	3	1 LAR, 2 diagnostic laparoscopy with ileostomy creation
Total	460	242:177	2.8	7.0		32–131	10 (2.2%)	12
Quaresima <i>et</i> <i>al.</i> , 2016 (1)	31	14:17	2.4 (1.0–5.0)	9.5	SILS, GelPOINT	NR	5 (16.1%)	2 TAE

B, benign; M, malignant; SILS, single incision laparoscopic surgery; SSL, single site laparoscopy; SD, standard deviation; NR, not reported; LAR, low anterior resection; TAE, transanal excision.

there continues to be a lack of data to support the validity of these propositions.

With the growing experience with TES, indications have recently expanded to include transanal endoscopic proctectomy with complete rectal and mesorectal dissection for locally invasive rectal cancer, with TAMIS becoming the transanal platform of choice. That being said, TAMIS for the local excision of benign and low-grade rectal lesions remains a relatively new technique lacking long-term clinical and oncologic outcomes. The published work by Quaresima *et al.* represents their initial experience with TAMIS. Thanks to their extensive prior experience with single incision laparoscopic surgery and careful patient selection, their demonstrated results are equivalent or slightly better than those reported in the TAMIS literature. This work is an important contribution to validate the short and long-term benefits of TAMIS as a safe platform for local excision of benign and early rectal cancers.
Table 2 Postope	rative (	outcomes of publis	thed clinical ser	ries on TAMIS w	vith N>15					
Author	z	Tumor fragmentation	Positive margins	Pathologically upgraded	Intraoperative complications	Morbidity	Mean LOS (days)	Mean follow-up (months)	Local recurrence	Functional outcomes
Lim <i>et al.</i> , 2012 (10)	16	0	ο	NR	NR	0	3.6	ĸ	NR	RN
Albert <i>et al.</i> , 2013 (11)	50	2 (4.0%)	3 (6.0%)	1 (2%)	က	3 (14.0%)	0.6	20.2	2 (4.0%)	RN
Lee <i>et al.</i> , 2014 (12)	25	0	0	5 (20%)	0	1 (4.0%)	3.0 (median)	9.8	0	None
McLemore <i>et al.</i> , 2014 (13)	32	0	0	1 (3%)	0	11 (28.0%)	2.5	2–23 (range)	0	Fecal incontinence [3] resolved in 2–4 weeks
Maglio <i>et al.</i> , 2014 (14)	15	N	0	0	0	0 (0.0%)	2.0 (median)	9	0	RN
Hahnloser <i>et al.</i> , 2014 (15)	75	6 (8.0%)	3 (4.0%)	0	7	15 (27.0%)	3.4 (median)	12.8 (median)	NR	Normal continence per Vaizey score 1.5
Schiphorst <i>et al.</i> , 2014 (16)	37	0	6 (16.2%)	NR	0	4 (14.0%)	1.0 (median)	11 (median)	2 (5.0%)	Improvement in FISI
Gill <i>et al.</i> , 2015 (17)	32	0	0	NR	RN	11 (50.0%)	1.1	2.7	2 (6.3%)	RN
Sumrien <i>et al.</i> , 2016 (18)	28	0	6 (21.4%)	ЯN	Ŋ	9 (50.0%)	1.5	NN	2 (7.1%)	ICIQ bowel symptoms questionnaire, median score 15
Haugvik <i>et al.</i> , 2016 (19)	51	16 (31.0%)	11 (22.0%)	17 (33%)	0	6 (12.0%)	1.0 (median)	7.0 (median)	NR	RN
Verseveld et al., 2016 (20)	24	0	0	ЯN	0	1 (4.2%)	1.0 (median)	7.0 (median)	NR	5 patients/minor deterioration in FISI score
Keller <i>et al.,</i> 2016 (21)	75	1 (1.3%)	5 (6.7%)	5 (6.7%)	0	3 (4.0%)	1.0 (median)	36.5 (median)	5 (6.7%)	RN
Total	460	25 (5.6%)	34 (6.4%)			64 (18.8%)			13 (3.7%)	
Quaresima <i>et al.</i> , 2016 (1)	31	0	1 (3.2%)	NR	RN	3 (9.6%)	б	30	1 (3.7%)	RN
FISI, fecal incon	tinenc	e severity index; I	CIQ, Internatic	onal Consultatio	on Incontinenc	ce Modular Que	estionnaire; LOS	, length of stay; N	IR, not reporte	d.

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# Footnote

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

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# Transanal approach for rectal tumors: recent updates and future perspectives

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**Abstract:** Local excision of rectal tumors has long been performed. With the development of new technologies for endoluminal operation, there have been significant advances in the transanal approach in the last 30 years. It started with conventional transanal excision (TAE) and was developed by introduction of transanal total mesorectal excision (taTME). Appropriate patient selection for transanal approaches is the key for good outcomes. TAE of rectal tumors has been advocated for premalignant lesions and used as definitive treatment for early rectal cancers in select groups without adverse prognostic features. Regardless of procedures, the morbidity and mortality of tansanal technique are lower than for radical surgery. According to the experience in the last decades, transanal endoscopic surgery has been accepted as effective treatments in selected patients with early rectal cancer, with similar oncologic outcomes to and better functional effects than those of radical surgery. The latest development in transanal approaches is taTME. Although taTME is another new technique with great promise, the supporting data are preliminary, and further studies with larger cohorts of patients are needed to evaluate long term functional and oncological outcomes. Transanal approaches including taTME should be considered as good options for the treatment of rectal cancer because these techniques are definitely useful in selected patients.

Keywords: Transanal approach; rectal tumors; transanal endoscopic surgery

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#### Introduction

Local excision of rectal tumors has long been performed. The transsphincteric and transcoccygeal approaches had been used for local excision, especially for high-lying rectal tumors. The transcoccygeal (Kraske) approach requires mobilization of posterior pelvic floor muscles away from the coccyx to expose the rectum and the transsphincteric (York-Mason) approach involves complete division of the anal sphincter. With the development of new technologies for endoluminal operation, the transsphincteric and transcoccygeal approaches are rarely used today. Transanal excision (TAE) was first described by Parks as an alternative endoluminal treatment for certain rectal tumors in 1970 (1). After 10 years, anorectal surgical procedures with the use of different endoscopic devices into the anal canal were introduced. Transanal endoscopic microsurgery (TEM) was first described by Buess *et al.* in 1984 (2). A few years later, a newer and simpler alternative transanal endoscopic operation (TEO), was introduced and widely implemented. Maeda *et al.* (3,4) proposed a new transanal local excision procedure, minimally invasive transanal surgery (MITAS), for excising a proximal tumor at more distal sites. Recently, transanal minimally invasive surgery (TAMIS) has become increasingly more popular.

Selecting the appropriate surgical approach to rectal tumors is important. The approach must balance successful tumor eradication with functional implications for the patient. Owing to the significant morbidity and alterations in quality of life associated with rectal surgery (low anterior resection and abdominoperineal resection), a lot of time and research have been devoted to transanal approaches for rectal tumors. Several retrospective studies since the 1970s reported that TAE of early tumors with negative margins may provide similar outcomes those of radical resection (5). Since then, there had been many studies assessing the role of TAE of rectal cancer (6). Thereafter, the use of TAE had increased to 17.1% for T1 lesions and 11% for T2 lesions from 1989 to 2003 (7).

During the recent decades, total mesorectal excision (TME) has become the standard technique for the surgical treatment of rectal cancer (8). Nowadays, transanal TME (taTME) has been proposed as a new option in cases for which laparoscopic transabdominal TME (laTME) is difficult. TaTME is not a completely novel concept and it has benefited from previous experience of transabdominal-transanal (TATA) operations, TEM, TAMIS and natural orifice transluminal endoscopic surgery (NOTES) (9-11). Since the first taTME resection assisted with laparoscopy was reported in 2010 (12), taTME has shown promising results with regard to pathological quality and short- and mid-term outcomes (13-15).

#### **Indication for TAE to rectal tumors**

Local excision of rectal tumors has been advocated for premalignant lesions and used as definitive treatment for early rectal cancers in select groups without adverse prognostic features (16). Atypical rectal tumors such as neuroendocrine tumors and gastrointestinal stromal tumors are also usually approached through the transanal.

Local excision is suitable for Tis (carcinoma *in situ*) or T1 cancers with a favorable histology. The criteria for local treatment include T0 or Tis lesions; low-risk differentiated (well-to-moderately) T1 cancer; absence of lymphatic, vascular, or perineural invasion; and tumors  $\leq 3$  cm in diameter occupying  $\leq 40\%$  of the circumference of the rectal lumen. These principles apply to all local excision techniques. However, with the development of the technique and increased experience of surgeons, the indications have expanded. These technical approaches have extended beyond local excision, with the development of taTME being the most important in

recent years. Additionally, for accurate patient selection, routine preoperative cardiopulmonary assessment, physical examination with digital rectal examination, fecal incontinence test, endoscopy, trans-rectal ultrasound (TRUS), and in case of malignancy; complete staging workup with pelvic magnetic resonance imaging and abdominal computed tomography, are recommended. For determining local excision, local T staging should be accurate. TRUS allows predicting early T1 lesions that might be suitable for local excision. Hildebrandt *et al.* (17) proposed a preoperative tumor staging system based on ultrasonic determination of the infiltrative depth of tumors, so-called uTNM, and this technique contribute to a more accurate determination of the depth of invasion with classification of the rectal wall layer.

#### **Techniques for the transanal approach**

- ✤ Conventional TAE.
- ✤ MITAS.
- Transanal endoscopic surgery (TES).
  - TEM;
  - TEO;
- TAMIS;
- ✤ taTME.

# TAE

TAE has been the mainstay of treatment for many years. TAE is a simple method that can be easily performed if the tumor is located in the anal canal and easily accessible under adequate exposure of the anal canal. There is no need for additional equipment, and it can be performed in the outpatient department. An additional benefit to this approach is the minimal, if any, compromise of anorectal and urogenital function. These factors make TAE the most common method of local excision (18).

Conventional TAE is often limited to tumors  $\leq 4$  cm in diameter that lie within 6–8 cm of the anal verge (16). Lesions in the middle and upper rectum are usually inaccessible with TAE because of their distance from the anal verge, and attempted excisions are hampered by inadequate surgical exposure, confinement of the operating field, and uncertainty of a clear surgical resection margin (19).

Patients should undergo preoperative assessment including digital rectal examination and rigid sigmoidoscopy to confirm location and mobility. Patients receive a cleansing enema the day before the operation; prophylaxis with antibiotics and antithrombotics is usually recommended. After the induction of local, regional, or general anesthesia, the patient is placed in position. Some authors additionally propose pudendal nerve block for sphincter relaxation. The positioning of the patient is dependent on the preference of the surgeon; however, the orientation of the lesion is usually the deciding factor, with preference taken to operating downward. Most operations are performed with the patient in the prone jackknife position; however, some posteriorly located lesions may be better approached with the lithotomy position. The perianal area is exposed by taping the buttocks apart; the lesion is exposed with direct vision by using a Hill Ferguson, Park, or Barr retractor. Traction sutures can be placed distal to the lesion to improve visualization. The calculated excision margin (10 mm) is typically marked by using electrocautery in a circumferential pattern around the lesion. The specimen must be carefully taken so as not to manipulate the lesion or handle it with instruments. After a full thickness excision of the lesion, the specimen is oriented on a needle board and sent to the pathology laboratory. After irrigation, the defect can be either left open or closed transversely with absorbable sutures. If the lesion is posterior to the rectum and above the puborectalis muscle, the defect is closed with absorbable sutures. In case of anteriorly located lesions, repair should be conducted to avoid injury of adjacent structures, such as the prostate, urethra, or vagina. At the end of the procedure, a proctoscopic examination is essential to confirm that the rectal lumen was not inadvertently closed or narrowed.

Complications associated with TAE include urinary retention, urinary tract infection, infections of the perirectal and ischiorectal space, fecal impactions, and delayed hemorrhage. Nevertheless, the incidences of these complications and mortality are very low. TAE has several limitations. In general, this approach is technically difficult with higher lesions owing to poor visualization. More important, visualization during TAE can be suboptimal, which can affect the quality of an oncologic resection margin. Concerns have also been raised about the high rates of tumor fragmentation and recurrence with TAE. The high rates of recurrence are likely due to rates of margin positivity that exceed 10% in even the most experienced and expert case series (6,18). Patients treated with TAE compared with those treated with radical surgery for T1 rectal cancer had a significantly higher 5-year local recurrence rate (12% vs. 6%) and lower 5-year survival rate (70% vs. 80%) and 5-year disease-free rate (64% vs. 77%) (20).

#### MITAS

A new transanal local excision procedure, MITAS, has been developed with a specially designed anal retractor connected to the Octopus retractor holder, a stapler device, and several newly developed techniques to excise a proximal tumor at a more distal site (21).

Operation was usually performed under spinal anesthesia with the patient in lithotomy or jackknife position, according to the site of tumor (4). The procedure consists of inserting into the rectum an originally designed E- or F-type anal retractor [a modified K-type anal retractor (22); Yufu Itonaga Co Ltd.] connected to the Octopus retractor holder, long type, 22 inches (Mednosbro AG).

To enable excision of a proximal tumor at a more accessible site, shortening or roll-in technique, intussusception, or invagination technique with retraction stitches is used. The retractor is inserted into the anus and rolled to pull the rectum in and permit easy access to the tumor in the proximal rectum (3). When the tumor is still beyond the surgical field, the retractor is opened and fixed and two Babcock forceps are used to pull the tumor gradually (21). Retraction stitches are passed under the tumor, from one side to the other with a minimum macroscopic margin of 5 mm from the boundary of the tumor to the adjacent normal mucosa by a 36-mm-long atraumatic needle with absorbable 1-0 thread, enough to retract the tumor fully and pull the rectum down. ENDO GIA (Tyco Co Ltd.) is used for excision and anastomosis while fully retracting the rectum with retraction stitches distally. Application of a stapler is usually done transversely, but oblique application is sometimes needed because of the difficult angle in the rectum or size of the tumor.

# TES

# TEM

Gerhard Buess of Germany pioneered TEM (Richard Wolf, Germany) in the early 1980s as a minimally invasive technique allowing the resection of adenomas and early rectal carcinomas unsuitable for local or colonoscopy excision, which would otherwise require major surgery (23). This method was basically designed from the idea of laparoscopic surgical techniques so-called because it is a minimally invasive technique and has proved to be useful for treating lesions in the mid or upper rectum. The main indications for TEM are rectal tumors that are out of reach for TAE and are unsuitable for endoscopic removal (24).

In addition, this technique can even be extended to lesions in the low sigmoid colon, with success reported up to 20 cm from the anal verge (25). Since its development, TEM has been also used for a variety of other rectal pathologies including neuroendocrine tumors, rectal prolapse, early stage carcinomas, and palliative resection of rectal cancers (26).

The orientation of the lesion is usually the deciding factor for the positioning. The lesion needs to be situated at the 180 degree angle of the scope view. For a posterior lesion, the patient is placed in a lithotomy position. For an anterior lesion, the patient is placed in the prone jackknife position. The operative technique for TEM involves three main components: a rigid operating rectoscope, a laparoscopic camera, and modified laparoscopic instruments. The operating rectoscope is typically 4 cm in diameter and varies from 12 to 20 cm in length. The rectoscope maintains an airtight seal at the anus once inserted in the rectum, and is held in place by the obligate articulating arm, which fixes the rectoscope to the operating table. The rectoscope has a port for the inflow of CO<sub>2</sub> for the pneumorectum, and an outflow for smoke evacuation during cauterization. The faceplate on the rectoscope has four ports through which a stereotactic telescope with connection to a three-dimensional video system and three modified laparoscopic instruments are connected to facilitate dissection and suturing (26). While the instruments are specialized, the operative steps are otherwise no different than for TAE. The lesion is then centered in the scope view. By using scissors, cautery, and graspers, a dotted line is burned around the target lesion with a 10-mm margin. Care must be taken to avoid trauma to and fragmentation of the specimen. After homeostasis is obtained, the defect is closed with absorbable full-thickness sutures in a transverse line. The defect can be left open to heal secondarily if the defect is posterior and surrounded by mesorectal fat. An anterior defect must be closed; closure is facilitated by placing a central stay suture and sewing from each corner to avoid tension on the suture line.

The limitation of TEM is that the equipment is designed to operate from the top-down; thus, the lesion must be oriented toward the floor to be compatible with the equipment. This means that the patient's positioning is dependent on the tumor location, and sometimes specialized split-leg operating tables are necessary to resect anterior tumors requiring the prone jackknife position. Distal lesions near the sphincter are difficult to excise with TEM owing to the configuration of the equipment and inability to maintain insufflations of  $CO_2$  to distend the rectum. This is the reason why TAE is easier to use for low-lying lesions. Other limitations to TEM focus on specialized equipment, which have a steep learning curve and high associated costs for the hospital (27,28).

#### TEO

A few years later a cheaper alternative was introduced compared with TEM. The TEO (Karl Storz, Germany), which was a newer and simpler system, has become widely implemented. Indication of TEO is similar to TEM.

TEO platform was performed in a lithotomy position using a 30° forward-oblique telescope, adequate adjustment of the rectoscope, and curved laparoscopic operating instruments. TEO procedure was carried out under general anesthesia. After installation of the holding system, the anus was gently dilated, and the operating rectoscope (7.5 or 15 cm long, 4 cm in diameter) with obturator was inserted in the rectum with copious lubricant and fastened to the support arm attached to the operating table. The working attachment used with the rectoscope had two channels for instruments of 5 mm and one channel for instruments up to 12 mm. After achieving the pneumorectum with insufflations of CO<sub>2</sub> to 12 mmHg or more, a high definition (HD) 5-mm diameter endoscope with fiber-optic light transmission and 30° angled view was inserted through a 5-mm endoscope channel and the rectoscope was adjusted to achieve the best position for procedures (Figure 1A). Except the instruments are specialized, the operative steps are otherwise no different than those for TEM.

Similar to TEM, lesions near the anal verge are difficult to excise with the TEO. Standard laparoscopic instruments, equipment, and set up costs are lower, potentially opening the technique to any surgeon with previous laparoscopic experience. Hur *et al.* (29) performed initial experience of TEO and reported the mean operative time was 85 minutes, and the mean postoperative hospital stay was 4.5 days, a positive resection margin was documented for 9% patients. Furthermore, they demonstrated that according to the cumulative sum analysis, the operation time and hospital stay significantly decreased after 17 case experiences (29). Several studies have compared TEO with TEM for benign and malignant lesions and have shown satisfactory outcomes (30,31).

### TAMIS

In recent years, TAMIS has become increasingly more popular. Reported by Atallah *et al.* (32) in 2010, the



Figure 1 Procedure and position for TEO (A), single-incision assisted laparoscopic surgery port (B), GelPOINT path transanal access platform (C), glove port for robotic TAMIS (D). TEO, transanal endoscopic operation; TAMIS, transanal minimally invasive surgery.

technique stems from the use of a single port initially designed for abdominal surgery. Since the inception of TAMIS, at least 390 procedures were reported worldwide from 2010 to 2013 (33). This technique uses a single, disposable, multichannel port inserted into the anus as opposed to the rigid operating rectoscope. Currently in the United States, two ports are approved for TAMIS by the Food and Drug Administration: single-incision assisted laparoscopic surgery port (Covidien, USA; *Figure 1B*) and GelPOINT Path Transanal Access Platform (Applied Medical, USA; *Figure 1C*).

The indications of TAMIS are the same as those of other TES. The main benefits of TAMIS are the relative ease of use and low cost, owing to the use of conventional laparoscopic instruments, including a laparoscopic camera, graspers, energy sources, and a standard laparoscopic  $CO_2$  insufflator. It is ideal for lesions at 8–12 cm from the anal verge; however, it has been successfully performed in the

lower and mid rectum (34). Distal lesions are covered by the transanal port, and excision of very proximal lesions can cause entry into the peritoneal cavity.

Mechanical bowel preparation or enema, antibiotics and antithrombotic prophylaxis are usually recommended. Anesthesia may be general or spinal. Lee *et al.* (35) have reported a series of 25 TAMIS procedures in which spinal anesthesia was used. In TAMIS, most lesions can be excised with a lithotomy position. However, we still recommend the prone position for the patients with large anterior lesions, especially if the distance from the anal verge is in a range in which there might be a risk of perforating the peritoneum. After the patient is positioned and the port is placed, pneumorectum is achieved with the standard  $CO_2$ insufflator, with pressures ranging from 15 to 25 mmHg. Several different cameras can be employed, including those with a flexible tip. One common practice is to use the 5-mm, 30-degree bariatric camera with a right-angle light cord

adaptor. Conventional graspers, scissors, and electrocautery devices are employed, along with ultrasonic or bipolar energy devices as needed. Owing to the technical challenges of suturing in this confined working space, many techniques similar to TEM have been employed, including the use of clips and beads, barbed suture, and specialized suturing devices.

When compared with other platforms, TAMIS has several advantages. Devices that are used for TAMIS are more pliable than the 40-mm rigid scope used for TEM, and possibly lead to less impairment of sphincter function; the set-up time is significantly lower for TAMIS. Use of regular conventional laparoscopic instruments, as opposed to the fixed evepiece of the TEM rectoscope, enables advancing the scope into the proximal rectum to look beyond the tumor. TAMIS is easily learned by surgeons because of its simplicity and similarity with conventional laparoscopic surgery, and it is a cost effective alternative to TEM (32). For some authors, the introduction of the TAMIS port into the anal canal makes it more complex than TEM or TEO (36). A disadvantage of TAMIS is that the rectoscope cannot be mobilized at the site of the lesion; rectal lesions behind a rectal haustral valve may be more difficult to access and remove. The longer channels associated with TEM and TEO equipment facilitates intraluminal rectal retraction. Moreover, an assistant is required to hold and manipulate the laparoscope during the TAMIS procedure.

The authors who introduced TAMIS went on to describe the use of a robotic platform for TAMIS in a cadaveric model in 2011 (37), and then extended that robotic TAMIS platform to live patients in 2012 (38). Since then, its use in in humans has been described with both the GelPOINT Path platform (Applied Medical, USA) and a glove port (*Figure 1D*) (39).

The authors suggested that the transanal glove port facilitated the robotic setup, enabling flexibility and allowing docking of the cannulas away from the limited perianal workspace (40). Furthermore, the glove port provided a wider axis of movement for instruments inside the rectum, or allowed them to be easily rotated and/or crossed. Although robotic TAMIS has been shown to be feasible, this technique is still relatively new, and more studies are necessary before to widespread adoption.

### Postoperative complication of TES

Regardless of procedures, the morbidity and mortality are lower than for radical surgery. Operative mortality is less than 0.5% and morbidity ranges from 4% to 30% in large series, depending on the inclusion of minor complications. The most frequent complications include acute urinary retention, bleeding requiring reoperation, abdominal perforation and recto-vaginal fistula (41). Kumar et al. (42) found that complications correlate with tumors located laterally and more than 8 cm from the anal verge. Pelvic sepsis, which occurs in about 3% of cases, is more common in lesions within 2 cm of the dentate line. The conversion rate to TAE is around 5%, and the main reason for conversion is technical difficulties (24,26). Peritoneal perforation, which was thought to represent a complication requiring conversion to laparotomy, can usually be salvaged with TES for experienced surgeons (43,44). A multicenter study by Baatrup et al. (45), performed by using database of 888 TEM procedures, found 22 perforations in the peritoneal cavity. They reported no association with major short term complications or adverse long-term oncological outcomes (45).

#### **Outcomes of TES**

Radical surgery with TME is still the treatment of choice for rectal cancer, offering patients the best results in terms of local recurrence and survival (46). However, TME is associated with significant mortality and morbidity (47). According to the experience in the last decades, TEM and TEO have been accepted as effective treatments in selected patients with early rectal cancer, with similar oncologic outcomes to and better functional effects than those of radical surgery (48,49). Recently, TAMIS has been proposed as an alternative technique; however, the experience with this approach for rectal cancer is still limited because of short follow-up (27,33,50-55).

TEM has a lower positive resection margin rate than TAE, with less fragmented specimens and better oncologic outcomes (56,57). Elmessiry *et al.* (50) showed that TAE was an independent predictor of local recurrence compared with TEM. The rate of reported positive resection margin in the surgical specimen in TAMIS was 4.4–6% (27,33,54), similar to those obtained with TEM, and seems to be related with the T stage (26,58,59). Some studies have compared TEM with radical surgery in early rectal cancer, showing similar results in terms of local recurrence and survival (60,61). In a meta-analysis, Winde *et al.* (62) demonstrated that the rate of local recurrence was higher with TEM (12% *vs.* 0.5%); however, no difference in survival was found.

TES seems to be a reasonable alternative to radical surgery in patients with low-risk rectal cancer (26,41,47,

48,52,61,63,64) with local recurrence rates ranging from 0% to 39%. These wide differences in range can be explained by the heterogeneity of cases, different selection criteria, risk characteristics, and surgical techniques; however, most local recurrence rates are under 10% (24,26,60,62,65-70). TES alone is not appropriate for patients with T2 or worse tumors, considering that the risk of local recurrence varies between 9.5% and 47% (24,26,47,52,58-61,64,68-72). However, even in these studies there are considerable differences between low- and high-risk cancers (73). TES may be performed on patients with high-risk T1 or T2–3 tumors with poor life expectancy and severe morbidity, or those unfit for major surgery, or simply as palliative treatment in case of disseminated disease (47,61,63).

Salvage surgery for recurrence after TES demonstrated disappointing oncologic outcomes; the stage is usually more advanced than in primary lesions and may require multivisceral resection and an ostomy in up to 43% of cases. Survival is seriously compromised, with a 5-year survival ranging from 43% to 68%, dropping to 29% in patients with unfavorable histology (63,68,74). In contrast, Levic *et al.* did not find any difference in outcome between patients with rectal cancer undergoing immediate salvage TME after TEM and those undergoing primary TME (75). Despite contrasting conclusions, all authors warned that perforations into the original operating field during subsequent TME can occur owing to fibrotic changes to the bowel wall, which might allow microscopic tumor spillage.

#### **Future perspectives**

Several new techniques and approaches are still under investigation, currently in preclinical or experimental stages, such as transanal natural orifice transluminal endoscopic surgery (NOTES), taTME, and robotic-TES (26,51,76). TES platforms seem to be safe for both transanal NOTES and taTME (77,78). Robotic technology can lower the difficulty inherent in TES platforms (79). However, clinical trials are necessary for full evaluation of these techniques.

## taTME

The latest development in transanal approaches is taTME. Transanal TME was introduced in 2010 with the aim to cope with all these limits and improve the quality of mesorectal dissection even in the most challenging cases (11). Dissection of the distal rectum according to TME principles may be somewhat cumbersome in cases of narrow pelvis, bulging tumors, and obese patients. In adequate exposure and loss of the good plane of dissection require finding another alternative treatment approach. During the last decade, transanal approaches have been extensively used to overcome the inherent shortcomings of laTME (69,77). Among these emerging transanal techniques, taTME is a new minimally invasive procedure with the essential aim of improving oncological treatment quality and avoiding pelvic nerve injury in patients with mid or low rectal cancer. Given the encouraging outcomes of systematic investigation of taTME for patients with rectal cancer (80,81), taTME may be optimized as a surgical approach for rectal cancer. In comparison with conventional laTME, taTME defines the distal resection margin more precisely, with better visualization of the distal rectum, and allows the surgeon to perform deep pelvic dissection without the need for difficult retraction (82). However, the benefits of taTME compared with laTME must be confirmed before conducting multicenter randomized controlled trials (RCTs) and unifying taTME procedures. According to a meta-analysis study, the percentage of patients with complete mesorectum was 83.4% in the taTME group and 73.4% in the laTME group (83). In addition, achievement of complete plus near complete mesorectum was also greater in the taTME group (95.3% vs. 88.2%) (83). Hence, for patients with mid or low rectal cancer, taTME may achieve a complete or near complete resection of the mesorectum relative easily, compared with laTME. However, whether a higher quality of mesorectal resection will result in good survival remains unknown. Safety is always the most important issue for a new technique. The meta-analysis indicated a comparable rate of intraoperative complications and a significantly lower incidence of postoperative complications in the taTME group than in the laTME group (83).

As the new surgical technique of taTME is adopted increasingly by surgeons, the patient selection criteria will be crucial and will continue to inspire debate. Of note, the protocol published recently for a multicenter RCT comparing taTME with laTME (COLOR III) has formulated strict criteria for patient selection (84). According to the selection criteria of this protocol, T3 tumors with margins <1 mm to the endopelvic fascia, tumors with ingrowth in the internal sphincter or levator ani muscle, and all T4 tumors staged before preoperative therapy were excluded (84). However, the nature of the surgical candidates best suited to taTME treatment requires further studies.

In a matched case-control study from Taiwan, Chen

et al. (85) demonstrated that compared with laTME, taTME not only achieves identical circumferential margin status without compromising other operative and quality parameters but also benefits patients by achieving a longer distal margin. Additionally, Denost et al. (86) performed a randomized trial in France, and reported that the rate of positive circumferential resection margin decreased significantly after taTME compared with abdominal low rectal dissection (4% vs. 18%; P=0.025). Currently, RCTs examining taTME are under way; the COLOR III study has been designed to compare taTME versus laTME for mid and low rectal cancer. TaTME is expected to be superior to laTME in terms of clear circumferential resection margins in case of mid and low rectal carcinomas (84). Although taTME is another new technique with great promise, the supporting data are preliminary, and further studies with larger cohorts of patients are needed to evaluate long term functional and oncological outcomes.

#### Conclusions

There have been significant advances in the transanal approach in the last 30 years. Appropriate patient selection is the key for good outcomes. These techniques have enabled mid and upper rectal lesion and sphincter salvage, leading to a better quality of life. From the point of view of technical advancement, it would be better to adopt this technique as a treatment option, and prospectively randomized comparison clinical trials should be conducted. When we are planning treatment for patients with early rectal cancer, the risk of local recurrence must be balanced with the quality of life. Nowadays, transanal approaches including taTME should be considered as good options for the treatment of rectal cancer because these techniques are definitely useful in selected patients.

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# Footnote

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

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# Transanal minimally invasive surgery is becoming more commonly used for rectal lesions

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Traditionally, rectal neoplasms were managed via transanal excision (TAE) with a retractor. However, TAE is limited to tumors that are located within the lower rectum, and lacks precision and visibility. Transanal endoscopic microsurgery (TEM) was introduced to improve the precise dissection and en bloc excision of tumors located in the mid to upper rectum, with stable visualization, in the early 1980s by Buess et al. (1). Transanal minimally invasive surgery (TAMIS) was subsequently developed as a novel approach for rectal lesions in 2009 (2). This procedure offered a feasible alternative to TEM and is becoming more commonly performed worldwide; in fact, several articles regarding this technique have been published. In particular, the article entitled "Transanal minimally invasive surgery for rectal lesions" by Silvia and colleagues revealed that TAMIS is a feasible and safe technique in benign and malignant tumors located in the mid to upper rectum (3).

Silvia and colleagues performed TAMIS in 31 patients with rectal tumors. They used a platform such as SILS PORT or Gelpath and laparoscopic instruments. The patients were placed in the Lloyd-Davis position and most received general anesthesia. The authors closed the surgical defect with interrupted or running barbed sutures. The study showed excellent results compared to previous studies. The postoperative complication rate was 9.6% (3/31) in that study, although previous studies reported an average rate of 16.5% (range, 0–23%). The R0 resection rate was 96.8% (30/31), and there was no local recurrence overall mean follow-up of 30 months. Thus, the study of Silvia emphasized the benefits of this new technique and indicates its potential. Our center reported the feasibility of TAMIS for mid rectal lesions 4 years previously (4). There are similarities between these two studies in terms of indications, preparation, and surgical techniques; on the other hand, the differences include patient position and suture technique, depending on the surgeon's preferences.

One of the advantages of TAMIS is the use of accessory devices such as automated suturing devices and knot pusher. These devices offer significant aid during the more technically difficult parts of TAMIS, such as the closure of the surgical defect. When the rectal lesion site is surrounded by the mesorectum, the unsutured surgical defect can be considered safe (5). However, data on this topic are limited, and Carl *et al.* reported that open management of the rectal defect after TEM can lead to additional postoperative complications and readmission to hospital (6). In our experience with knot pusher, the surgical defect can be closed using interrupted absorbable sutures without difficulty, without any wound-associated complications. The pneumorectum had deflated during tying, but recovered quickly; thus, the procedure was tolerable.

Most of the reports on transanal endoscopic surgery involve TEM, and describe its advantages and disadvantages. TEM facilitates the local excision of large polyps and early rectal cancers located in the mid to even upper rectum. It provides the potential benefit of precise dissection and en bloc excision, aided by enhanced and stable visualization (7). Moreover, TEM obviates the need for radical resection in certain cases. Although TEM yields superior outcomes, it has not been universally adopted by colorectal surgeons due to the considerable cost of the apparatus and the steep learning curve required to master the TEM technique (8). Wound dehiscence occurs more commonly in TEM; in fact, the specific incidence remains unknown as most surgeons do not routinely inspect the wound during the first 2 weeks, and the addition of neoadjuvant radiation therapy significantly increases the incidence of wound complications (9). Moreover, it has been reported that the dilatation of the anal canal due to the use of a rigid proctoscope and a prolonged operation led to short-term reduction in anorectal function (10).

TAMIS is a fairly new technique with short-term followup, with several advantages and disadvantages as compared to TEM. TAMIS does not offer stereoscopic visualization, and it is difficult to excise tumors beyond the upper rectum with this method. In contrast, the main benefit of TAMIS is the relatively low cost, as it involves the use of regular laparoscopic instruments. This also reduces the learning curve for surgeons due to the simplicity of the technique and its similarity with conventional laparoscopic surgery. Moreover, the platforms used for TAMIS are more pliable than the rigid scope and possibly result in reduced impairment of anorectal function. The minimal setup time is another advantage. The TAMIS platform is becoming more commonly used, primarily because it provides easy accessibility to the rectum, which enables its adoption in various other applications. Robotic TAMIS and transanal total mesorectal excision with TAMIS were recently introduced, and several reports involving modified versions of these procedures have been published. Nevertheless, the evolution of TAMIS and these new approaches over the next decade will be interesting, as they will change the way colorectal surgeons perform transanal surgery.

TAMIS is used for the local excision of rectal neoplasia, from benign adenomas to carcinomas. At present, the local excision of early rectal cancer is an attractive alternative to radical surgery, because it is less invasive and avoids the morbidity associated with radical resection. However, the local excision of early rectal cancer is controversial, due to the lack of adequate lymphadenectomy. Nevertheless, several studies have shown that the local excision of T1 cancer is effective (11,12). In addition, the role of local excision, including transanal endoscopic surgery, has expanded due to the use of neoadjuvant chemoradiotherapy. The application of chemoradiotherapy, followed by the local excision of T2 and T3 cancer, might improve the oncologic outcomes in responder patients (13-15). In addition, controlled trials on the use of TEM are currently ongoing, including the CARTS study and UK TREC trial. TAMIS can also be widely used for rectal cancers that show a good response to chemoradiotherapy. However, further clinical trials with long-term outcome are needed to determine the risk of local recurrence and distal metastases with these organ-preserving strategies.

In conclusion, TAMIS cannot currently be considered equivalent to TEM, because of the short-term follow-up oncologic data. However, TAMIS is a promising technique, and can serve as a feasible and safe modality for rectal tumors in select rectal cancer patients. Both TAMIS and TEM are effective transanal endoscopic surgical techniques. However, TAMIS can serve as an alternative to TEM, and further developments are possible. Thus far, no clinical prospective studies have compared TEM and TAMIS. Hence, further multicenter prospective randomized studies are needed.

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## Footnote

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# Modular approach for single docking robotic colorectal surgery

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We have read the article by Priatno and Kim with great interest (1). The article and attached video describe the single docking technique for rectal resection using the da Vinci<sup>®</sup> Si system. Robotic rectal surgery has shown steady increase during recent times. With challenging ergonomics of heavy mechanical arm of the robotic Si system, arm collision was often quoted as the main reason for limited adoption. With this in mind, surgeons have tried various other techniques such as hybrid, laparoscopic assisted or double docking as possible solution to this problem (2-4). We concur with authors regarding the stepwise approach for single docking robotic rectal surgery. This technique is now well established for robotic rectal cancer surgery (5,6).

Single docking approach is slightly demanding especially during learning curve. In addition, while performing the splenic flexure mobilization, collision of robotic arms during dissection in left upper compartment of abdominal cavity may pose further challenges. Hence, splenic flexure mobilization is probably the most challenging part during single docking approach, while using Si robotic system, as patient remains in the maximum Trendelenburg and right tilt position during the entire procedure. Applying similar principles of stepwise technique, we have published our three steps standardized approach for complete mobilization of splenic flexure during single docking colorectal surgery (7).

We agree with authors that this technique is safe, feasible and may reduce some operative time due to single docking. Perhaps now, the single docking technique has become easier and hassle free with the use of next generation of robot da Vinci<sup>®</sup> Xi surgical system. It has different port configuration and has ability to change patient's position, during various steps of operation, through an integrated cart and table motion system, without undocking.

In our practice, we have developed and described the modular stepwise approach for the laparoscopic colorectal surgery and later on the same standardized approach was applied for the robotic colorectal surgery (5,8,9).

We believe a standardized and stepwise technique is the key aspect of minimally invasive surgery. It is an effective method for learning complex surgical procedures. The stepwise approach is also useful for trainee surgeons to learn and master the operation. Furthermore, it helps to develop a sense of pattern recognition of surgical planes, which is vital for dissection in the correct operative field. The dissection between the true embryological layers i.e., correct planes enables to operate in bloodless field. We have published the largest case series from the UK that has demonstrated robotic surgery involves minimal blood loss (5).

In conclusion, authors have made an excellent effort to demonstrate the stepwise approach in this video article, and we believe this approach has significant inherent benefits for patients as well as training and learning robotic surgery.

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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 3<sup>rd</sup> most common cancer worldwide (1) and the 5<sup>th</sup> 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, intraoperative 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 indocvanine 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 perioperative 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 bepatectomy

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 KRASmutations (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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## Footnote

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# Multidisciplinary approach and targeted agents increase resectability of liver-limited metastases from colorectal cancer

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The outcome of patients with initially unresectable metastatic colorectal cancer have greatly improved in the past years (1) and at least three important factors have certainly contributed: a multidisciplinary approach, the availability of targeted agents and the knowledge of the molecular pathways of metastatic colorectal cancer. On June 2013, Ye et al. (2) published on the Journal of Clinical Oncology the results of a single-center randomized trial investigating the effect of the addition of cetuximab to first-line chemotherapy for radical resection rate of liver metastases from colorectal cancer. An editorial by N. Kemeny accompanied the paper (1) and, on December 2013, a correspondence between the authors and other international working groups was published on the same journal (3-5). Overall 138 Chinese patients affected by unresectable synchronous liver-limited metastases (LLM) from KRAS wild-type resected colorectal cancer were enrolled and they were randomized to receive anti-EGFR monoclonal antibody Cetuximab plus first-line fluorouracilbased doublets of chemotherapy (FOLFOX or FOLFIRI) or chemotherapy alone as first-line treatment. The mean age of study population was young, nearly 58 years, with 80% of patients with optimal general condition and ECOG performance status 0. The two arms of treatment (cetuximab plus chemotherapy versus chemotherapy alone) were well balanced regarding the motivation of non-resectability; at the same time, the experimental arm had 22% less patients with features indicating a worse prognosis (1). Nearly 30% of patients received the fluorouracil plus irinotecan combination (FOLFIRI) and a further 20% of patients received the sequence of both irinotecan and oxaliplatin-based doublets. One of the most significant aspects of this trial was that

resectability was evaluated, before and after treatment, by a multidisciplinary team involving at least three liver surgeons and one radiologist. After treatment, all of the following issues must be present in order to undergo resection:

- (I) Capability to obtain a radical resection;
- (II) Preservation of at least two contiguous liver segments;
- (III) Preservation of adequate vascularization and biliary drainage;
- (IV) Preservation of an adequate hepatic function (at least 20% of healthy liver).

At a median follow-up of 25 months, the radical resection rate (RRR) was respectively 25% and 7% in the cetuximab plus chemotherapy and in the chemotherapy alone arms, with an odds ratio in favor of the experimental arm of 4.37 (primary endpoint). Overall survival in the two groups of resected patients was comparable and about 40 months but, unfortunately, nearly 66% of resected patients recurred. Relatively to the safety, adding cetuximab to chemotherapy increased uniquely the occurrence of severe acneiform rash (12.9% versus 2.9%).

The results of this study confirm the concept of "conversion chemotherapy" in which a marked tumoral shrinkage after first-line chemotherapy can lead to the radical resection of liver metastasis with a relevant prolongation of survival, although often the disease will recur. Even in the setting of unresectable metastases, the addition of targeted agents to standard chemotherapy has improved outcomes (6,7) while, on the contrary, when metastases can be initially resected nor "standard" chemotherapy (8) nor addition of Cetuximab (9) have demonstrated to increase OS. Despite encouraging premises, there aren't at the moment randomized multicentric trials able to confirm if

chemotherapy plus cetuximab can be considered the standard of care for patients with LLM from resected, KRAS wild type, colorectal cancer. However the encouraging results of Ye et al. (2) about RRR in LLM can be updated by some recent trials conducted in the setting of "conversion chemotherapy. The recent update of the CELIM phase II trial (CEtuximab in neoadjuvant treatment of unresectable colorectal LIver Metastases), conducted on 114 European patients with unresectable LLM, show RRR data comparable between Cetuximab plus FOLFOX and Cetuximab plus FOLFIRI (10). Median OS and progression-free survival for resected patients were comparable to the trial by Ye et al. (2). 53 versus 46 months and 10 versus 10.7 months; overall survival at 5 years was 46% in the CELIM trial (10). In a Japanese trial by Kataoka et al. (11), 115 patients with LLM and resected primitive carcinoma were treated with the association of chemotherapy with various targeted agents. A multidisciplinary team evaluated resectability and allocated patients to three groups: resectable, "conversion therapy" and unresectable. An overall 18% resection rate was obtained with a statistically different survival between the "conversion" and the unresectable group. However PFS in the "conversion" group was clearly inferior respect to the "resectable" group (3 versus 16 months), thus confirming that the initial extent of the disease remains the more relevant prognostic factor and that respectability is often not equivalent to cure.

Taken together with recent advances in molecular biology, the results of these trials can ameliorate our clinical practice. First, in patients with LLM, the definition of resectability must be performed by a multidisciplinary team involving both liver surgeons and liver radiologists; particularly, the use of second-level imaging techniques mainly magnetic resonance (MR) or positron emission tomography/computed tomography (PET/CT) scan should be strongly considered (12), owing in mind that the potential benefit of a prolonged survival is realistic. Moreover, when resectability is the aim of treatment, the choice of first-line drugs, particularly in KRAS wild-type patients should comprehend, in fit patients, more than a standard doublet FOLFOX/FOLFIRI. The addition of cetuximab is a valid option (1,10) with a toxicity profile involving mainly the skin: in the CELIM trial grade 3-4 skin toxicity was present in 15-22% of patients (13); in the trial by Ye et al. in 13% (2). These data are in accord with available literature, from which it appears that these toxicity is in part preventable (14) and in the majority of cases manageable with dedicated algorithms (15). At the same time, recent evidences showed that a comprehensive analysis of both KRAS and

NRAS should be performed before treatment with anti-EGFR monoclonal antibodies (7). Moreover a possible role for the analysis of further genes such as BRAF, PIK3CA and PTEN is under evaluation (16). Facing such complexity, tools able to perform molecular analysis during chemotherapy, like for example, liquid biopsy of circulating tumor DNA, could be in the future fundamental elements in order to personalize the treatment (17).

It is not clear if a chemotherapy with three drugs is better than the association of cetuximab plus FOLFOX/FOLFIRI. The FOLFOXIRI triplet (fluorouracil/irinotecan/oxaliplatin) showed an overall 36% RRR in patients with LLM, superior to those from the trial by Ye et al. (2) and the CELIM trial (10), but with a clear increase in toxicities, especially hematological and neurological (18). Recent data from the TRIBE (Combination Chemotherapy and Bevacizumab as First-Line Therapy in Treating Patients With Metastatic Colorectal Cancer) trial showed that the addition of bevacizumab to FOLFOXIRI probably has no effect on resectability (19). Regarding the addition of Cetuximab to FOLFOXIRI, to date only small phase II trials are available, showing the feasibility of these combination with resection rates superior to 30% (20,21). Furthermore, when considering the continuum of care of patients, the use of a doublet, respect as a triplet, has the advantage that the remaining non-cross resistant doublet can be utilized as second-line chemotherapy.

In conclusion, when facing a relatively young and healthy patient affected by LLM from colorectal cancer, RAS (and possibly BRAF) wild-type, only after a multidisciplinary and multi-imaging evaluation of non-resectability with at least CT scan and MR or PET/CT, the treatment with the association of cetuximab with fluorouracil-based doublets should be strongly considered. We can in fact expect the conversion to resectability in up 25% of patients with, in this case, a prolonged survival in 30-50% of patients. Lacking phase III trials in this setting, it is advisable that new multicentric trials will analyze these aspects (22,23) and that new molecular techniques con improve the personalization of treatments in the various subgroups of patients (16,17).

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#### Footnote

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to declare.

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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 highrisk 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 wildtype 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 protooncogene BRAF. The gene is mutated in multiple tumors including CRC. In general, BRAF mutations portend worse outcome for patients with CRC. In a populationbased 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

Study	Dto (n)	Median FU (month)	3-Year	RFS (%)	3-Year OS (%)							
Sludy	FIS (II)		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						

Table 1 Differential survival of CRLM treated at three institutions

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.

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# Laparoscopic liver resections in two stages for the treatment of colorectal metastases: a review

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**Abstract:** Recent progresses in minimally invasive surgery have made complex hepatobiliary operations possible with a laparoscopic approach. Classic two-stage hepatectomy (TSH) and more recently associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) are getting reported more often as feasibility, safety and oncological efficiency have been demonstrated in selected cases. Herein we review the available literature in the field of laparoscopic liver resections in two stages with a focus on the management of colorectal liver metastases (CRLMs).

**Keywords:** Laparoscopy; two-stage; hepatectomy; associating liver partition and portal vein ligation for staged hepatectomy (ALPPS); liver metastases

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# Introduction

Colorectal cancer is one the most common malignant disease, accounting for 1 million cases worldwide every year. Colorectal liver metastases (CRLMs) occur in 40–60% of patients and surgery represents the treatment of choice, resulting in a 5-year survival rate up to 58%. On presentation, only 20% of patients with bilobar CRMLs are resectable up front. This is due to the extent of the metastatic burden to the liver and the amount of parenchyma to be excised in order to achieve a curative resection (1). In order to prevent postoperative liver failure, it is routine practice to aim for a future remnant liver volume (FRLV) of more than 20–25% in patients with healthy livers, of more than 30% after chemotherapy, and more than 40% in chronic liver disease (2).

The two-stage hepatectomy (TSH) strategy was originally developed by Adam *et al.* to allow a curative surgical treatment in otherwise unresectable patients due to a predicted low FRLV. Such approach consists of a combination of a first operation that clears up the least diseased lobe, usually the left, and a second one that involves the contralateral lobe. Between the two stages, hypertrophy of the future remnant liver is induced by means of either portal vein ligation (PVL) applied during the first operation or portal vein embolization (PVE) performed percutaneously after the first stage (3,4). Despite rendering many patients operable, TSH still carries a risk of disease progression between the two stages, with a reported dropout rate ranging between 15% and 30% (5).

More recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been proposed as an alternative two-stage approach with the same intent of inducing hypertrophy of the FRLV. ALPPS was first introduced in 2012 by Schnitzbauer *et al.* and has now been performed in more than 700 patients (6). It consists of a first stage during which more often the left lobe clearance is performed in association with right PVL and in situ splitting along the right side of the falciform to induce a rapid hypertrophy of the FRLV, followed Spoletini et al. LLS in two stages for the treatment of colorectal metastases

by the second stage major resection after few days or weeks (7). Enthusiastic reports regarding faster growth kinetics of the FRLV have been mitigated by reported increase in morbidity and mortality associated with ALPPS in comparison to TSH (8).

Despite their aggressive nature, both types of such twostage operations have been performed laparoscopically with different modifications to the classical first descriptions and in many cases a first laparoscopic stage was followed by an open second stage.

This article aims to review the current literature about laparoscopic TSH and ALPPS.

## Laparoscopic two-stage hepatectomy

The first case of a pure laparoscopic two-stage hepatectomy was reported by our group in 2010. The patient had two metachronous CRLMs, one in the left lateral section and a larger one in the centre of the right hemiliver, 2 years following a laparoscopic anterior resection of the rectum. A left lateral sectionectomy was performed as a first stage procedure, followed by a right-sided percutaneous PVE a week later. The patient eventually underwent a laparoscopic right hemihepatectomy 6 weeks after compensatory hypertrophy was achieved (9).

In the same year, Machado *et al.* reported the case of a patient with synchronous liver metastases with a small left hemiliver. The first stage consisted of a laparoscopic segment 3 resection and right sided PVL. After 4 weeks, 43% FRLV was obtained and a laparoscopic right hemihepatectomy was performed (10).

Prior to the described pure laparoscopic cases, Are *et al.* described the feasibility and safety of laparoscopic right PVL in a population of 9 patients (out of whom 5 with CRLMs) in 2008. Three patients also had wedge resections of left-sided metastatic deposits. Neither mortality nor morbidity related to PVL was registered. Only five patients could progress to an open second stage major hepatectomy whilst the other four experienced disease progression, which precluded further resection (11).

Similarly, in a case series of 6 patients in Manchester, laparoscopic right PVL was applied at the time of staging laparoscopy in patients requiring a right hepatic trisectionectomy in the presence of a small FLR and as part of a staged liver resection in patients with bilobar liver disease sparing segments 1 and 4 (12).

Our group described the first series of 7 patients undergoing laparoscopic TSH in 2012, highlighting a clear

benefit in terms of minimal adhesions encountered at the time of the second stage. All patients had left-sided liver resections and 2 had right PVL during the first stage. A right hepatectomy was performed laparoscopically (one required conversion) in three patients for the second stage while the remaining were carried out with an open approach (13).

Kilburn *et al.* reported a series of 7 patients who underwent a laparoscopic first stage followed by an open second stage, thus reinforcing the concept of safety and feasibility when utilizing a minimally invasive approach in patients who are expected to receive multiple procedures (14).

In 2015, Fuks *et al.* published the largest series of laparoscopic TSH so far. Thirty four patients were planned for TSH. All patients underwent a laparoscopic first stage (five with concomitant PVL) and 26 progressed successfully to a laparoscopic second-stage, including 18 laparoscopic right or extended right hepatectomies. The reported low conversion rate, small amount of blood loss and limited morbidity, suggest that this complex surgery is feasible and safe using the laparoscopic approach. In addition, the oncological efficiency of laparoscopic TSH has been confirmed by the low incidence of R1 resections. The authors recognise that this kind of surgery is of the highest complexity and should be considered only in centres with advanced expertise in hepatobiliary "open" and laparoscopic surgery (15).

#### Laparoscopic ALPPS

The first totally laparoscopic ALPPS was reported in 2012 by Machado et al. During the second stage, the authors were favourably impressed by the small amount of adhesions and completion of surgery was easily done (16). Again, after a seminal experience with two laparoscopic ALPPS procedures and more than 20 performed in open settings, the same group from Sao Paulo, Brazil, started to offer ALPPS laparoscopically as their standard practice. Comparing 10 laparoscopic ALPPS (out of which 9 for CRLMs) with those 20 done through laparotomy, they registered less severe complications and no postoperative liver failure in the laparoscopic group despite achieving a lower grade of hypertrophy in the FRLV. Despite the intrinsic selection bias of the study, the authors argued that minimising surgical related invasiveness might contribute to lower morbidity associated in particular with the first stage (17). The group also emphasised on the advantage

encountered during the second stage after they stopped mobilising the right hemiliver during the first stage. On a later report they introduced a technique of selective arterial clamping to replace Pringle manoeuvre. Common hepatic artery clamping was found to reduce blood loss by antagonising the compensatory arterial overflow that follows the deprivation of portal flow to one liver lobe (18). Several modifications to the original description of ALPPS have been proposed with the intent to overpass issues related to the increased rates of bile leak, surgical trauma and different indications for ALPPS other than CRLMs (19-21).

The use of ablative techniques in a laparoscopic setting for simplifying the first stage ALPPS in patients with CRLMs has also been described. Cillo et al., after ligating the right portal branch, applied ultrasound-guided microwave ablation with multiple antenna insertions within the future liver transection plane on the right side of the falciform ligament in order to create an avascular groove between the cancer and the FLR; during the second stage, a laparoscopic right trisectionectomy was carried out along a bloodless transection line with both scissors and an ultrasound dissector. No Pringle manoeuvre was necessary (22). Based on the same principle, Jiao et al. described the first totally laparoscopic radiofrequency assisted liver partition with portal vein ligation (RALPP) after having authored and gained experience with such technique in a series of 11 cases done with a first laparoscopic stage followed by an "open" second stage (23,24).

Robotic ALPPS has been shown in a video case report by Vicente *et al.* and remains the first published of its kind in the literature so far (25).

### Discussion

Laproscopic liver surgery (LLS) has been expanding in the last 20 years. Initial reports have confirmed its feasibility, safety and oncological efficiency in minor and major hepatectomies, although many expected that different factors such as liver lesions of large size, close to major vessels, located within the less accessible posterior segments and finally an unfavourable distribution of lesions could have limited further expansion of LLS. Our team, within other enthusiastic laparoscopic units, have already reported excellent results in this field for almost all of the abovementioned potential obstacles (26-28).

Two stage liver resections represent a relevant turnaround in the history of the treatment of CRLMs.

Nevertheless, TSHs are associated with major technical difficulties, which can be augmented with a laparoscopic approach. Thus, reports of laparoscopic TSH are still scarce and often only the first of the two stages is carried out laparoscopically (29). The much desired hypertrophy of the remnant liver can be associated with serious anatomical distortion making the intraoperative findings difficult to interpreter. In addition, hilar adhesions caused by the PVL or the periportal fibrosis encountered after the portal vein embolization can add a significant challenge to the hilar dissection during the second stage (30).

With ALPPS, the interval between the two stages is shorter and the adhesions are reported to be more inflammatory and less fibrous comparing to TSH (31). Nevertheless, almost all authors highlighted the benefit of less adhesions and blood loss with laparoscopic surgery in both TSH and ALPPS, consistently with the widely accepted benefits of laparoscopy, such as minor parietal incisions, fewer foreign bodies, reduced and gentler manipulation of tissues, and a close and humid environment with pneumoperitoneum (32).

Despite the help from finer instrumentation in the last decade, laparoscopic major liver surgery remains a technically challenging field of action. The use of robotic assistance has been advocated to help overcoming technical barriers and to promote more widespread application of a minimally invasive approach in TSH and ALPPS (33). As yet, case series with robotic ALPPS are lacking. Laparoscopic TSH and ALPPS are gaining acceptance and enthusiastic reports continue to emerge. Notably, such literature is produced by centres with great expertise in both advanced laparoscopic and hepato-biliary surgery.

In conclusion, laparoscopic liver resections in two stages for the treatment of colorectal metastases are technically feasible in selected cases, without compromising oncologic principles. However advanced experience in open and laparoscopic liver surgery is needed for a safe completion of such procedures.

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#### Footnote

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

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# Are the clinical risk scores of survival after colorectal liver metastases still valuable in the era of laparoscopic liver surgery?

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*Comment on:* Barkhatov L, Fretland ÅA, Kazaryan AM, *et al.* Validation of clinical risk scores for laparoscopic liver resections of colorectal liver metastases: A 10-year observed follow-up study. J Surg Oncol 2016;114:757-63.

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We read with interest the article by Barkhatov *et al.* reporting on laparoscopic liver resection for colorectal liver metastases with the aim to validate different clinical risk scores (1). This elegant study shows that excellent long-term results (e.g., up to 32% 10-year survival) can be achieved with adequate surgical resection in selected patients with laparoscopic approach. Interestingly, the Fong score, pre- and postoperative BPI and the Nordlinger score systems can be used to predict survival for laparoscopically operated patients in the era of multimodal-treatment.

A prediction of the risk of recurrence after resection that is as precise as possible is essential for maximizing the benefit from such an invasive strategy. A lot of clinical scores have been proposed by different surgical institutions over the years and all were based on easily available parameters associated with the extent of the primary tumor and colorectal liver metastases or grossly defining the aggressiveness of the disease course. Probably one of the most relevant attempt to define prognosis after surgery on colorectal liver metastases was conducted by Fong et al. at the Memorial Sloan-Kettering Cancer Center (MSKCC); the authors analyzed a large database of all patients admitted to their institution for liver surgery from 1985 to 1998. Among the 1,001 patients identified resected for colorectal liver metastases, the authors investigated characteristics of the primary tumor and related colorectal liver metastases or extrahepatic disease, identifying seven parameters that independently predicted outcome after resection: (I) positive

surgical margin; (II) presence of extrahepatic disease; (III) number of lesions; (IV) preoperative carcinoembryonic antigen level >200 ng/mL; (V) size of the largest lesion; (VI) nodal status of the primary tumor; (VI) disease-free interval from the primary to diagnosis of colorectal liver metastases and (VII) bilateral tumors as variables.

Limiting to the five factors that can be accessible before resection and not considering the variables that represented absolute contraindication to resection at the time (i.e., positive margin and the presence of metastases outside the liver, which are both associated with a 1.7-times higher risk of death), a clinical risk score was developed assigning each criterion one point; the MSKCC score proved to be highly predictive of long-term outcome after surgery for colorectal liver metastases, with the risk of death increasing when the number of concomitant risk factors increased. In fact, prognosis varied from patients with no risk factors, who achieved a 5-year actuarial survival rate of 60%, to patients with all the five points, who had a 5-year actuarial survival rate of 14%. The clinical risk score proposed by Fong et al. has been subsequently validated by independent data sets and should therefore guide patient selection and treatment allocation but should not be interpreted as absolute contraindication to surgery.

These results are in line with the study from our group published last year in Annals of Surgery concerning longterm outcomes following second and third laparoscopic hepatectomies for patients with recurrent CRLM (2). While

tumor recurrence is frequent after either a first or second resection, the benefit provided by second and third LLRs was suggested by the excellent 5-year survival rates, which were both better than those obtained after a first LLR and comparable to those observed by open approach. Likewise, Allard *et al.* showed that laparoscopy yields better operative outcomes without impairing long-term survival in a cohort including more than 2,500 patients (3).

Potential benefits of laparoscopic approach compared with open in liver resection have been largely investigated. The different results suggest the superiority of the laparoscopy in terms of length of hospital stay, transfusion rate, and morbidity. Indeed, the role of the pneumoperitoneum and the magnification achieved by 2D or 3D cameras enable excellent control of small intrahepatic vascular structures and this contributes to limit bleeding during the parenchymal transection. Of course, the laparoscopic approach may be impaired by tumor location, adequate resection margins, and complete intraoperative exploration of the liver. This may lead to worse oncological results in patients operated by laparoscopy for CLM and prefer open hepatectomy.

Overall, these data strongly suggest that in both laparoscopic and open approaches bring equivalent longterm outcomes. In their study the Norvegian teams show that the actual survival exceeded the predicted value by the scoring systems. The reason is more probably due to the multimodal treatments than the mini invasive

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approach itself. In this setting, the Fong score, even with an underestimation of 16.8% for 5 years survival and 20 months for median survival is the closest of the currents results and can be used to predict survival in all patients

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#### Footnote

with CRLM.

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# Comparison of laparoscopic versus open liver resection for colorectal liver metastases using propensity score matching

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"Laparoscopic hepatectomy versus open hepatectomy for colorectal cancer liver metastases: comparative study with propensity score matching" has recently been published by Untereiner et al. in "HepatoBiliary Surgery and Nutrition" (1). Here we reviewed the surgical impacts of a laparoscopic liver resection (LLR) compared to a conventional open liver resection (OLR) for colorectal liver metastases (CRLM) patients.

# **Comparative study of LLR versus OLR for CRLM**

A liver resection is the gold standard treatment for CRLM and can provide excellent long-term survival (2-4). Nowadays, LLR has become a popular treatment for CRLM (5,6). Not only a focal minor hepatectomy but also a major hepatectomy, such as a hemihepatectomy, can be performed for CRLM patients according to the 2014 2nd world consensus meeting in Japan (7).

Numerous papers have demonstrated that LLR can provide better short-term outcomes, including reduced intraoperative bleeding, a lower morbidity rate, shorter hospital stay, and a lower overall cost compared to a conventional OLR (8-14). Nevertheless majority of these findings were based on investigations of retrospective casematched studies or meta-analyses of non-randomized studies. In clinical CRLM patients, various selection biases can exist with regard to selecting LLR; therefore, the results are not conclusive.

# Randomized control study (RCT) of LLR versus OLR for CRLM

Unfortunately, there have been no RCTs comparing the oncological values of LLR and OLR. A major problem to achieving an RCT is that patients may not be willing to be randomized into the OLR group. Additional reasons are some kind of learning curve, lack of standardized techniques, or high cost of LLR (15). In our knowledge, two RCTs comparing LLR and OLR are currently in progress—the OSLO CoMet study (http://clinicaltrials.gov/ct2/show/NCT01516710) and the ORANGE II PLUS trial (http://clinicaltrials.gov/ct2/show/record/NCT01441856) (7,16). The former is an RCT that compares LLR and OLR for CRLM; however, the final result is still unknown.

# LLR versus OLR for CRLM using propensity score matching (PSM)

There are many background selection bias factors in an LLR cohort. A PSM analysis is a quite useful tool to compare different therapies with a reduced selection bias in retrospective studies (17,18). Lately, it has been reported that treatment effects were not statistically different between non-randomized studies using a well-designed PSM analysis and an RCT (19).

Cannon et al. (15) first reported a PSM study that

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Ref	Pts' number LLR/OLR	Operation time	Blood loss	Morbidity	Mortality	Hospital stay	RFS/DFS	OS			
(15)	35/140	Equal	LLR less	LLR less	Equal	LLR shorter	Equal	Equal			
(20)	171/342	Equal	LLR less	Equal	Equal	LLR shorter	Equal	Equal			
(21)	52/52	Equal	LLR less	Equal	Equal	LLR shorter	Equal	Equal			
(22)	36/36	LLR longer	LLR less	Equal	Equal	LLR shorter	Equal	Equal			
(23)	153/153	NA	LLR <sup>#</sup> less	LLR less	Equal	LLR shorter	Equal	Equal			
(24)	133/133	LLR longer	LLR less	LLR less	Equal	LLR shorter	Equal	Equal			
(1)	18/18	Equal	LLR less (P=0.07)	Equal	Equal	Equal	Equal	Equal			

Table 1 Outcomes in CRLM patients undergoing LLR and OLR using PSM

<sup>#</sup>, blood transfusion rate. Ref, reference number; Pts, patients'; LLR, laparoscopic liver resection; OLR, open liver resection; RFS, recurrence-free survival; DFS, disease-free survival; OS, overall survival; NA, not available.

compared the oncological effects of LLR and OLR for CRLM patients; however, they included a relatively small sample size of 35 LLR patients. To include enough CRLM patients, we conducted a multicenter study including specialized centers for both hepatobiliary and endoscopic surgery in Japan (20). After one to two PSM analyses, 171 LLR and 342 OLR were enrolled; this study includes the greatest number of patients reported thus far. Before and after our publication, several PSM studies were published regarding LLR and OLR for CRLM patients (Table 1) (1,15,20-24). After PSM matching, 18-171 LLR patients and 18-342 OLR patients were analyzed. In terms of perioperative parameters, the operation time for LLR was similar in five studies and longer in two compared with OLR; similarly, the blood loss amount or blood transfusion rate was less in six of seven studies. Morbidity was equal in four studies and less in three for LLR compared with OLR; mortality was comparable in all studies. The hospital stay was shorter in all studies except one. Recurrence-free or disease-free survival and overall survival were comparable in all studies.

In conclusion, LLR can provide excellent perioperative benefits without oncologic disadvantages for properly selected patients with CRLM. These PSM studies clearly demonstrated that LLR is certainly recommended as a standard practice for selected patients with CRLM.

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# Abdominal metastases from colorectal cancer: intraperitoneal therapy

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**Abstract:** Patients with peritoneal metastasis from colorectal cancer represent a distinct subset with regional disease rather than systemic disease. They often have poorer survival outcomes with systemic chemotherapy. Optimal cytoreductive surgery and intraperitoneal chemotherapy (IPC) offers such patients a more directed therapy with improved survival. In this review, we discuss the diagnosis, evaluation and classification, as well as rational for treatment of peritoneal carcinomatosis (PC) secondary to colorectal cancer.

Keywords: Colorectal peritoneal carcinomatosis (PC); intraperitoneal chemotherapy (IPC); cytoreductive surgery

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### Introduction

The peritoneum represents the third most common site of metastatic disease of colon cancer, following the liver and lungs (1). The prevalence of synchronous peritoneal disease is 4.3%, while the peritoneum is the first site of subsequent metastasis in 4.8% of patients (2). Though there have been significant advances in systemic cytotoxic chemotherapy for extra-peritoneal metastatic colorectal cancer with overall improvements in survival (3), patients with peritoneal carcinomatosis (PC) treated with systemic chemotherapy continue to have poorer survival outcomes (4,5). A subset of PC is thought to represent regional rather than systemic disease and could be managed accordingly. In this circumstance, peritoneal implants appear to develop after shedding of malignant cells once a tumor has broken through the peritoneal lining of the organ; hence the rationale for regional therapy with optimal surgical cytoreduction and instillation of intraperitoneal chemotherapy (IPC) (6).

Historically, the median survival of patients with synchronous PC has been reported to be as short

as 5.2-7 months, even when treated with systemic chemotherapy (7). Patients who present with malignant small bowel obstruction tend to have a particularly grim outlook with survival of 3-3.5 months (8,9). The median time to diagnosis of PC from colorectal cancer is 16-21 months (1). Risk factors for development of PC include right sided tumors, advanced T stage, positive lymph nodes, less than 12 lymph nodes being examined, emergency procedures, an incomplete resection of the primary lesion (R1/R2 resection), venous or perineural invasion, and liver metastases (2,10).

Prior to the concept of peritoneal debulking, PC was considered a terminal diagnosis that most oncologists palliated with systemic chemotherapy. However, cytoreductive surgery and IPC has shown improved survival outcomes in non-gastrointestinal malignancies, particularly ovarian cancer. For instance, in a randomized trial by Alberts *et al.* in which patients with ovarian peritoneal metastasis received a combination intraperitoneal cisplatin plus intravenous cyclophosphamide or intravenous cisplatin and cyclophosphamide, patients receiving IPC had significantly improved overall survival, with decreased toxicity in the IPC group (11). Armstrong et al. randomized patients with ovarian cancer and no residual mass greater than 1 cm to intravenous paclitaxel followed with intravenous cisplatin or intraperitoneal cisplatin and intraperitoneal paclitaxel. Patients receiving IPC had overall improved survival, although a significantly higher proportion experienced severe or life-threatening complications on this regimen (12). Although such studies illustrated the improvement in survival that can be achieved with IPC, hence extending such concepts to other malignancies such as colorectal, there is more work necessary to optimize delivery methods, agents used, and overall treatment. The initial experience with cytoreductive surgery and IPC in gastrointestinal malignancies was first reported by Sugarbaker, who published his experiences with peritoneal disease with the expectation of improved survival (13,14).

# **Diagnosis of peritoneal carcinomatosis (PC)**

Patients with PC commonly present with non-specific symptoms such as abdominal discomfort or pain, and extreme fatigue. They may also present with abdominal ascites causing abdominal bloating (15). Malignant obstruction tends to be a late presenting symptom that is an especially difficult problem to manage. Although abdominal imaging in the form of CT or PET/CT may be helpful in making the diagnosis, such imaging modalities have been shown to have poor predictive value of the extent of peritoneal dissemination (16-18). In an observational prospective study by Esquivel et al., the authors evaluated the accuracy of CT based peritoneal carcinomatosis index (PCI) in comparison to operative findings across multiple institutions. They found that CT based PCI significantly under estimated the intra-operative PCI in 33% of the cases. Utilizing a preoperative PCI of 20 as a threshold score for selection of patients eligible for treatment, 12% of patients selected for cytoreduction were deemed unresectable at time of surgery (16). This underscores the importance of consideration for a diagnostic laparoscopy to assess the extent of peritoneal disease before proceeding to debulking and IPC (19). However, laparoscopy may not be feasible in many patients due to benign or malignant adhesions to the abdominal wall and is used selectively.

Beyond making the diagnosis, predicting which patients are best suited for cytoreductive surgery and IPC is challenging without direct operative exploration. Van Oudheusden *et al.* attempted to define clinical characteristics that would predict resectability prior to the operating room; the presence of a prior colostomy or an American Society of Anesthesiologists (ASA) score greater than 3 were the only significant variables associated with suboptimal cytoreduction (20). These two variables are present in a minority of potentially eligible patients and stress the difficulty in predicting the true extent and location of peritoneal disease based on current clinical findings and imaging modalities.

# **Classification of peritoneal metastasis**

There are six notable classification indices developed for the measurement of PC. Such indices attempt to quantify peritoneal disease and offer prognostication based on the severity of disease (21). The most commonly utilized measure is the PCI devised by Sugarbaker (21-23). This index divides the abdominopelvic region into nine regions. Additionally, another four regions are scored that include the peritoneal surfaces on the small bowel and its mesentery, extending from proximal jejunum to distal ileum. Each region is assigned a score from 0 to 3, for a total maximum score of 39. The scoring of each region is based on the largest lesion size (LS) after full lysis of adhesions. A score of LS-3 is assigned for lesions 5 cm or greater in diameter, LS-2 for lesions greater than 0.5-5 cm, and LS-1 from lesions less than 0.5 cm. A score of zero is given if no lesions are visible. A PCI score of less than 20 has been correlated with better survival and thus suggested it as a cut off for disease amenable to debulking (24). Although high PCI scores indicate more bulky disease that is more difficulty to optimally treat surgically, other variables such as location of disease, initial presentation, tumor histology, and lymph node status must also be taken into consideration when evaluating patients for debulking and IPC (20,24,25).

A second score developed by Jacquet and Sugarbaker is the completeness of cytoreduction (CCR) score; which aims to quantify the extent of disease after cytoreductive surgery (21,22). In this system, a score of 0 to 3 is assigned based on the largest size of lesion deemed un-resectable after cytoreduction. A CCR-0 implies no visible peritoneal disease is noted. A score of CCR-1 is assigned when peritoneal lesions less the 2.5 mm are left after cytoreduction, while a CCR-2 is for lesions between 2.5 mm and 2.5 cm. A CCR-3 score is assigned for lesions greater than 2.5 cm. IPC is suspected to work by diffusion, thus penetrating the outermost cell layers of a tumor (26-28). Hence optimal debulking to no visible disease or no lesions greater than

2.5 mm must be obtained and is considered appropriate for peritoneal chemotherapy penetration (23,29,30).

A newly introduced scoring system with prognostic significance is the Peritoneal Surface Disease Severity Score (PSDSS) (31). The PSDSS system is calculated based on three variables at the time of diagnosis: burden of carcinomatosis as define by the PCI, histopathology of the primary tumor, and presenting symptoms. Each one of the components is given a weighted score, and the sum of each gives the final PSDSS score. The PCI score is broken into three sub-categories (<10, 10-20, >20). The symptom severity is based on amount of weight loss, extent of ascites, and abdominal pain severity. The histopathology is based on the aggressiveness of primary tumor. After the final score is calculated, the PSDSS is broken into four groups (I-IV), each providing prognostic value (31).

The advantage of the PSDSS system is that it can be calculated at the time of diagnosis without operative exploration since the PCI is calculated based on imaging (CT ± F-18 FDG PET) and the histology utilized is the primary tumor histopathology (32). The prognostic utility of PSDSS was evaluated by the American Society of Peritoneal Surface Malignancies (ASPSM) in a multiinstitutional study involving 1,013 patients with colorectal cancer PC (32). In patients in the PSDSS I group treated with chemotherapy alone, median survival was 45 months (95% CI: 1.1-89.6 months), while for the PSDSS IV group it dropped to 6 months (95% CI: 5.0-7.3 months). In patients treated with cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC), the median survival for the PSDSS I group was 86 months (95% CI: 64.4 to not available) and 28 months (95% CI: 19.9-32.0 months) for PSDSS IV group. In multivariate analysis, the PSDSS, as well as the location for where patients were enrolled, type of treatment, and timing of occurrence were independent prognostic factors for survival. The PSDSS IV group had a higher risk of death compared to the other scores (32).

# **Rational for cytoreduction and intraperitoneal chemotherapy (IPC)**

It is commonly believed that PC develops after implants from the primary tumor are shed when the tumor breaks through the peritoneal lining of the organ (6). Systemic chemotherapy agents may have poor penetrance of the peritoneal cavity due to the peritoneum's poor blood supply and the rapid clearance of such agents. As such, directed therapy with instillation of chemotherapy agents into the peritoneum appear to provide higher drug concentrations and penetrance of tumor deposits (28,33). Additionally, agents with a higher molecular weight achieve greater concentration in the cavity since they do not readily diffuse across the parietal peritoneum into the systemic circulation. This also limits the systemic toxicity of such agents (33,34). Additionally, as mentioned previously, complete cytoreduction of peritoneal deposits prior to the administration of IPC appears to be critical to the success of IPC (23,29,30). The agents utilized in IPC are thought to penetrate tumor cells by diffusion (26-28). Therefore, complete cytoreduction allows IPC to treat the remaining disease not visible to the eye during exploration or small deposits less than 2.5 mm in which the agents can effectively diffuse the superficial layers of cells, providing potentially effective therapy.

# **Treatment of isolated peritoneal metastasis**

Interest in resection of peritoneal metastasis from colorectal cancer has intensified over the last decade. Despite this, there have been only a limited number of randomized trials published in the literature.

The largest to date (30) included 105 patients with peritoneal metastasis from a colorectal cancer primary without evidence of liver or lung metastasis. Patients were randomized to systemic treatment (5FU and leucovorin) with or without palliative surgery or to cytoreductive surgery with HIPEC, followed by systemic therapy. The initial publication followed patients for a median follow up of 21.6 months. The authors found that patient in the cytoreductive surgery and HIPEC group had significantly longer survival (22.3 vs. 12.6 months, P=0.032) compared to the standard therapy patients. In addition, the authors found that survival was increased in those patients in which all macroscopic disease could be resected compared with those with gross residual disease (P<0.0001). The treatment related mortality was 8% in the cytoreductive surgery and HIPEC group. A follow up report of long term survival was published by the authors in 2008 (35). Median survival in those with an R1 resection was 48 months compared with 18 months in those with an R2a resection and 8 months in those with an R2b resection. This trial offered some evidence in support of the effectiveness of regional therapy for colorectal cancer; however, the trial's small numbers, high mortality, high rate of suboptimal cytoreduction, and use of now outdated systemic chemotherapy (5FU/ leucovorin only) have limited the acceptance of this approach. Furthermore, as cytoreductive surgery was performed only in the HIPEC arm, the incremental effect of IPC remains unknown.

The other attempted randomized controlled trial (RCT) in patients with peritoneal metastasis from colorectal cancer was terminated due to poor accrual (36). Only 35 of 90 patients were enrolled over the study period. The study attempted to assess the effect of early postoperative intraperitoneal chemotherapy (EPIC) plus systemic chemotherapy *vs.* systemic chemotherapy alone in patients who cytoreductive surgery. Patients with liver metastasis were included if there were 1 or 2 liver lesions that could easily be resected. A 60% 2-year survival was found after complete macroscopic resection of disease (R1 resection). Due to the small sample size and early termination, definitive recommendations could not be made.

Comparative retrospective studies were published by both Elias et al. (37) and Franko et al. (38) that compared cytoreductive surgery and HIPEC to standard therapy (chemotherapy ± palliative surgery). The study by Elias et al. included 48 patients in the cytoreductive surgery (CRS) + HIPEC group and 48 patients in the standard therapy group. Five year overall survival was 51% in the CRS + HIPEC group, compared with 13% in the standard therapy group. Median survival was 62.7 months in the CRS + HIPEC group, compared with just 23.9 months in the standard therapy group (P<0.05) (37). The study by Franko et al. included 67 patients undergoing CRS + HIPEC and 38 patients undergoing standard therapy. The CRS + HIPEC group had fewer patients with liver metastasis (15% vs. 35%, P=0.014). Median survival was longer in the CRS + HIPEC group (34.7 vs. 16.8 months, P<0.001) (38). These small studies had limited ability to control for confounding factors.

Larger observational studies published by Elias *et al.* (39) and by Glehen *et al.* (29) did not include systemic chemotherapy only patients. Both studies were authored by the same group, and the overlap of patients between studies was unclear. The study by Elias *et al.* included 523 patients with colorectal cancer treated by either HIPEC or EPIC following cytoreductive surgery. Both isolated peritoneal metastasis and combined liver-peritoneal metastasis patients were included. Postoperative mortality was 3.3% in the entire population, with 31% of patients experiencing grade 3 or 4 complications. Median survival was 30.1 months, with 5-year survival of 27%. Of those with an R1 resection, the 5-year survival was 29%, whereas those with nodules >2.5 mm remaining, the 5-year survival was 0%.

There did not appear to be any advantage to HIPEC or EPIC in overall survival (P=0.965) (39). The study by Glehen *et al.* found similar results. Postoperative mortality was 4% and morbidity was 22.9%. There was a strong association between completeness of cytoreductive surgery and overall survival (P<0.0001). Again, no difference was seen between HIPEC or IPEC or HIPEC + EPIC (P=0.61). Median overall survival was 19.2 months, with a 5-year survival of 19% (29).

#### Importance of optimal cytoreductive surgery

Both of the large series reviewed above by Elias *et al.* (39) and Glehen *et al.* (29) assessed the importance of optimal cytoreductive surgery. In the study by Elias *et al.*, patients with no gross disease left *in situ* had a median survival of 33 months and a 5-year overall survival of 29%. This is in comparison with those with remaining tumor nodules <2.5 mm (20-month median survival, 14% 5-year survival) and those with tumor nodules  $\geq$ 2.5 mm (7-month median survival, 0% 5-year survival). After adjusting for important prognostic variables, this difference persisted (P<0.001) (39).

Similar findings were published by Glehen *et al.* Their group found a median survival of 32.4 months in those with complete cytoreduction, compared with 24 months in those with tumor nodules <5 mm and 8.4 months in those with residual tumor nodules of  $\geq 5 \text{ mm}$  (P<0.0001). After adjusting for important prognostic variables, this difference persisted as well (P<0.0001) (29). These findings have been consistently upheld by other investigators and failure to achieve optimal cytoreduction is considered a contraindication to radical surgery except in the purely palliative setting.

# Patients with combined peritoneal metastasis and liver metastases

The outcomes in patients with liver metastasis who underwent cytoreductive surgery and IPC chemotherapy have been evaluated; however, most series have a small subset of such patients. The largest series with such analysis are those by Elias *et al.* (39) and Glehen *et al.* (29) mentioned previously.

The study by Elias *et al.* (39) included 77 patients who had synchronous liver lesions which were resected. In the univariate analysis, this group had a similar median survival (23 *vs.* 31 months) and 5-year overall survival (21% *vs.* 27%) (P=0.15). However, the authors of the study performed a multivariable analysis adjusting for extent of carcinomatosis,

the institution performing the surgery, lymph node status and the use of adjuvant chemotherapy. This regression showed that the rate of death was higher in those with liver metastasis (hazard ratio 1.623, P=0.01).

Glehen *et al.* (29) also found that those with liver metastasis had a shorter median survival compared with those without liver metastasis (16.8 *vs.* 20.4 months, P=0.008). After multivariate, Cox regression (adjusting for important variables including completeness of cytoreductive surgery, preoperative chemotherapy and adjuvant therapy), the presence of liver metastasis negatively affected survival (Cox coefficient 0.52, P=0.004).

# Conclusions

PC from colorectal cancer represents a distinct subtype of metastatic disease that is regional rather than systemic. Significant changes in our understanding of this disease pattern have allowed different strategies to target PC. Optimal debulking and IPC are critical variables in improving survival for this patient population. However, more studies are needed to define better patient selection, optimal therapy, delivery methods, and overall outcomes.

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### Footnote

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# Neoadjuvant chemoradiation therapy for rectal cancer: current status and perspectives for the surgeon

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**Abstract:** Modern management of rectal cancer has become increasingly complex over the last decades. The introduction of neoadjuvant chemoradiation to the treatment strategy of locally advanced and distal rectal cancers has added numerous variables that may ultimately affect final surgical or even non-surgical management. Specific chemoradiation regimens, intervals after neoadjuvant treatment completion and tools for the assessment of tumor response may all affect final surgical decision and should be interpreted with care. The present study attempts to provide a review of commonly used neoadjuvant chemoradiation regimens, specific intervals and final surgical or non-surgical management of rectal cancer in current clinical practice.

Keywords: Rectal cancer; neoadjuvant therapy; total mesorectal excision (TME)

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# Introduction

Significant changes in the clinical management of rectal cancer over the past 15 years have occurred. Prior perioperative chemotherapy or radiation therapy, recurrence rates could reach 40% in patients with locally advanced rectal cancers (1). Over the years, the increasing importance given to pre- and post-treatment staging, pre-operative multimodal treatment, new surgical techniques and detailed pathological analyses has contributed to improvement in the treatment and survival of these patients. Therefore, the management of patients with rectal cancer has become multidisciplinary requiring a coordinated effort from physicians and surgeons and with regular multidisciplinary requiring a coordinated effort from multiple specialties and with regular meetings as the best way to obtain synchronization (2).

The changes incorporated in the management of advanced

rectal cancer have emphasized a more individualized approach aiming to provide oncological safety preserving functional outcomes and quality of life. Alongside with the establishment of total mesorectal excision (TME) (3), one of the most important interventions pertains the use of chemoradiation therapy (CRT), which has been part of the treatment of rectal cancer since the 1990s. Therefore, treatments potentially associated with decreased morbidity, improved functional and quality of life outcomes are of significant interest to patients and payer stakeholders (4).

In the following pages, we review the current evidence on the present and future use of CRT in the treatment of patients with locally advanced rectal cancer.

# First things first: the role of TME

For patients with advanced rectal cancer, surgery remains the

pillar of curative treatment. Complete TME accomplished through an appropriate surgical technique is required to assure adequate oncological outcomes and minimize intra and postoperative complications (5,6). A precise dissection between the visceral mesorectal fascia and the parietal endopelvic fascia using a conventional or minimally invasive approach enables complete *en bloc* removal of the primary tumor and associated mesorectal lymph nodes. Proper TME also prevents autonomic nerve injuries and intraoperative bleeding. This operation should be conducted by experienced surgeons in the management of rectal cancer, with lower complication rates and improved survival (7).

One of the major determinants for local recurrence is the presence of neoplastic foci within parts of mesorectum left behind (non-resected) (5). Distal mesorectal spread often extends further than intramural spread, resulting in nests of cancer cells away from the primary tumor as far as 3 to 4 cm (8). Therefore, in upper rectal tumors, the mesorectal excision (also called tumor-specific or partial) should extend at least for 5 cm beyond the distal edge of the primary tumor, whereas TME is required mid and low rectal tumor (9). These issues were addressed by Heald *et al.* with the first description of TME reported in 1982 (3). TME alone in selected cases may provide rates of local recurrence as low as 5-10%.

Another crucial surrogate marker used for local control is obtaining an adequate circumferential radial margin (CRM). Addressed in the pre-treatment staging most commonly through dedicated high-resolution magnetic resonance, imaging studies are mandatory for TME planning and decision for the need of neoadjuvant therapy (10). A pathologically compromised ( $\leq 1$  mm) circumferential resection margin [(+) CRM] is an independent predictor of local recurrence and decreased survival (5).

# Neoadjuvant chemoradiation therapy (nCRT): since when and why?

Multimodality treatment, instead of surgery alone, was initially given postoperatively, for the curative treatment of locally advanced rectal cancer. Before broad adoption and practice of TME surgery, multimodality therapy had become standard for patients with locally advanced rectal cancers (2). The efficacy of postoperative CRT was demonstrated in the GTSG and NSABP R-01 trials (11,12). In the GTSG-7175 study, it was observed a significant decrease in the overall recurrence rate after adjuvant CRT when compared to the surgery alone group (33% vs. 55%) (11). Despite not showing a difference in overall survival (OS) among groups, the CRT group had a longer time to (tumor) recurrence. Conversely, in the NSABP R-01 trial, in which surgery alone was compared with surgery plus adjuvant radiation or plus adjuvant chemotherapy, patients treated with adjuvant chemotherapy had an improved disease-free survival (DFS), despite similar rates of local or distant recurrences (12). The results of these two studies formed the basis for the 1990 U.S. National Cancer Institute Consensus Statement, that recommended adjuvant therapy for stage II and III rectal cancer (13). It was not before 1991 that the first study reporting benefits of adjuvant CRT for decreasing local recurrence rates and prolonging 5-year overall and DFS was published (14).

The initial considerations among investigators regarding neoadjuvant CRT (nCRT) was based on its potential to promote primary tumor and lymph nodes downstaging in a more oxygenated and unscarred tumor tissue allowing easier resection and eventually increasing the chance of sphincterpreserving surgery. Additional benefits included decreased toxicity due to smaller volume of irradiated small bowel, and improved functional outcomes for not irradiating a low colorectal or coloanal anastomosis.

Neoadjuvant therapy for rectal cancer is accomplished more commonly by selecting one of two main strategies: preoperative short-course radiotherapy (SCRT), and long-course nCRT. The SCRT consists of 5 Grays (Gy) of external beam radiotherapy delivered daily for 5 days ( $5 \times 5$  Gy) without chemotherapy and surgery performed within 1 week. In the long-course nCRT, preoperative external beam RT using 1.8 to 2 Gy daily doses are delivered with concurrent administration of 5-fluorouracilbased chemotherapy over 5–6 weeks. The full dose reaches 45 to 50.4 Gy and is followed by radical surgery after 8–12 weeks of resting period.

The Swedish Rectal Cancer Trial reported that patients submitted to SCRT have a lower recurrence rate (11% vs. 27%), a higher 5-yr OS (58% vs. 48%; 75 months followup), and cancer-specific survival at 9 years (74% vs. 65%) when compared to patients without radiotherapy (15). Moreover, better long-term oncologic outcomes were confirmed in a later update (16). A survival benefit for rectal cancer patients assigned to preoperative SCRT remains exclusively associated with this trial. As TME was not the standard technique during this trial, the external validity of the Swedish trial is difficult to estimate, especially if we highlight a 27% local recurrence rate in the surgery alone group.

Meanwhile, the Dutch TME trial also demonstrated better local control after 2 and 10 years for tumors located below 10 cm from the anal verge, when comparing SCRT and TME alone (17,18). However no impact on OS was observed. Moreover, if we consider a subgroup analysis of patients with pathological stage III rectal cancer undergoing TME and negative CRM, survival was better after 10 years (50% vs. 40%; P=0.032) in the SCRT group.

The next logical step would be to verify the potential advantages of neoadjuvant compared to adjuvant CRT. The German trial randomized patients to nCRT and TME or TME followed by adjuvant CRT (19). The experimental group treatment consisted of 5,040 cGy, concurrently with infusional 5-FU. All patients underwent TME 6 weeks after the completion of CRT and had 4 additional cycles of adjuvant 5-FU, one month after TME. The control group had identical postoperative treatment, except for the delivery of a 540 cGy boost in this group. Those that received nCRT had significantly lowered 5-yr (6% vs. 13%; P=0.006) and 10-yr local recurrence rates (7% vs. 10%; P=0.048) (19,20). Distant recurrence, overall, and DFS rates were similar between the two groups. Downstaging was significantly more frequent in the preoperative group as expected. In the nCRT group, 8% had developed pathologic complete response (pCR), and 25% had positive lymph nodes (40% in the postoperative group). In addition to the benefits in final pathological staging, the preoperative group had a higher chance of completing the treatment than the control group.

Although two other trials aimed to compare nCRT with postoperative CRT in the U.S., both the Radiation Therapy Oncology Group and the National Surgical Adjuvant Breast and Bowel Project were prematurely terminated due to insufficient accrual.

Current evidence supports that, combined with radical surgery, nCRT for advanced rectal cancer, results in a statistically significant reduction in local recurrence rates. Additionally, long-course CRT may reduce the odds for a CRM+ and may positively impact the rates of sphincterpreserving operation even though there is still insufficient evidence to fully support this (21). Altogether, following the publication of the German Trial, long-course nCRT became the new standard of care for patients with advanced rectal cancer.

# nCRT: how? Short- versus long-course nCRT

An alternative strategy to long-course nCRT is the use of

SCRT for the treatment of patients with operable rectal cancer, as previously reported by the Swedish and Dutch studies. A shorter neoadjuvant approach at a reduced cost are main attractive when considering SCRT.

The comparison of clinical results between SCRT and nCRT was addressed in two main trials.

In the Polish trial, no difference regarding sphincterpreserving rates was observed between the two groups (respectively, 61.2% and 58%). However, long-course nCRT was associated with more tumor donwnstaging (pCR: 16.1% after nCRT vs. 0.7% after neoadjuvant SCRT) and a lower rate of (+) CRM (12.9% vs. 4.4%) (22). In the longterm follow-up no difference was observed between the groups regarding local recurrence and overall survival. It is important to notice though that this trial was designed to evaluate if long-course CRT could lead to more sphincterpreserving surgery, and was not properly powered to evaluate difference regarding recurrence and survival. Despite meaningful downsizing, long-course nCRT did not result in increased sphincter preservation rate. The issue of defining the type of operation to be performed based on pre-multimodality treatment tumor characteristics may have certainly contributed to the results of this trial.

In the Trans-Tasman Radiation Oncology Group (TROG) Trial, the main outcome was local recurrence after treatment. Also in this study no difference was observed among the two groups in local or distant recurrence rates and overall survival. Again, after long-course nCRT, tumor downstaging was more frequently observed. However, when Annual Percentage Rates (APRs) are considered in each treatment, as observed in the Polish trial, no benefit (79% vs. 77%) could be attributed to a long-course treatment (23).

According to the MERCURY trial, magnetic resonance imaging (MRI) may have established standards for the identification of patients with high-risk rectal cancers (24). For patients with clearly resectable cancers, TME alone may provide excellent local and systemic control. On the other hand, for patients harboring features associated with a high risk for local recurrence, long-course nCRT remains the preferred option. Finally, in an intermediate group, SCRT followed by immediate surgery is an undeniably clever strategy.

The main drawback for nCRT is treatment-related toxicity, especially in frail patients. The efforts in avoiding toxicity, by omitting chemotherapeutic agents may negatively affect efficacy. Ultimately, since there is significant morbidity associated with radical surgery for rectal cancer, complicated cases may not be fit enough to receive adjuvant chemotherapy leading to low overall compliance rates.

Despite the disadvantages of long-course nCRT toxicity, SCRT is still not the new standard of care (25). In the currently ongoing RAPIDO trial, patients with high-risk rectal cancer as determined by MRI are randomized to nCRT ( $25 \times 1.8$  or  $25 \times 2$  Gy with capecitabine) and selective postoperative adjuvant chemotherapy or SCRT ( $5 \times 5$  Gy) followed by full-dose chemotherapy (26). These results may significantly contribute to the understanding of current options in neoadjuvant therapy.

# Optimal interval between nCRT and radical surgery: pursuing pCR

In an attempt to increase tumor response to nCRT and the rates of pCR, some groups proposed to increase the interval between CRT and radical surgery. Most commonly, TME has been recommended 6–8 weeks after CRT completion to maximize tumor regression and avoid extensive fibrosis (27-30). However, several studies have shown that longer intervals between CRT and surgery may increase the rates of pCR without increasing perioperative complications or worsening the oncologic outcomes (27,29,30). This is still a matter of debate in rectal management, without agreement over which is the best interval.

The issue concerning the interval between nCRT completion and radical operation exists for a long time. In the Lyon R90-01 Trial, patients were randomized to be operated after 2 or 6 weeks after CRT completion (31). Clinical response increased from 53.1% to 71.7% in the group randomized for longer interval. Since these results were published, 6 weeks become the standard of interval for operation after CRT.

However this interval did not seem enough. In 2004, Moore *et al.* have shown that the rate of pCR increased from 9% to 23% comparing patients operated before 6 weeks after nCRT completion and those that waited more than 7 weeks (27). A few years later, Tulchinsky *et al.* demonstrated that the pCR rates were higher after a longer (>7 vs.  $\leq$ 7 weeks) interval between nCRT completion and surgery: 35% vs. 17% (P=0.03). And that those patients operated after 7 weeks had significantly better DFS (P=0.05) (28).

Habr-Gama *et al.* waited longer in their retrospective study comparing patients operated  $\leq 12$  weeks with those operated >12 weeks from nCRT completion (30). They observed similar rates of OS and DFS suggesting the safety of this approach. Also Kalady *et al.* observed higher rates of pCR when waiting longer than 8 weeks, and that these patients had better OS and local recurrence-free survival after 5 years than patients with incomplete response (32). Moreover, the local recurrence rate after 3 years was significant lower in the >8 weeks group (1.2% *vs.* 3.9%). Ultimately, the same group observed that the postoperative morbidity or mortality were similar between the two groups (29).

Probst *et al.* have published a retrospective observational study comprising information from the U.S. National Cancer Data Base (33). In this study, the association between interval time and pCR, surgical morbidity and tumor downstaging were evaluated in 17,255 patients using different cut-offs (<6, 6–8, >8 weeks). Longer interval was associated with higher pCR rates and tumor downstaging.

Even though a significant amount of retrospective studies supported the potential benefits of prolonged intervals between CRT completion and surgery, the recently reported results from the GRECCAR-6 study has reported rather disappointing outcomes. The comparison between 7 and 11 weeks after CRT completion and radical surgery not only resulted in no differences in pCR rates but also showed inferior outcomes for the 11 weeks interval group in terms of quality of the mesorectum and postoperative morbidity (34).

After standardization of multimodality treatment and proper TME surgery, the development of distant relapse became more relevant than local recurrence. Consequently, postoperative adjuvant chemotherapy should be recommended at least to some (if not all) patients treated with nCRT. However up to 27% of patients eligible to adjuvant chemotherapy never actually receive treatment as a significant amount of patients fail to receive the fullprescribed treatment due to postoperative complications or stoma closure. A systematic review including more than 15,000 patients demonstrated that a 4-week delay in treatment is correlated with a 14% decrease in OS (35). Moreover, the use of chemotherapy in the resting period between nCRT completion and response assessment could potentially increase rates of clinical complete response (cCR). Habr-Gama et al. added chemotherapy during this interval, demonstrating an increased rate of cCR. In this prospective study, 34 patients with rectal cancer underwent radiation and 5-fluorouracil-based chemotherapy every 21 days in six cycles (36). The complete response rate was 65% for at least 12 months after nCRT. The authors concluded, although in a preliminary basis, that the addition of chemotherapy during the resting period (also known as

"consolidation" chemotherapy) and after nCRT resulted in considerably high rates of complete response.

Patients harboring tumors that achieve a pCR after nCRT have a better prognosis than the non-responders. In these patients, local recurrence is uncommon and survival is excellent. However, response to chemoradiation is variable. Moreover, the proportion of patients achieving a pCR remains not only unpredictable, but small. Garcia-Aguilar *et al.* conducted a non-randomized trial adding cycles of mFOLFOX6 between nCRT and surgery (37). In the group without additional mFOLFOX6 cycles 18% of patients achieved pCR. In the groups of patients receiving two, four, or six cycles of mFOLFOX6 the pCR rates were 25%, 30%, and 38% respectively.

Current recommendation suggests surgery to be scheduled after 6 to 8 weeks following nCRT completion as the standard. Still, optimal timing of surgery remains controversial with evidence supporting that longer interval may increase tumor downsizing.

# Complete clinical response after nCRT and the watch and wait (WW) strategy

nCRT for rectal cancer may result in significant primary tumor downstaging. In fact, the degree of tumor downstaging may lead to clinically relevant consequences in terms of long-term oncologic outcomes. Survival and local disease control seem to be directly related to tumor regression, while complete pathological response is clearly associated with improved oncological outcomes (38). Radical surgery remains the cornerstone of the treatment of patients with locally advanced rectal cancer. However, up to 33% of patients treated with nCRT exhibit a pCR at the time of surgical resection (31). In the setting of a pCR, local recurrence rates lower than 1% and 5-year survival rate higher than 95% lead us to question the true benefit of TME for these patients (38). Moreover, tumor downstaging and pCR may offer the possibility of sparing patients from significant postoperative morbidity associated with TME, avoidance of a definitive stoma or even the need of any surgical resection with an organ-preserving strategy. Also known as the WW approach, it was pioneered in an institutional level in Sao Paulo (39-42).

Regarding radical surgery for rectal cancer after nCRT, several perioperative complications, including vascular injury and presacral bleeding, infection, wound complications, ureteral injury, and both urinary and sexual dysfunction, are associated with this procedure (43). The Dutch TME trial observed in-hospital postoperative mortality and overall complication rates of 3% and 47%, respectively (17,44).

If there is not a viable cancer cell left after nCRT, then radical surgery may not add a clinical benefit at the expense of adding risk for increased morbidity (45). WW precludes pathologic confirmation of the primary tumor and lymph node response. As a result, a cCR is used as a surrogate for pCR. The determination of a cCR is defined after assessment through a combination of digital rectal examination, direct visualization by proctoscopy, and imaging studies with or without biopsy confirmation. The definition of a complete clinical response should be based on strict clinical and endoscopic findings. The finding of any residual superficial ulceration, irregularity, or nodule should prompt surgical attention, including transanal fullthickness excision or even a radical resection with TME. Standard or incisional biopsies should be avoided in this setting (46). Endorectal ultrasound (ERUS) imaging and MRI are useful techniques for rectal cancer staging. In one meta-analysis, ERUS was found to have increased sensitivity for perirectal tissue invasion in comparison with MRI (90% vs. 82%). However, regarding imaging of lymph node involvement, both methods had similar rates of sensitivity and specificity (66-67% and 76-78%, respectively) (47). In contrast to the results of baseline imaging evaluation, in a meta-analysis both techniques overstaged (73% and 66%) patients with pCR (vpT0), respectively (48), and also had a poor sensitivity (MRI, 15%; ERUS, 37%) but high specificity (95% for both). Moreover, the accuracy for nodal restaging for both MRI and ERUS has been reported to be approximately 72% (48).

The experience with WW for potentially curable advanced rectal cancer has evolved with time. Most patients in early studies were not staged or followed with modern imaging techniques, including MRI and ERUS, mainly because these techniques were not widely available. Therefore, the assessment of cCR was almost exclusively based on clinical/endoscopic examination. Habr-Gama *et al.* defined that the follow-up of cCR demands intensive followup evaluations every 8 weeks after nCRT completion (46). Moreover, a 1-year disease-free interval has been arbitrarily defined in earlier studies for the classification of a cCR in order to rule out early regrowths requiring immediate salvage procedures.

In an early publication, Habr-Gama *et al.* reported the outcomes of 265 patients with distal rectal adenocarcinoma treated with nCRT (5,040 cGy with infusional

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5-fluorouracil) (40). Only 26.8% of patients had cCR, 2.8% of patients developed an endoluminal recurrence, successfully salvaged, and 4.2% metastatic disease (57 months follow-up). A larger report confirmed the safety of this approach (42).

Following the published experience regarding WW led by the group of Sao Paulo, other institutions have reported small series regarding multimodality treatment of locally advanced rectal cancer without immediate surgery. Maas *et al.* using MRI found that only 11% of patients were eligible for WW. These patients had a 2-year DFS (89% *vs.* 93%) and OS rates (100% *vs.* 91%) similar to pCR patients. Patients who were treated operatively had more bowel dysfunction.

Appelt *et al.* prospectively evaluated patients with resectable distal rectal adenocarcinoma (49). In this trial, patients underwent high-dose external beam radiation therapy (60 Gy with a 5-Gy endorectal boost) and oral tegafur-uracil. Seventy-eight percent of patients diagnosed with cCR were initially managed without radical surgery. Cumulative local recurrence rates were 15% and 26% for 1- and 2-year follow-up. All patients were surgically salvaged.

Smith *et al.* reported the outcomes of 32 patients with rectal cancer after a 28-month follow-up. Local recurrence for WW group was 21% versus 0% in patients with pCR treated at the same institution (50). Successful salvage surgery was performed on all patients with local failure and outcomes were similar between the groups. This updated data from 73 patients achieving cCR, showed local tumor regrowth in 26% (3.5 years follow-up) and almost all patients were surgically salvaged. Rectal preservation rate for the series was 77%. Overall and DFS were similar between groups.

Habr-Gama *et al.* published the results of 70 patients treated with extended nCRT (also referred to as consolidation nCRT) chemotherapy (51). Forty-seven out of 69 (68%) patients that completed the treatment had cCR 10 weeks after nCRT. Of these, 39 sustained cCR for 12 months. Four developed local recurrence more than one year after nCRT. Overall, 35 (50%) patients have not undergone surgery after a median follow-up of nearly 4 years.

A significant proportion of patients with initial cCR may still develop local failure during the first 12 months of follow-up meaning that significant improvements in appropriate identification of cCR are warranted.

More recently, the OnCoRe project evaluated the acceptance of WW in what they have called "a real

world multicentric setting". In this trial, 109 patients who developed cCR after nCRT were managed with no immediate surgery and 109 patients were operated. Patients not operated on immediately had a slight difference in 3-year DFS (88% *vs.* 78 and better colostomy-free survival (74% *vs.* 47%).

Despite these favorable experiences with no immediate surgery after a complete clinical response following nCRT, two studies have been reported recently attempting to caution the use of this WW approach. By querying the National Cancer Database (NCDB) in the U.S., Ellis et al. have tried to correlate the absence of surgical resection after nCRT with low-volume centers, uninsured patients and worse long-term survival. However, these studies underscore the importance of restricting such approach only to highly selected patients with thorough assessment of response after nCRT and achieving a complete clinical response. In the NCDB, no information is available regarding tumor response and it is likely that patients in both studies never underwent surgery for reasons other than presenting a cCR. In other words, no surgery after nCRT is very different from no immediate surgery after complete clinical response following nCRT (52-55).

Finally, efforts have been made to minimize the use of neoadjuvant RT. After the experience with exclusively chemotherapy for metastatic disease, the PROSPECT study is investigating the impact of neoadjuvant chemotherapy alone for locally advanced rectal cancer. Patients that develop favorable response to chemotherapy alone may undergo radical surgery or even WW (if complete clinical response is achieved) while only poor responders to chemotherapy are still referred to further (standard) CRT. The idea of delivering upfront chemotherapy is to address micrometastatic disease in addition to avoid the potential disadvantages of radiation therapy to the pelvis. Preliminary data have reported promising outcomes with nearly 30% complete pathological response rate (56).

### Conclusions

In conclusion, management of rectal cancer has evolved significantly over the past decades and requires a multidisciplinary approach. Even though local control is now more easily achieved with proper surgical resection, neoadjuvant approaches may provide significant tumor regression allowing for organ-preserving strategies, provided assessment of tumor response shows evidence of complete tumor regression. Future studies addressing

oncological and functional outcomes with these various treatment strategies are warranted to further optimize the roles of surgery, radiation and chemotherapy in this setting.

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# Footnote

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# Hyperthermic intraperitoneal chemotherapic perfusion in colorectal cancer

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#### Introduction

The term peritoneal carcinomatosis (PC) includes all tumoral dissemination, either local or massive, to the peritoneal serosa and neighbouring anatomical structures. The term PC was first used by Simpson in 1931 to describe the peritoneal dissemination of an advanced ovaric cancer (1).

Traditionally, the PC is considered a stage IV tumour indistinguishable from other metastatic sites (2).

The PC may manifest very differently, since few millimetric implants adjacent to the primary tumour to the occupation of the entire abdomen and pelvis of bulky tumour masses. Most patients with PC progress to intestinal obstruction, ascites formation, tumour cachexia or combination of them all. The term PC is associated with very advanced tumours without therapeutic possibilities. Patients often suffer a significant deterioration in their quality of life before death (3-5).

The incidence of PC is difficult to establish with certainty due to the diagnostic limitations of image-based media and current biological measurement. The ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are sensitive to diagnose visceral recurrences, retroperitoneal, and some indirect signs of PC, but miss infracentimétric peritoneal disease (6).

Laparoscopy seems to be an effective method for diagnosis, establishing the location extension of peritoneal disease and to determine tumour histology, but has technical limitations, and involves a risk of peritoneal extent of spread (7).

Over 400,000 new patients/year are diagnosed of

colorectal cancer in Europe, wherein PC is detected to coincide with the diagnosis of primary tumour in 10% of the patients (8). Recurrence is only at peritoneum in 10-35% of the patients who relapse after treatment of the colorectal tumour (3-5,9,10).

The usual treatment of the PC is palliative and therefore with limited survival. A prospective, multicenter study included patients with PC from colorectal cancer showed a survival of only 5.2 months (11). In other reports published before 2002, including large series of patients with PC of colorectal origin, the mean survivals were referred from 5 to 9 months (12). Current chemotherapy protocols that include new systemic drugs such as oxaliplatin or irinotecan alone or in combination with biologic agents get to prolong survival of these patients from 21.5 to 24 months. These studies have been conducted in patients with colorectal cancer who had any kind of metastatic disease (13-19). It is known that the natural history and response to systemic chemotherapy of the peritoneal disease are significantly worse than in other metastatic sites, such as liver or lung (13). To date, there are no published studies that have evaluated the response of patients with peritoneal metastatic disease exclusive to these new lines of chemotherapy. Surgery as sole treatment in the PC is associated, to a new peritoneal recurrence (14,20,21). It is rare that a patient diagnosed with PC treated with any type of palliative treatment, remains alive at 5 years.

In recent years, interest in the peritoneal dissemination of tumours has increased due to better clinical outcomes achieved with multimodal treatments and recent knowledge on the development and peritoneal tumour growth, which allowed considering the PC as a locorregional disease (22).

PC may benefit from intensificated regional therapy as successfully as metastatic liver disease.

In late 1980, Sugarbaker laid the foundations of a multidisciplinary approach that combines the PC radical surgery and immediate administration of intraperitoneal chemotherapy with or without hyperthermia, designed to eradicate microscopic residual tumour. This treatment has been quite favourable in the treatment of low-grade tumours, especially in the peritoneal pseudomyxomas from appendiceal origin and in some peritoneal mesotheliomas. In recent years, several working groups specialised in many centres in America and Europe are applying multidisciplinary treatment in the PC, and indications have been extended to other types of malignant tumours of the peritoneum, due to the good results published.

Controlled prospective studies are conditioned by the difficulties in recruiting patients with rare tumours with highly variable clinical presentations, the complexity of homogenisation of each of the elements of a complex treatment, especially surgery, and the patients agreement to be assigned to a palliative treatment arm versus the possibility of potentially curative treatment (23).

### Pathophysiology of peritoneal carcinomatosis

The peritoneum is an organ that covers the threedimensional structures contained in the abdominopelvic cavity. It coomprises a single layer of mesothelial cells on a basal membrane and five layers of tissue with a total thickness of 90 microns. The layers of tissue includes interstitial cells and a matrix of collagen, hyaluronic acid and proteoglycans (24). The known functions of the peritoneum are the production of a lubricating substance to facilitate contact between the elements of the abdominal cavity to act as an important organ of defense against intraabdominal infections. It is now recognised another function of the peritoneum in the development of neoplasms, acting as a first line of defense against the introduction and tumour development (25). Any injury or wound the peritoneum acts as a facilitator of tumour cell implantation into the abdominal cavity and is involved, along with other elements in tumour proliferation (26).

Neoplasms of the digestive, gynaecological and other sources often use the coelomic route for the tumour spreading.

Tumour cells can be released into the abdominal cavity from the serosal surface of the organ infiltrated by the tumour (27). Surgery can contribute very significantly to the exfoliation of tumour cells into the abdomen. It has been shown that during the extensive removal of primary tumours and/or lymph node involvement, a significant number of tumour cells are released into the abdominal cavity (28-30).

The meaning of free tumour cells in the abdominal cavity is still unknown. The number of tumour cells that are required to effectively implant in the peritoneum is much lower than those necessary for the development of other types of metastasizing tumour. This phenomenon is known as "metastatic inefficiency" and was corroborated by animal studies that demonstrated the greatest tumour tropism of some strains by peritoneum (31,32).

Free tumour cells in the abdominal cavity have to evade the immune system and develop a network of vascular substitution to meet their metabolic needs in order to survive. Due to the complexity of these processes, many tumour cells cannot become metastatic tumour deposits.

Tumour cells that remain viable are moved into the abdominal cavity by hydrodynamic movements associated with breathing and following predictable routes, which would explain the predominance of tumour implants on the surface of the right hemidiaphragm. The presence of ascites and resorption areas with high phagocytic capacity, as the omentum and epiploic appendices, justify the very large tumour accumulations, known as omental cake. Intestinal peristalsis, together with the effect of gravity, facilitate the distribution of the tumor in most areas slopes, such as Douglas sac, the parietocolic gutters, retrohepatic fossa and those fixed anatomical structures such as the ileocecal region and the first jejunal portion (33).

In women, tumour cells very often affect the ovaries, especially at points of follicular rupture. Tumour cells have high affinity for the intercellular matrix of the injured peritoneum or bloody areas caused by the surgery. The tumoral entrapment process is especially fast and can occur in minutes facilitated by the effect of integrins, cell adhesion molecules, and production of growth factors such as growth factor for fibroblasts (fibroblast growth factor, FGF), epidermal growth factor (epidermal growth factor, EGF) and transforming growth factor beta (transforming growth factor beta, TGF-) (34). All these molecules appear during the physiological mechanisms of inflammation and tissue healing. The binding of tumour cells with the intercellular matrix of tissues is also very strong and impossible to avoid using washing/stripping solutions commonly used during conventional surgery. After surgery, the implantation of tumour cells in the intercellular matrix is usually immediate and once they are coated with fibrin and other products in

the processes of tissue repair, they become "sanctuaries" where cells can proliferate protected from the external environment. Tissue adhesions formed early after surgery avoids the cytotoxic effect of intraperitoneal chemotherapy and the absence of a neovascular network prevents the access of systemic chemotherapy.

# **Multimodality treatment - Therapeutic basis**

The approach and development of multidisciplinary treatment of the PC (radical surgery plus intraperitoneal chemotherapy +/- hyperthermia), also known as regional treatment of malignant diseases of the peritoneal surface or Sugarbaker's technique, is related to the current understanding of the pathophysiology of the peritoneum and the mechanisms for implementation and growth of tumours in the abdominal cavity.

In 1989, Sugarbaker defined PC as a locoregional manifestation of neoplastic nature. He proposed a treatment of "regional therapeutic enhancement" for the PC, based on a radical surgery, designed to remove the entire macroscopic tumour of the abdominal cavity, followed by immediate administration of intraperitoneal chemotherapy, with or without the use of hyperthermia (35,36).

The more widespread use of multidisciplinary treatment has advanced the definition and practice of the radical surgery, the type and timing of intraperitoneal chemotherapy, the adaptation of the techniques of hyperthermia, the protocols of care and postoperative controls and, particularly, in the appropriate selection of patients. Biannually since 1998, meetings of experts from the Peritoneal Surface Oncology Group International (PSOGI) are being held, and experiences are addressed and discussed on the treatment of these diseases. The 5th Workshop Meeting, held in Milan, was particularly relevant, since it addressed controversial issues of each part of the therapy and established consensus on issues as important as the methodology of the radical surgery, intraperitoneal chemotherapy and hyperthermia, the role of the various specialties involved in the management of these patients and, especially, the criteria for patient selection and multidisciplinary treatment indications. The most important conclusions of this meeting in Milan were published in a special issue of the Journal of Clinical Oncology (37).

# Radical surgery

The prognosis of patients with PC undergoing

multidisciplinary treatment is directly related to the extension of the disease and surgical radicality (38). The aim of radical surgery is to remove the abdominal tumour without leaving any visible macroscopic residual disease. The extent and distribution of the PC must be fully established before starting the process. The highest concentration of tumour is usually located in the retrovesical space, the pouch of Douglas, the parietocolic gutters, the right subhepatic space and more posterior subdiaphragmatic areas. Very often, the omental transcavity, the retrogastric compartment, the splenic hilum and the mesentery of intestinal segments, more fixed and less mobile (duodenojejunal angle, distal ileum and sigmoid colon) are affected. The postsurgical adhesions and structures with low venous return (hernia sacs) present special predisposition to tumor development. All anatomical regions of the abdomen and pelvis may be affected by tumour seeding and should be explored carefully. An important step of this operation corresponds to the identification of all tumour foci present in the abdominal cavity. The correct characterization and quantification of PC allows determining the technical and clinical benefits of the radical surgery. Sugarbaker described the peritonectomy procedures which are a key therapeutic element in the multidisciplinary treatment of PC (39). Peritonectomy procedures can eliminate the gross tumour present in the peritoneal serous as well as the removal of the viscera and surrounding structures deeply infiltrated by the tumour.

The removal of the implants with diffuse and extensive distribution in the peritoneal surface requires the stripping of the entire peritoneum of the corresponding anatomical region. Few isolated implants of visceral or parietal peritoneum that infiltrate can be completely removed or electrovaporised by high voltage electric scalpel.

Bulky implants invading deeply into an organ or anatomical structure may obly to associate an excision of it. In the extensive or limited but high volume PC may require multivisceral resections and/or large bowel resections, sometimes multisegmental, followed by digestive anastomosis. Tumour involvement of a significant portion of the small intestine may limit or prevent any radical surgery. When the length of residual intestine does not ensure an adequate supply, surgery should be avoided. In addition to the extensive involvement and/or multisegmental bowel, other operative findings that impair or limit the complete cytoreduction in patients with CP, is the gross involvement of the hepatobiliary hilum, full retraction of the mesentery and/or massive retroperitoneal nodal involvement (40). The

use of electrocautery provides hemostasis while a bed of sterilized dissection plane of tumour cells

#### Intraperitoneal chemotherapy

Chemotherapy administered regionally aims to achieve high concentrations of a cytotoxic agent in tumours located at a particular point of the body. Administered intraperitoneally, enables a very intensive treatment of tumours located in the abdominal cavity in relation to the dose of drug used. Dedrick showed that in various chemotherapeutic drugs, hydrophilic peritoneal permeability was considerably less than its plasma clearance, resulting in proportionally much higher concentrations of intra-abdominal chemotherapy (41).

The primary objective of intraperitoneal chemotherapy is to achieve high concentrations of drug in the site of the tumour, minimizing the systemic side effects.

The first use of intraperitoneal chemotherapy correspond to Spratt, who used the intraperitoneal thiotepa in a patient with peritoneal pseudomyxoma, Speyer used 5-fluorouracil (5-FU) and methotrexate. Koga then associated intraperitoneal chemotherapy with hyperthermia in the treatment of gastric carcinomatosis (42).

The molecular weight of the drug, its lipid solubility and capillary permeability determines its passage into the systemic circulation. Other requirements that must be taken into account in the choice of intraperitoneal chemotherapy are the time of removal from the systemic circulation, the ability to pass the portal system and the empowerment of their effects by hyperthermia. Cell cycle-nonspecific drugs are a priority for the intraperitoneal use (43,44).

Several studies have established a maximum of 2-3 mm penetration of chemotherapeutic agents in tumour tissue. This ability to penetrate tissue explains that the ideal limit set of residual disease after radical surgery considered is equal to or less than 2.5 mm (45,46). Peritonectomy procedures do not affect the pharmacokinetics of intraperitoneal drugs (47,48). The molecules used are 5-FU, mitomycin C, oxaliplatin and irinotecan. Drugs can be administered alone or in combination (49).

The dose of chemotherapeutic agents administered in HIPEC is calculated from the body surface that correlates with drug metabolism and systemic toxicity. Nevertheless some authors propose to dosify based on drug concentration (mgr/L) (50).

The procedures for intraperitoneal administration of chemotherapy vary according to time and how to apply them in the abdominal cavity. The maximum benefit is achieved when used immediately after surgery, before the "entrapment" of tumour cells by fibrin and the partitioning of the abdominal cavity for surgical adhesions.

When chemotherapy is administered intraperitoneally from days 0 and 5 of immediate postoperative period is called early postoperative intraperitoneal chemotherapy (EPIC). The EPIC was initiated after tumour removal, allowing fibrin and microscopic cellular remnants removal from the abdominal cavity, which is then bathed with the chemotherapic solution. The solution is stored for 23 hours and removed daily through catheters (51). Several cycles of intraperitoneal chemotherapy are given to increase the chances of exposure of chemotherapy to tumour cells, but has the disadvantage that produces greater systemic adverse effects and allows the partitioning and sequestration of chemotherapeutic agents located favouring infection (52,53).

# Hyperthermia

The association of heat to intraperitoneal chemotherapy enhances the therapeutic effect of some chemotherapic drugs and creates a "toxic shock" directly on tumour cells. At a meeting of the international medical community held in Madrid in 2004, it was agreed that this technique should be referred to as HIPEC (54).

Some animal studies show that chemohyperthermia offers a greater therapeutic benefit above that of hyperthermia or chemotherapy administered intraperitoneally alone (55). Hyperthermia destroys tumour cells when temperature reaches 43 °C. Normal cells are heat resistant up to 45 °C (47). Cellular metabolism increases with temperature until a point at which irreversible damage occurs. The critical point of human cells is 43.5 °C, while in vitro temperature of 42.5 °C produces a high cytotoxic effect by acting on the interstitial pressure in tumour tissue, favouring the penetration of drugs such as mitomycin C, cisplatin, oxaliplatin and irinotecan, or acting directly on the cell itself and its molecular composition. It has been described effects on the cytoskeleton, such as changes in the stability and fluidity of cell membrane alterations in cell shape, decreased intercellular transport mechanisms, alterations in membrane and induction of apoptosis. Also, alterations in protein synthesis, protein denaturation, aggregation of nuclear matrix proteins and induction of synthesis of heat shock proteins (HSP) have been demonstrated in the intracellular proteins. Heat has also shown effects on nucleic acids, decreased synthesis of RNA/DNA, inhibition DNA repair enzymes and alteration

of the latter. Hyperthermia influence cellular function by affecting the metabolism of several intracellular substrates expression of the genes and signal transduction. Other effects are related to the cellular immune response with the induction of those already mentioned HSP involved in antigen expression and tumoral immunity.

Hyperthermia has shown clinical efficacy in several randomized studies, either as direct mechanism or due to the enhancing effect on radiation therapy and chemotherapy. Clinically, the major tumoricidal effects of hyperthermia are achieved between 41 and 43 °C (56).

There are two ways to settle the perfusion. The technique described by Sugarbaker, called open technique or coliseum, is the most widespread. It involves the administration of HIPEC leaving the abdomen open.

The other mode, called the closed technique is applied with a temporarily closing of the abdomen for the administration of chemohyperthermia. This type of HIPEC is supposed to increase the drug penetration in the tumour by an increased abdominal pressure. There are no studies to demonstrate which mode provides greater clinical benefit to patients. The technical feasibility of HIPEC has been established in recent years by several authors (57,58).

The optimum temperature of the HIPEC is a very important parameter. Most chemotherapeutic agents used are chemically stable to 50 °C. Studies *in vitro* and in cell culture show that the cytotoxicity is more effective at 45 °C than at 41 or 42 °C, so it would be reasonable to use the maximum temperature within the limits of clinical tolerance checked, which, as we mentioned above, is marked by tolerance of the small intestine and corresponds to 43 °C (59,60).

#### Other parameters

The carrier solution used in intraperitoneal chemotherapy can modify the exposure time of chemotherapeutic agents in the abdomen. With the aim of increasing the exposure time, various types of solutions have been used. A high molecular weight creating ascitis maintains a higher availability of the drug. The selection of the solution is particularly relevant in the EPIC (61,62). In HIPEC, with a dwell time relatively short, one might expect that a hypotonic solution increases the uptake. But Elias demonstrated that dextrose solution of 100 and 150 mOsm/L, which not only does not increase tumour penetration, but also is associated with a high rate of serious complications (50%) and peritoneal bleeding and thrombocytopenia, so this author contraindicated hypotonic solutions as transport solution for HIPEC (63).

The duration of HIPEC is an issue still debated. The safety of hyperthermia has only been demonstrated in established empirically based schemes: temperature of 41 °C for 90 minutes or 43 °C for 30-40 minutes. In clinical practice, the duration of administration of HIPEC is set between 30 and 90 minutes, and varies according to the pharmacokinetic characteristics, the total dose of chemotherapy and the protocols. The intra-abdominal pressure during HIPEC directly influences the diffusion and penetration into the tissues and, consequently, a greater cytotoxic effect of chemotherapy.

# **Multidisciplinary treatment indications**

The multidisciplinary treatment is widely recommended for the PC secondary to colorrectal tumours (33,34,37). Current indications were recently updated in the Journée Nationale du Traitement par des Carcinoses Peritoneal Chirurgie et Chimiothérapie Intrapéritoneale (Paris, May 2008).

These Indications were previously discussed at the Fourth International Workshop on Peritoneal Surface Malignancy (Madrid, December 2004) and Peritoneal Surface Malignancy in the Workshop-Consensus Statement (Milan, November 2006). Data from the United States calculates an incidence of 130,000 new cases per year, in colorectal cancer, of which between 10-15% will start with peritoneal involvement.

In Europe, annual incidence data of the PC are even higher: 25,000 to 37,500 new cases annually of PC of colorectal origin. An analysis by the French groups dedicated to the treatment of PC, estimated that approximately 10% of patients with CP can benefit from a multidisciplinary treatment applied with curative criteria (64).

### **Patient slection**

#### Preoperative assessment

The indication of the multidisciplinary treatment of PC has to be done from a strict selection of patients. The highest survival rates described with this treatment correspond to those patients who were able to perform a complete tumour debulking. The incomplete cytoreduction was associated with a mean survival about 6 months (65,66). The distribution and especially the extension of the PC are the main determinants to achieve complete cytoreduction, so it is essential to establish preoperatively the characteristics of

the PC to define the indications.

There are several techniques to help identify patients likely to undergo multidisciplinary treatment: CT, MRI, PET, laparoscopy and tumour markers.

There is consensus on the need to perform a colonoscopy in all patients. The CT has great value in the detection of primary lesions or recurrences affecting solid organs and retroperitoneum, but has limitations in identifying small peritoneal implants, particularly those located in the small intestine, and mesenteric leaves. When CT fails to detect this type of implants, the disease is usually advanced and we consider a limiting data to achieve a complete cytoreduction. The CT findings of small bowel obstruction in several segments or the presence of tumour greater than 5 cm located outside the terminal ileum are associated with 88% chance of incomplete surgical resection. Contrary, the absence of these two radiologic findings, achieves a 92% complete cytoreduction. Helical CT was compared with operative findings and the sensitivity obtained was 25% to 37% with a negative predictive value ranging from 47% to 51% (67).

MRI is an exploration that provides a sensitivity and specificity of intestinal tumour involvement in the PC of 73% and 77%, respectively (68). Other studies provide a sensitivity of 84-100% for detecting peritoneal metastases with this test (69). In patients undergoing surgery, chemotherapy or prior radiotherapy and/or associated inflammatory diseases, the specific diagnosis of peritoneal involvement is difficult to determine by MRI.

The PET scan has a low sensitivity in small tumours (<1 cm), poor specificity and limitation in low-grade tumours. It also presents difficulties in the interpretation of lesions in the diaphragm, lung bases and top of the liver due to breathing artephacts. Any of the current means of imaging has limitations to establish the extent and exact location of the peritoneal tumour disease. The use of CT, MRI, PET and/or laparoscopy should be individualised and considered as part of a diagnostic-therapeutic approach of patients with PC, which may depend on the availability, cost and experience of the radiologist. The result of the consensus of Milan was to consider CT as the imaging technique essential to investigate the indications of multidisciplinary treatment.

Some centres use laparoscopy to determine the possibilities of multidisciplinary treatment, as it has the advantage of providing direct visualisation, allows detection of small lesions and practice biopsies. The disadvantages of this technique are its relative invasiveness, technical difficulties due to adhesions, limitations on access to the retroperitoneal compartment, the risk of implantation at trocar sites and the increased cost to the overall therapeutic process. There is a study evaluating the role of exploratory laparoscopy in the selection of patients with PC candidates for complete cytoreduction. In this study laparoscopy could be performed in all patients with a mean operative time of 38 minutes (range, 23-75 minutes) was well tolerated in all patients, it achieved a very accurate set of the real characteristics of the peritoneal disease and adequately identified patients for complete cytoreduction (70).

Another study, involving 97 patients with PC undergoing laparoscopy for peritoneal staging, concluded that laparoscopy allowed establishing the extent of PC in 96 of the 97 patients and only two were classified in a lower stage. It shown a good correlation between the findings of laparoscopic exploration and open surgery. Laparoscopy showed no mortality in this group of patients and observed no tumour implantation at port sites. In patients with inadequate or contradictory information on the extent of the PC, laparoscopy is a useful technique to establish the extent and distribution of the PC, to visualise the small bowel involvement and determine the possibility of a complete debulking more accurately (71).

#### Intraoperative assessment

The importance of establishing with certainty the distribution and extent of peritoneal disease to determine the applicability of multidisciplinary treatment has forced to design intraoperative quantification of the extent of the PC.

Currently we have three staging systems to assess the intraoperative peritoneal spread of the disease, none of which has been shown to have prognostic value for all types of PC. Gilly et al. (72,73) described a system for intraoperative measurement of the PC and it has shown to correlate with the patient outcomes in certain types of PC. Zoetmulder et al. established a simplified system of Sugarbaker's classification (74). Simplified Peritoneal Cancer Index (SPCI) demonstrated the validity in peritoneal pseudomyxoma and PC of colorectal origin. This system is also a predictor of complications and acts as a guideline in selecting patients for multidisciplinary treatment. The most universally used system of quantification is the Peritoneal Carcinomatosis Index (PCI) described by Jacques and Sugarbaker (75). It describes 13 anatomical regions, dividing the abdomen into 9 regions and the small intestine in 4. It rates each region from 0 to 3 depending on the size of the tumour lesion: 0 point, no macroscopic lesion;
1 point, tumour exceeding 0.5 cm; 2 points, a tumour of 0.5 to 5 cm and 3 points, greater than 5 cm or tumour confluence, resulting in a maximum score of 39 points. The PCI ranks of the PC extension, determines the possibilities of radical surgery and helps to establish the prognosis of patients. It also has proven to be predictive in survival of patients with PC of colorectal origin being PCI 20 the cutting point (76). This system of intraoperative tumour quantification was considered in the consensus meeting of Peritoneal Surface International Workshop Malignancy, in Milan, as the most useful, reliable and reproducible in the multidisciplinary treatment of the PC (77).

Intraoperative determination of the intensity of the radical surgery has the same importance as determining the extent of the PC. There is a direct relationship between the size of residual disease after surgery and the survival of patients undergoing multidisciplinary treatment. We have several systems that classify the size of residual disease after debulking. Most of these classifications belong to the R residual tumour classification and correspond to changes in the American Joint Committee on Cancer (78): Lyon (79) classification, Netherland's classification (80) and Winston-Salem's (81). The classification used is the Completeness of Cytoreduction Score (CC) (82), which rates residual disease after surgery in: CC-0 in the absence of gross residual disease, CC-1 if the residue tumour is equal to or less than 2.5 mm, CC-2 if the residue is 2.5 to 25 mm and CC-3 when the residue is above 25 mm or confluent persists after tumour surgery. This system does not provide the definition of microscopic residual disease in PC. The rationale for setting between 0 and 2.5 mm size limit of residual disease and appropriate to establish the concept of complete cytoreduction is due to the ability of a chemotherapeutic intraperitoneal to penetrate the tumour tissue.

But the definition of complete cytoreduction currently most accepted corresponds to the CC-0 and CC-1 cytoreduction and incomplete, CC-2 and CC-3. The CC has been associated with patient survival in carcinomatosis of colorectal origin (74,83-85).

In the future the use of more active chemotherapeutic agents can modulate the effort of the cytoreductive and the definition of radical surgery matches other criteria of residual tumour volume.

The type of previous surgery performed on the primary tumour has also been associated with chances of achieving a complete cytoreduction and the prognosis of patients who undergo multidisciplinary treatment. Sugarbaker introduced the Prior Surgical Score (PSS) (83). The PSS determines the number of regions dissected during surgery prior to the multidisciplinary treatment, and has been shown to correlate with survival.

#### Inclusion and exclusion of patients

The multidisciplinary approach provides a significantly higher survival rates than conventional palliative treatments, but is associated with significant morbidity and mortality. The identification of factors associated with the outcome of multidisciplinary treatment application and the patient selection is important to establish the treatment indications and maximise the clinical benefit (86).

Currently the parameters considered most useful are the following:

- Performance status (Eastern Cooperative Oncology Group): 2.

- Absence of extra-abdominal tumoral disease.

- Less than three hepatic lesions which are technically resectable.

- Absence of biliary obstruction.

- Absence of ureteral obstruction.

- Unique location intestinal obstruction.

- Absence of intense involvement of the small intestine disease.

- Little bulky disease in the gastrohepatic ligament.

ECOG patients with 2 to 3 have a median survival of 9.5 months, while patients classified from 0 to 1 is significantly higher, 21.7 months. Patients with bowel obstruction or malignant ascites and subsequent malnutrition have a worse survival than those without these complications, 6.3 and 23 months, respectively (87). Even so, in patients with malignant ascites multidisciplinary treatment prevented the recurrence of ascites in 75% of patients, being HIPEC recommended in these clinical circumstances (88). Regarding the extension of PC, Sugarbaker refers to the prognostic value of PCI in patients with PC of colorectal origin. A PCI below 10 was associated with 50% survival at 5 years, while survival was 0% in those cases with a PCI greater than 20 (P<0.0001). This author considers this treatment contraindicated in patients with PCI over 20, while others raise the PCI to values of 26. Verwaal used as a criterion for extension of PC the level of affectation of the different regions. Of the total of seven, more than five affected regions are associated with lower survival benefit and high morbidity rates (65). There is consensus among experts that the best long-term clinical benefits with the multidisciplinary treatment are achieved

in patients with limited extent of the peritoneal disease (89). In the evaluation of preoperative CT, patients with PC of colorectal origin class III presenting involvement of the small intestine or the mesentery (as classified by Yan), bulky retroperitoneal lymph node involvement and/or radiological PCI over 20 should be excluded for multidisciplinary treatment.

There are other useful recommendations on patient selection and indication of the multidisciplinary treatment of colorectal origin with PC that are based on primary tumour staging (90):

- T4 N0 M1 tumours (in the form of limited peritoneal disease): upfront multidisciplinary treatment.

- T4 N2 M1 (with limited peritoneal disease): treatment with chemotherapy for 3 months followed by multidisciplinary treatment and best systemic chemotherapy.

- Clinically asymptomatic patient with resectable extensive disease, ascites and small bowel involvement: multidisciplinary treatment followed by the best systemic chemotherapy.

- The multidisciplinary treatment should be scheduled at least 1 month after the last administration of systemic chemotherapy.

The type and degree of histological differentiation of the tumour causing the PC have also shown to impact on survival.

The most suitable application of multidisciplinary treatment corresponds to: "young" patients with good general condition, no previous treatments, localised PC caused by tumours of low mitotic activity and completely resectable. The short-term clinical outcomes (morbidity and mortality) and long-term (survival and quality of life) of the multidisciplinary treatment are closely related to the proper application of these criteria in the selection of patients.

Exclusion criteria accepted by most of the groups are:

- Patients who have a PC judged unresectable by clinical or paraclinical: mesenteric retraction evident on CT, infiltration/retraction bladder by endoscopy.

- Extrabdominal metastases or unresectable liver metastases or requiring major hepatectomy conditioning a limited hepatic reserve.

- The presence of other malignant disease.

- Multisegmental complete bowel obstruction.

- Active infection or other condition that prevents or incapacitate the patient to receive the proposed treatment per protocol.

#### **Results of multidisciplinary treatment**

#### Morbidity

Complications can arise directly from surgery,

chemotherapy, hyperthermia or the sum of these. Radical surgery in the treatment of CP is usually the most important cause of complications and the main reason to alter the therapeutic process. Elias recently described a specific classification system for complications related to the multidisciplinary treatment of PC (91). This author considers 6 degrees of complications, defined as grade 0: no complications, grade 1: complications that do not require action or minor treatment as oral antibiotics, basic controls..., grade 2: complications requiring moderate actions, as intravenous medication, parenteral nutrition, prolonged nasogastric tube, pleural drainage, grade 3: complications requiring hospital readmission, reoperation or interventional radiology, grade 4: chronic complications, removal of organs or digestive derivations, and grade 5: complications leading to death of the patient. At the consensus meeting in Milan was agreed to use the new Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 as a system of classification of complications. This is an extensive guide which includes types of complications in 28 categories, based on the anatomy and pathophysiology (92). The complication rate grade III-IV is around 30 to 65%. Specific surgical morbidity is 30% and relates mainly to digestive sutures dehiscence, perforation, intestinal fistulas, collections, intra-abdominal abscesses and postoperative bleeding. Around 10% of patients require one or several surgical operations (93-95). A multivariate analysis fulfilled by the group from Washington Hospital Centre determined that the rate of postoperative complications is related to the extension of the PC (PCI), duration of surgery and the number of digestive anastomosis performed (96). Although the morbidity described in this complex treatment is not higher than that referenced in the gastrointestinal major surgery extreme care is required, especially in the immediate postoperative period. Systemic complications correspond to those of any major surgery but may be covert or increased by the effects of systemic toxicity, gastrointestinal or haematological of HIPEC. Patients undergoing peritonectomy have an altered inflammatory response caused by surgical removal of the peritoneum and the effect of intraperitoneal chemotherapy, which often affect an evident decrease in peritoneal-abdominal pain that hinders the clinician to early diagnose postoperative abdominal complications. The immediate follow-up of these patients should be performed in a unit of critically ill patients with specific clinical protocols and expert staff.

#### Mortality

The reported mortality in the multidisciplinary treatment of PC ranges from 0 to 14%. Mortality rate of 2-6% are the most frequent in most published studies. Mortality is related with the intensity of surgical invasiveness, reflected in the number of peritonectomy procedures performed, the PCI, the number of digestive anastomosis and volume of perioperative blood transfused (97).

The causes of mortality referenced in the literature are related to intestinal perforations, bone marrow suppression, respiratory failure, pulmonary embolism and infection by methicillin-resistant Staphylococcus aureus. There are several factors that predict mortality in the multidisciplinary treatment of PC, as the presence of abundant ascites, bad general status and bowel obstruction (87). Both the morbidity and mortality in the multidisciplinary treatment are directly related to the surgical team's experience and proven the importance of the learning curve in this treatment. The series providing 100 or more patients usually have a lower rate of complications, and these are less severe (98,99).

#### Quality of life

Studies addressing the quality of life of patients undergoing HIPEC conclude that it is a complex and invasive therapy but generally well tolerated (100,101). Usually patients can be with a similar activity pattern to its previous one at 3 months after surgery. Almost half of the survivors at 3 years return to work with the same intensity as before treatment. The groups of patients who benefit the most, according to the quality of life scales applied, were those with ascites before surgery. These results were similar to those published by the National Cancer Institute (Bethesda) about a group of patients assessed at 3, 6 and 9 months after surgery (102). The interpretation of the evidence of the published studies on quality of life in the multidisciplinary treatment is difficult to establish by several factors(103-107): the clinical heterogeneity given by the variation in the type of underlying disease, degree of surgical cytoreduction and the mode to administer intraperitoneal chemotherapy, the methodological heterogeneity between studies and variations in the scales used to measure the quality of life and the lack of a control group using the assessment of patients with the same condition subject to other treatments. The clinical significance of these variations is difficult to establish.

#### Failure of multidisciplinary treatment

Peritoneal recurrence occurs in 70% of patients (108-109).

Patterns of recurrence following multidisciplinary treatment can help to detect the cause of treatment failure and to modify it. A localized form of peritoneal recurrence could correspond to a failure of the surgery for "forgetting" a tumour foci between the adhesions and scar tissue where intraperitoneal chemotherapy is less effective against free tumour cells. Peritoneal recurrence detected in the intestinal wall may be due to a failure of the electrofulguration, while the diffuse peritoneal recurrence may be due to failure of intraperitoneal chemotherapy to eradicate minimal residual tumour disease after surgery.

It is important to determine the characteristics of the multidisciplinary treatment failures in order to advance in its development and to establish which patients may benefit from a new therapeutic approach. Another type of multidisciplinary treatment failure, is the spread of peritoneal carcinomatosis in the pleural cavity or the lung parenchyma, which occurs mainly in low-grade mucinous tumours associated with peritoneal pseudomyxoma. Sugarbaker considered the most likely mechanisms for the extension of the disease to extra-abdominal compartment were: (I) presence of congenital diaphragmatic hiatus holes or, (II) laceration of diaphragm muscle fibres caused by surgery, (III) communication openness and surgical abdominal and pleural cavities, and (IV) pulmonary tumour emboli.

It is very important to avoid aperture, and if it occurred, should be left the peritoneal-pleural communication open during the HIPEC phase to allow removal of the tumour cells migrated to the thorax by chemohyperthermia.

#### Summary

As occurred in the past with metastatic liver disease from colorectal cancer, peritoneal dissemination in colorectal cancer is still considered a widespread condition and treated with palliative procedures. For years, the locoregional treatment of liver metastases by the combination of liver surgery and chemotherapy has modified previous therapeutic concepts and criteria and has provided significant benefits on the survival in these patients. Currently the PC of colorectal origin is also considered a locoregional tumour manifestation confined to the abdomen.

Evidence in the different studies regarding the efficacy of

HIPEC for the PC from colorectal origin show that the survival after treatment varies between 22 and 60.1 months, and that survival rates at 5 years are between 11% and 48.5%, with a disease free survival of 34% for the same time period (66).

The 2-year survival of these patients is higher than that observed with the treatment without surgical cytoreduction and intraperitoneal chemotherapy, as evidenced by a properly randomized study (65). Patients in which it was possible to achieve a complete cytoreduction had better results. The results of a phase III trial demonstrated the clinical benefits of the multidisciplinary treatment compared with systemic chemotherapy and palliative surgery, and was first published survival rates of 5 years in the treatment of colorectal PC (11).

Elias presented 5-year survivals of 48.5% of patients with 34% of patients free of disease in this same period and a median survival time of 60.1 months using the open technique and a bidirectional chemotherapy consisting of application, 1 hour before HIPEC, a dose of 5-FU + folinic acid systemically. The intraperitoneal chemotherapy used was oxaliplatin at a dose of 460 mg/m<sup>2</sup> administered over 30 minutes at 43 °C. Patients followed adjuvant chemotherapy. The risk for this clinical benefit was a 27% chance of developing complications grade III or higher toxicity (91).

In the past 10 years a large number of specialized centres have incorporated this therapeutic modality in the treatment of malignant diseases of the peritoneum, with improvements in therapeutic procedures, criteria for patient selection in the adjuvant chemotherapy and subsequent monitoring for the detection of early peritoneal recurrence and radical rescue surgery. The standardization of the entire therapeutic process has been reflected in better survival rates at 3 and 5 years and declines in the figures relating to morbidity and mortality, particularly evident in those studies involving over 100 patients in their series. It is considered that 130 patients treated by the same team, are the appropriate number of patients to complete the learning curve with this type of treatment.

Most important groups consider appropriate selection of patients according to their general, the extension of the PC (five or least affected regions or ICP <25) and the absence of multiple interventions and/or lines of chemotherapy failed. The feasibility of a complete cytoreduction (CC0-CC1) is crucial as an inclusion criterion (110).

It has been shown that the survival of the patients with PC of colorectal origin undergoing multidisciplinary treatment depends basically on the extent of PC at the time of surgery and the completion of surgical debulking. Almost all studies agree on the impact of the debulking with no macroscopic residual tumour in terms of survival. The patients who achieved a complete cytoreduction had a survival rate nearly twice that those patients in whom it was not possible to perform (111).

The risks are that between 25-50% of major complications (surgical or medical), although they do not significantly differ from those referred for patients undergoing major digestive surgery.

The multidisciplinary treatment is associated with risk of death by 5-12%.

Although there are two randomized controlled trials, only one could conclude as planned, while the other had closed prematurely due to difficulties in recruiting patients (66). So most of this evidence is level 3 (case series, most of them retrospective), and part was summarized as intermediate quality in a systematic review of the literature (112).

It has been shown that the survival of colorectal origin of PC patients undergoing multidisciplinary treatment depends largely on the extent of the PC at the time of surgery (PCI) and the completion of the surgical cytoreduction (CC). Almost all studies agree on the important impact that involves debulking with no macroscopic residual tumour (CC0) on survival.

Most groups consider important the proper selection of patients according to their status, the PCI <26 (<10 according to Sugarbaker) and the absence of previous surgery and/or lines of chemotherapy failed and the chances of achieving full cytoreduction (CC0-CC1) are crucial to the outcome of these patients.

An ongoing Phase III trial (NCT00769405) addresses this question of how much of the survival benefit is derived from the cytoreduction and how much from hyperthermic intraperitoneal chemotherapy, as patients will be randomly assigned to hyperthermic intraperitoneal chemotherapy or no hyperthermic intraperitoneal chemotherapy after complete cytoreductive surgery.

It is important to conduct controlled clinical trials that redefine the role of HIPEC in the era of new biological molecules and the effect of the best selection of patients using the benefits of recent genomic studies on biopsy material, to establish predictive factors associated with this treatment.

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#### Footnote

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## The influence of anastomotic leakage on patients' outcomes after rectal cancer surgery

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Rectal cancer surgery is still evolving and various resection techniques such as laparoscopy, robotics, or transanal minimally invasive surgery have been introduced (1). However, establishing intestinal continuity following tumor resection is an unchanged part of rectal cancer surgery (2). Colorectal anastomosis is performed by stapled or handsewn method between the proximal colon and rectal stump (3).

Anastomotic leakage is one of most devastating complication after rectal cancer resection. Anastomotic leakage compromises immediate postoperative outcomes and, although controversial, oncologic outcomes. Earlier studies have reported that anastomotic leakage increases local recurrence rate (4-6) or local and distant recurrence rates (7-9). In some studies, anastomotic leakage deteriorated overall (5,7,10) and disease-specific survivals (5,8,9). Recently, Hain et al. (11) investigated the impact of anastomotic leakage on oncological outcomes after rectal cancer surgery. Laparoscopic total mesorectal excision was performed in all patients (n=428) and anastomotic leakage was occurred in 120 patients (28%). Based on multivariate analyses, symptomatic anastomotic leakage was an independent risk factor for local recurrence-free survival (odds ratio =2.13). However, asymptomatic anastomotic leakage was not a meaningful risk factor for local recurrence-free survival. In their series, 28% of anastomotic leakage rate (symptomatic: n=70, 16% and asymptomatic:

n=50, 12%) is somewhat high when compared to previous studies (12,13). This reason may be due to difference in definition of anastomotic leakage or study population.

Unfortunately, the mechanism for unfavorable survival rate has not been clearly elucidated. Potential mechanisms have been suggested that anastomotic leakage may cause implantation of occult tumor cells around the anastomosis site (14). Stress response following anastomotic leakage can suppress the function of cytotoxic T cells and natural killer cells and thereby promote cancer cell survival (15). Inflammatory reaction is related to cancer development and progression. Infectious condition by anastomotic leakage can induce systemic inflammatory response and thereby promote disease recurrence (16). In addition, anastomotic leakage may preclude appropriate adjuvant chemotherapy. Occurrence of postoperative complications such as anastomotic leakage is associated with the lack of chemotherapy or delayed commencement of chemotherapy (6). To understand the impact of anastomotic leakage on oncologic outcomes, underlying mechanism should be revealed. Future study should be directed to translational or prospective clinical studies.

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### Implication of the low anterior resection syndrome (LARS) score for bowel dysfunction after rectal cancer surgery with symptomatic anastomotic leakage

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Hain et al. investigated bowel dysfunction after laparoscopic sphincter-saving rectal resection. To assess the influence of anastomotic leakage (AL) they compared symptomatic AL with asymptomatic leakage and a matched control group without AL after low rectal surgery (1). Assessment of the low anterior resection syndrome (LARS) and postoperative quality of life was performed and scored by the LARS score and the disease-specific questionnaire of the European Organization for Research and Treatment of Quality of Life Questionnaire for Colorectal Cancer (EORTC QLQ-CR29). Data were received of a prospectively maintained database. Overall, out of 432 patients with laparoscopic low rectal cancer surgery 46 patients with a postoperative AL (symptomatic n=23, asymptomatic n=23) were identified between January 2005 and December 2014. Each patient with an AL was matched with all (one or more) similar patients without an AL. The following criteria were used: age (±2 years), sex, type of neoadjuvant treatment (no treatment or chemoradiotherapy), and type of anastomosis (colorectal stapler anastomosis or hand sewn coloanal anastomosis). All study groups were well balanced with respect to patients, tumor, and surgery characteristics. At least, to avoid any disturbing factors in the postoperative setting all patients had to have restoration of intestinal continuity (no temporary or permanent stoma) with a minimal follow-up of more than 1 year and no ongoing chemotherapy.

The study results demonstrated that patients with a symptomatic AL had impaired bowel function compared with the control group with somewhat greater, though of little consequence, LARS score {median: 30 [23-39] vs. 27 [15-34], P=0.02} and worse LARS categories (no LARS in 4% vs. 31%, minor LARS in 52% vs. 52%, and major LARS in 44% vs. 17%, P=0.004). In contrast to the patients with a symptomatic AL, the LARS score was not different between the asymptomatic AL group and the control group {median 24 [14-37] vs. 27 [15-34], P=0.70}. Multivariate analysis identified as independent risk factors for the onset of impaired bowel function after low rectal surgery the symptomatic AL, neoadjuvant radiotherapy, intersphincteric resection and a hand-sewn coloanal anastomosis. Furthermore, the results of the EORTC QLQ CR-29 questionnaires showed that patients with a postoperative symptomatic AL reported more blood and mucus in stool, frequent bowel movements per day, and frequent urination per day.

The presented results of this study by Hain *et al.* are of relevant clinical importance. With respect to the last two decades most studies about rectal cancer surgery were focused on oncologic results, namely the incidence of loco-regional recurrence rates and the frequency of AL. Postoperative bowel function and postoperative quality of life were secondary outcome parameters and were not accurately evaluated and reported. The presented study

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used for the first time adequately assessment instruments for this topic. Hain et al. found that patients with symptomatic AL have impaired functional results and that every second patient with a symptomatic AL had major LARS. In contrast to this finding, quality of life and function of patients with an asymptomatic AL can be considered close to those of patients without AL. These results are in good accordance with the everyday clinical work experience. Additionally, the results of this study also showed that independently of the onset of AL nearly 2/3 of our patients are suffering from the underestimated LARS. Overall, the presented data gave good reasons to start postoperative early evaluation of the LARS and initiating early postoperative treatment. Future studies should be initiated to identify and establish treatment modalities to improve long-term results of bowel function and quality of life after rectal surgery. This would best serve the interests for our patients.

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