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## Pushing the limits of liver surgery for colorectal liver metastases: Current state and future directions

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### Abstract

Liver surgery for the treatment of colorectal liver metastases is the standard treatment in a dynamic surgical field with many variables that should be considered in a curative intent scenario. Hepatectomy for colorectal liver metastases has undergone constant changes over the last 30 years, including indications until the need for rescue procedures of recurrent and advanced diseases as well as minimally invasive surgery. These advancements in liver surgery have not only resulted from overall improvements in the surgical field but have also resulted from a better understanding of the biological behavior of the disease, liver regeneration, and homeostasis during and after surgery. Improvements in anesthesiology, intensive care medicine, radiology, and surgical devices have correlated with further advancements of hepatectomies. Moreover, changes are still forthcoming, and both fields of augmented reality and artificial intelligence will likely have future contributions in this field in regard to both diagnoses and the planning of procedures. The aim of this editorial is to emphasize several aspects that have contributed to the paradigm shifts in colorectal liver metastases surgery over the last three decades as well as to discuss the factors concerning patient selection and the technical aspects of liver surgery. Finally, this editorial will highlight the promising new features of this surgery for diagnoses and treatments in this field.

**Key words:** Colorectal liver metastases; Cancer; Hepatectomy; Liver; Surgery; Oncology

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**Core tip:** Liver surgery for colorectal liver metastases is a dynamic field, and its limits have considerably changed over the last three decades. Many variables have influenced patient selection and surgical techniques, and more changes are forthcoming with improvements in minimally invasive surgery, radiology, and artificial intelligence. This editorial highlights the pathway of treating colorectal liver metastases over three decades and the promising features in this field.

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## INTRODUCTION

Liver surgery for the curative-intent of colorectal liver metastases (CRLM) cancer has been considered to be the mainstream treatment over the last three decades for advanced colorectal cancer. Hepatectomies for CRLM have been successfully performed since the 1980s at which point patients who underwent complete (R0) hepatic resections achieved an approximate 20% 5-year overall survival (OS)<sup>[1]</sup>. Arguably, the treatment of CRLM represents one of the best models of progress in liver surgery over the past few decades. Even when patients are facing a potential systematic disease, the oncological outcomes have been shown to improve over time with reports of 5-year OS ranging between 35% and 58%<sup>[2,3]</sup>.

These improvements have occurred because systemic chemotherapies and biological agents now provide more efficient treatments for the control of micro metastases and help in patient selection<sup>[4]</sup>. Moreover, enhancements in both surgical techniques and modern imaging techniques as well as the use of intraoperative ultrasonography, the control of inflow and outflow with pedicle clamping techniques, the control of low central venous pressure during surgery, pre-operative portal vein embolization for treatment of hypertrophy of future liver remnants, ablation techniques, and staged hepatic resections, in addition to the development of new devices for parenchymal transections and vascular control, have also contributed to better control of the disease. These changes have led to the widespread use of parenchyma sparing techniques. Furthermore, many paradigms have been broken over the last few decades, and these broken paradigms will likely have an impact on the future directions of liver surgery.

## OLD PARADIGMS AND CURRENT APPROACHES

In the 1980s and 1990s, most patients who were considered to be candidates for resections presented with few lesions (typically less than four lesions), the absence of extra-hepatic disease, unilobar presentations, and small lesions (lesions that are at or below 5 cm)<sup>[2]</sup>. However, this high selection of patients should be observed in perspective and in accordance with the time period because it occurred in an era before the use of modern chemotherapy (oxaliplatin- and irinotecan-based therapies) and without the same resources that are currently available in both clinical and surgical practices. The association of optimal chemotherapy treatments with biological chemotherapeutic agents has been able to convert liver metastases that were previously considered to be unresectable (metastases that were considered to be palliative and with no prospects of a cure or long-term survival) into resectable metastases in 21% of cases<sup>[5]</sup>. Improvements in preoperative image workups for the detection of small lesions and the presentation of anatomical relationships as well as enhancements in surgical techniques and devices, the development of better intraoperative imaging techniques (including fusion imaging techniques), enhanced results in post-operative care units, and the development of new systemic chemotherapy and biological agents, have contributed to the classical contraindications of the surgical management of CRLM and have shown them to be outdated<sup>[4]</sup>.

Currently, the old dogmas of the surgical treatment of CRLM that have been



previously cited have changed, and the basic, primary points of the current strategies are to obtain clear margins (R0), to spare the liver parenchyma as much as possible, and to provide surgical treatments for systemic disease that is under control or stable<sup>[4]</sup>. The previous concept of needing clear margins that are 1 cm or larger used to be a subject of debate, and this idea was mostly based on retrospective series. A series that consisted of 1019 patients who underwent hepatectomies for CRLM examined the role of margins and survival rates among three groups: a group with 1–10 mm clear margins *vs* a group with positive margins with a survival time of 42 mo *vs* 30 mo, respectively ( $P < 0.01$ ), and a group with  $> 10$  mm of clear margins *vs* a group with 1–10 mm of clear margins, with a survival time of 55 mo *vs* 42 mo, respectively ( $P < 0.01$ )<sup>[6]</sup>. This study recommended that a margin width of  $> 1$  cm was ideal and should be achieved because this margin width was identified to be an independent predictor of oncological outcomes in the surgical treatment of CRLM. However, the presence of subcentimeter margins should not exclude patients from receiving hepatectomies because they may still have favorable prognoses compared to patients with positive margins<sup>[7]</sup>.

Another paradigm that has been shifted is the concept of two-stage hepatectomy, which is used to promote resections in patients who are considered to be unresectable. This alternative strategy is useful for lesions that are considered to be initially unresectable due to multiple bilobar diseases or the risk of insufficient remnants for one-stage surgery. The original strategy consisted of resecting all of the lesions that were present in the future remnant, generally on the left side of the liver, as well as obtaining the remnant of the liver hypertrophy after a right portal vein embolization or an intra-operative right portal ligation<sup>[8]</sup>. The first-stage procedure implies the clearance of metastases in the left liver *via* resection or through the use of radiofrequency ablation as well as *via* an immediate right portal vein ligation. This tactic promotes hypertrophy of the future remnant liver because right portal vein ligation, or right portal vein embolization, creates a contralateral hypertrophy that increases the final volume of the residual left liver. This increase in volume promotes a safer and more acceptable remnant volume. Typically, 30% of the remnant liver is necessary after surgery; however, with the use of previous chemotherapy treatments, which can cause damage to the liver parenchyma, this volume may have to be augmented and may require further augmentation if liver cirrhosis is observed (at least 40%). Additionally, the degree of hypertrophy of the future remnant liver itself also predicts the risk of liver failure during the post-operative course and may represent a more significant predictor of liver failure than the volume of the isolated final remnant liver<sup>[9]</sup>.

Advancements in liver surgery over the past few years have made it a safer procedure based on a reduced amount of intraoperative blood loss due to the better comprehension of liver anatomy, more optimal preoperative and intra-operative imaging, and improvements in both the surgical techniques and numerous surgical devices that are used for liver surgery<sup>[10]</sup>. All of these improvements have supported the movement of favoring the resection of multiple lesions and of preserving more of the parenchyma instead of using major hepatectomies. The concept of sparing the liver parenchyma represents the balance of a minimal resection of the liver parenchyma in providing adequate surgical margins based on the need of having an adequate remnant liver for the prevention of liver failure. Moreover, the majority of recurrence after hepatectomy for CRLM occurs in the liver itself, and the role of re-hepatectomies with curative-intent treatment is a valuable and currently established strategy. However, it depends on the extension of the previous surgery as well as the preservation of the parenchyma, pedicles, and hepatic veins<sup>[11]</sup>. Torzilli *et al*<sup>[12]</sup> promoted the use of the enhanced “one-stage surgery” as an alternative to two-stage hepatectomies and recommended the use of intraoperative ultrasound, the detachment of CRLM from the intrahepatic vascular structures (possibly with the R1 vascular resection), and the evaluation of flow analysis in evaluating collateral communications among the hepatic veins.

The many types of ablative techniques, such as cryosurgery, microwave ablation, and radiofrequency ablation can be performed as alternatives when an exclusive hepatic resection demands an extensive hepatectomy with a large degree of parenchyma removal. However, the predictors of optimal responses to radiofrequency ablation include small lesions (lesions  $< 3$  cm), a lower level of carcinoembryonic antigen baseline values, and the presence of less than three lesions<sup>[8]</sup>. Recent studies have demonstrated the use of microwave ablation to be a quick and effective method. Leung *et al*<sup>[13]</sup> reported a study that examined 416 microwave ablation sites. They showed that the treatment of subcentimeter lesions was sustained for up to 4 years in approximately 98% of cases. Thus, ablation of small lesions can be a valid option for curative-intent treatment and can be used as a substitute for liver resection for patients who do not qualify for hepatectomy, while

also being a safer option compared to the higher risk of complications that are associated with hepatectomies either due to a high degree of tumor burden or small future remnant liver.

Over the last 10 years, associating liver partition and portal vein ligation for staged hepatectomy (ALLPS) has been described for extreme resections of an extended liver resection with a small residual remnant liver<sup>[14]</sup>. The technique was proposed for intraoperative salvage of a small remnant liver for extended right resections that involve right portal vein ligations and for in situ splitting of the liver parenchyma along the falciform ligament. Schnitzbauer *et al*<sup>[14]</sup> described 25 procedures with an increased median volume of the left lateral lobe in 74% of cases with a median time interval of 9 d. Despite the encouraging results, 64% of patients experienced complications with a mortality of 12% (three patients). Many changes in the technique, indications, and results of the procedures occurred in response to this issue. Regarding the morbidity of the procedures, it seems that ALPPS works better as an option in response to the failure of portal vein embolization or ligation in obtaining contralateral liver hypertrophy than the first option to obtain an increased remnant liver volume. Currently, there is an open trial underway comparing the use of portal vein embolization *vs* ALLPS in patients with small remnant liver volumes, and these data should provide some insight into this issue.

Liver surgery is a demanding surgery and may be the reason why the progress of the laparoscopic approach in this field has not been widely accepted at the start of the laparoscopy era. However, currently laparoscopy has been identified as having a role in liver surgery. Ciria *et al*<sup>[15]</sup> described more than 9000 procedures in the literature showing the evolution of only minor hepatectomies to major hepatectomies. Moreover, it seems that the use of the laparoscopic approach for CRLM represents a reality and does not impact surgical outcomes nor leads to additional costs compared to the use of open surgery<sup>[16]</sup>.

## FUTURE PERSPECTIVES

Regarding the advances in liver surgery, robotic surgery remains a technology that is currently in progress, and the pros and cons of the use of robotics are similar to those of laparoscopic liver surgery. These pros and cons are dependent on the evolution of medical robots. Retrospective series have demonstrated the feasibility of both minor and major hepatectomies, including the benefits of tridimensional views and forceps articulation from robots. Enhanced preoperative and intra-operative imaging is crucial for advances in liver surgery. Because patients have been exposed to preoperative chemotherapy treatments, the harm to the liver parenchyma has become consistent, and this harm may jeopardize the identification of lesions in the altered parenchyma. Even with the use of contrast-enhanced magnetic resonance or computerized tomography, the use of intraoperative ultrasound represents the most accurate method for detecting missing metastases, especially when it is associated with the use of micro bubble contrast techniques<sup>[17]</sup>. Currently, there is a need for augmented reality images to overcome the limits of identifying lesions and anatomical structures inside of the opaque organ for both open and minimally invasive surgeries. Convolutional neural networks have demonstrated success in natural image analyses and have dramatically outperformed alternative machine learning algorithms, and they seem to be valid for the planning of radiotherapy fields for the liver<sup>[18]</sup>. Regarding minimally invasive surgery, a unique issue is the use of the pneumoperitoneum that deforms the abdominal organs in regard to the typical and radiological anatomy, and the use of this adaptation remains a work in progress.

The emergence of liver transplantation for CRLM has been made possible due to the peculiar situation observed in Norway where there is an excess of liver donors (with the average waiting time being approximately 1 mo), and the initial wide inclusion criteria include the following: patients who received at least 6 wk of neo-adjuvant chemotherapy, patients who received complete radical excision of the primary metastasis, and patients who had optimal performance statuses<sup>[19]</sup>. Lung recurrence was the most common site of disease progression, but the Oslo experience showed that immunosuppression had a limited impact on the overall course of metastases. The author suggests that OS should be the goal instead of only disease free survival for those patients because lung recurrence does not necessarily represent fast progression of disease for these patients<sup>[19]</sup>. However, the optimal selection criteria are still not fully established, especially in the scenario of an organ shortage, which is the most common worldwide scenario.

Another approach, which has become more accepted in clinical practice, is the use of molecular markers as prognostic and predictive tools in aiding patient selection for

CRLM surgery. Many retrospective studies have explored KRAS/NRAS mutations and their impact as determinants of failure as well as local and systemic controls of disease after hepatic resections. KRAS mutations have been negatively associated with both relapse-free survival (Hazard ratio: 1.89) and OS (Hazard ratio: 2.23)<sup>[20]</sup>. Moreover, another meta-analysis of the V600 mutation in the BRAF oncogene reported that it was also negatively associated with inferior OS (Hazard ratio: 3.90)<sup>[21]</sup>. The presence of RAS mutations works as a predictor of treatment for the use of biological agents because it represents a resistance to anti-EGFR antibodies but does not represent a predictive factor for the use of systemic chemotherapy in advanced colorectal cancer. The presence of BRAF is observed in approximately 8%-10% of metastatic colorectal cancer, and it is related to worsened prognoses and habitually appears as a widespread metastatic disease with poor responses to curative-intent resections<sup>[22]</sup>. Recently, a molecular classification has been suggested for the consideration of four colorectal cancer subtypes and their different prognoses: CMS1 (microsatellite instability and immune activation features with a better prognosis), CMS2 (epithelial with marked WNT and MYC signaling activation), CMS3 (metabolic deregulation), and CMS4 (mesenchymal features with a worse outcome)<sup>[23]</sup>. Retrospective and prospective studies for the validation of these genetic signatures and molecular profiles are necessary and are currently ongoing to improve patient selection for both systemic and surgical treatments of CRLM with a consideration for the avoidance of futile procedures.

The use of artificial intelligence has become an unstoppable trend in medicine with the goal of aiding both clinical reasoning and therapeutic procedures. The classification of images *via* anatomical or pathological features is a fundamental cognitive task in diagnostic radiology, and its association with the use of convolutional neural networks has demonstrated success in natural image analyses and has dramatically outperformed alternative machine learning algorithms<sup>[24]</sup>. A digital image can be regarded as a matrix of numbers that encode the brightness and color of individual pixels, and in accordance with different arrangements of the pixels, some patterns can be created to help identify anatomical structures *via* ultrasound, computerized tomography, or magnetic resonance imaging<sup>[18,24]</sup>. These features are still being elaborated, but they can aid in planning both diagnostic and therapeutic procedures. It seems that artificial intelligence will likely find its place in the planning of standard procedures, not as a surrogate for the human brain but likely for the avoidance of risky surgical maneuvers or misinterpretations of images as well as anatomical variations in robotic scenarios and other minimally invasive procedures.

## CONCLUSION

Although liver surgery has been established for more than 40 years, it is still an exciting field in gastrointestinal surgery, especially with its interface with surgical oncology. None of the liver surgery fields have changed as much as the surgical treatment of CRLM. Many different treatments have been used for the surgical treatment of CRLM by oncologists with the use of chemotherapy agents, such as improvements in surgical techniques and the development of new surgical devices as well as incontestable improvements in radiology, anesthesiology, and intensive care treatments. The old paradigms have transitioned to more precise methods for the current principles of surgical treatment of CRLM with only two requirements remaining as necessities for curative-intent treatment: the achievement of free margins with no residual disease (*via* a R0 resection) and the preservation of an adequate remnant liver with a preserved inflow and outflow. Currently, minimally invasive liver surgery is a reality, but it will likely undergo many future transformations especially with the radiology and robotic platforms because augmented reality and artificial intelligence may be used together in the future. These arising features and the use of personalized therapy for investigating tumor biology could be the next treatment options for the surgical treatment of CRLM.

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