REVIEW ARTICLE

Colorectal Liver Metastases: A Perspective

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ABSTRACT

Surgical resection is the most effective treatment approach in colorectal liver metastases (CRLM). The improved survival in Stage IV colorectal cancer (CRC) is associated with a better diagnosis and evaluation, proper decision-making, improved chemotherapy, and the adoption of parenchymal-sparing hepatic resections. Liver surgery was one of the last frontiers reached by minimally invasive surgery. Surgical techniques and specialized equipment evolved to overcome the technical limitations making laparoscopic liver resections safe and feasible. The etiology and pathophysiology of hepatic metastases are discussed along with the rationale for and efficacy of minimally invasive surgery for CRLM. Improved imaging techniques, identification of genomic markers, advances in chemotherapy, and personalized therapy will further improve the outcome of minimally-invasive surgery in the management of Stage IV CRC.

Key words: Colorectal, liver metastases, minimally invasive surgery

INTRODUCTION

The natural history of hepatic metastases

The liver is the most common site for colorectal cancer (CRC) metastases accounting for 80% of Stage IV patients and 40% as the only site of distant disease. About 20–25% of patients with CRC present with synchronous metastases, and 50–60% will develop the metachronous disease.[1] Liver metastases (LM) develop in the absence of lymph node involvement, and presumably, this occurs through the hematogenous route (the portal circulation) in gastrointestinal tumors from where tumor cells can embolize through the mesenteric veins.[2] However, the fact that tumor cells from outside the gastrointestinal tract also commonly spread to the liver suggests that organ preference is not purely anatomical and the "seed and soil" hypothesis, first proposed by Paget in 1889[3] is still tenable. The complex tumor cell interactions that occur with the lining endothelial and lymphatic cells are in part, what determines their final organ distribution.[4] Tumor cells that invade lymphatics may also spread hematogenously through venolymphatic communications or directly through the thoracic duct.[5] Some large metastases do not demonstrate spread to local periportal lymph nodes even in the presence of extensive disease within the liver.[6] A LM may attain an enormous size, sometimes occupying much of the liver by concentric growth with extension in all directions and may occasionally spread to adjacent structures, such as the diaphragm, by penetrating the usually unyielding Glisson's capsule.[7] The right lobe of the liver is involved with metastases more frequently than the left lobe, although the reasons remain unclear as there is no gross difference of either arterial or portal blood received by each lobe. It may however be due to portal vein "streaming" resulting in tumor emboli preferentially entering the right portal vein branches.[8,9] About one-third of patients with colorectal LM (CRLM) will have disease located to one lobe,[10] whereas multiple deposits throughout the liver are more commonly seen in patients with breast, esophageal, gastric, and pancreatic cancer and indicative

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of a more widespread metastatic process.[11] It has been estimated that the subclinical phase of a LM (i.e., from a metastatic implantation to clinical appearance) may be 2.5–5 years.[12] This would suggest that the survival rate may be improved if LM are detected much earlier. A cluster of similar-sized metastases is suggestive of a common tumor embolic event clearly occurring in a segment or lobe will leave the residual liver disease-free. Metastases of differing sizes are probably indicative of showers of tumor emboli occurring at different times.[11,12] Small lesions within the liver are usually asymptomatic and patients with advanced disease usually present with a combination of the upper abdominal discomfort, weight loss, and general malaise. Pain may be due to unremitting rapid growth of large metastases and is occasionally referred to the right shoulder, although central necrosis and infarction may also cause pain and pyrexia transiently. Hepatomegaly is indicative of advanced disease and may occasionally be accompanied by fulminant hepatic failure if the metastases are rapidly growing. Evidence of advanced liver failure such as jaundice, ascites, and occasionally portal hypertension are late signs and indicative of an extremely poor prognosis.[7] In patients with carcinoid, the first presentation may be with the carcinoid syndrome, characterized by diarrhea, flushing, and wheezing due to excessive secretion of serotonin and tachykinin peptides from the hepatic metastases overwhelming its metabolism. Several staging systems for LM from CRC have been proposed along with the prognostic significance, but no single system is universally accepted. Current observations regarding the clinical course of the patients with CRLM support emerging arguments for a new staging system.[13-15] The TNM staging system does not adapt to recent advances in metastatic treatment. The survival of patients with resectable solitary metastasis (Stage IV disease) is better than that with of a patient with Stage II disease.[13,14] Tumor deposits in adjacent vessels are associated with peritoneal disease, and tumor deposit with nodal disease (N2) has worse survival.[14]

TREATMENT OF CRLM

There is no advantage in delaying hepatic resection following diagnosis and patients should undergo liver resection as soon as is feasible. The old dogma that a waiting period is necessary to evaluate tumor aggressiveness is no longer tenable. The median survival of untreated CRLM following diagnosis is 6–12 months and 5-year survival is extremely rare.[16,17] About 80% of CRLM are initially non-resectable due to tumor size, location, and functional liver reserve.[1] Other factors that may indicate a poor outlook and excludes the possibility of cure are the presence of abnormal liver function tests, spread of tumor to extrahepatic sites, and primary tumors that are not resected.[7] At present, the definitely unresectable may have widespread hepatic disease, non-resectable extrahepatic lesions, or multiple metastatic sites.[1] In untreated patients, tumor burden is the major determinant of outcome and patients with solitary metastases usually live longer than those with multiple, bilobar disease.[13] New chemotherapy regimens including biologicals are bringing more patients to resection, including resectable extrahepatic disease. Resectability is the complete removal of LM while leaving at least 30% of functional remnant liver. In several studies, metastases >5 cm were associated with poorer survival than smaller metastases.[8] Although larger LM have usually been present for a longer time than smaller lesions, in the situation of a giant solitary metastasis, the tumor biology may be such that the capacity for multiple metastases may well be limited and therefore outcome may be good after resection.[1] Although neoadjuvant chemotherapy such as FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment has improved tumor response, the median survival for patients with unresectable disease is poor and there is no 5-year survival. Resection, when feasible confers a higher chance of cure and can improve 5-year survival to 34–60%.[1,8,18-20] However, the rationale in using pre-operative chemotherapy for resectable patients has been supported by the better prognosis obtained compared to upfront surgery due to the lower rate of positive surgical margins and the rendered ability of identifying the subgroup of patients who will develop progressive disease while on chemotherapy.[19,20] The resectability criteria for CRLM are expanded in an advanced multidisciplinary team (MDT) meeting alongside the evolution of imaging, neoadjuvant and adjuvant techniques such as thermal ablation, selective internal radiation therapy, and transarterial chemoembolization.[21-23] Unresectable unilobar disease may be treated by neoadjuvant chemotherapy followed by extended liver resection with or without portal vein embolization to stimulate the size of the future liver remnant. For multiple bilobar CRLM, the strategies for improved margin clearance include stage resection which entails a first-stage local resection of metastases of the future left remnant liver followed by portal vein embolization/ligation and then a second-stage right hepatectomy 4 weeks later after the left remnant has hypertrophied.[1,21,22] Although high-quality contrast-enhanced computed tomography and liver magnetic resonance imaging are commonly used preoperatively, laparoscopic ultrasonography (LUS) usually performed with a high-resolution 7.5–10 MHz probe allows direct visualization of LM in regard to segmental anatomy, local vascular involvement, and regional nodal disease. LUS improves the diagnostic accuracy of staging laparoscopy alone, provides additional information on resectability in

14–25% of patients, and detects occult metastases and new findings in 40–55% of cases.[22,24] Intra-operative ultrasound (IOUS) through real-time imaging aid planning at the time of resection and allow safe removal of all viable tumor with a clear margin of >1 cm. It facilitates liver-sparing and microwave/radio-frequency (RF) thermal ablation techniques in patients with compromised parenchyma (chemotherapy-associated steatohepatitis [CASH], prior liver resection), and avoids the small for size syndrome.[22-25] Anatomical liver resections follow anatomical planes and thus have better oncological clearance than non-anatomical liver resections. Major anatomical resections have better oncological clearance than limited segmental resections with reduced recurrence rate and improved survival. However, segmental liver resection of localized tumors based on Couinaud's liver segmental classification shown in Figure 1, would improve vascular control (less blood loss), minimize the risk of recurrence from intrahepatic spread, and reduce the amount of normal liver unnecessarily removed.[26] Clearly, for small awkwardly located lesions (such as the apex of segment eight in the axilla of the right and middle hepatic veins), local resection might be preferable to formal hemihepatectomy, whereby a whole, healthy lobe may need to be sacrificed for a small deposit. For larger metastases or multiple deposits standard anatomical resections based on Couinaud segments should ensure adequate margins, unless this increases the risk of postoperative liver failure. Fortunately, liver secondary metastases from CRCs have better biology than metastases from other gastrointestinal sites and are amenable to non-anatomical surgical resections. Thus, the oncologically safe non-anatomical, parenchymal-sparing resections are used for CRLM to achieve a complete metastasectomy. Approximately 20% of patients have liver-only recurrence with more than a third occurring in the opposite side of the liver[27] and hence amenable for re-resection.[1,21,22,28,29] It is appropriately utilized in the modern setting of multimodal treatments and repeat resections. It may, however, result in compromise of the vascularity of the adjacent residual liver tissue and may be technically more difficult.[1,8,21,22] Simple wedge excision of peripheral lesions is not appropriate since it compromises the resection margin and risks the danger of leaving satellite metastases.[1,21,22] A diligent search for other metastases should be carried out using IOUS before attempting to "wedge out" an apparently superficial tumor nodule.[1,21,24] When disease recurs in the liver it is more often at some site distant from the original resection line and most likely to have arisen in undetected micrometastases present at the time of original liver resection.[1,21] This would corroborate the importance of perioperative chemotherapy in surgical oncology as it increase progression-free survival.[30] Thus, ideally, a resection margin of at least 10 mm should be attempted, judged by intraoperative ultrasonography, but if not technically possible narrow margins should not be an absolute contraindication to resection.[1,21] There is controversy as to the significance of resection margin status following ablation with hemostatic devices as this will destroy the margin to some extent (1–3 mm) giving an appearance of a "R0" margin (no tumor cells) in the patient remnant but an "R1" margin (tumor cells present) in the pathological specimen.[1,21,22] In general, the major determinant of success in the elderly (>80 years of age) is the volume of residual liver (since liver adaptations following resection diminishes with age), and fitness for general anesthesia.[1,8,21,22]

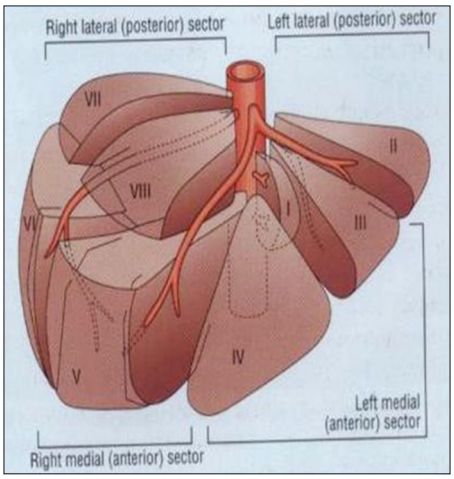

Figure 1: Couinaud's segmental anatomy of the liver

The advanced MDT working on stage IV CRC

The management of Stage IV CRC would be optimized by bringing together all relevant specialties involved in colorectal metastatic disease management in a centralized high volume center. A proficient advanced MDT for Stage IV CRC includes the colorectal surgeon, hepatobiliary surgeon, thoracic surgeon, dedicated CRC medical, and radiation oncologists, both imaging and interventional radiologists, dedicated CRC surgical pathologists, oncology nurse specialist, and nurse counselor centered on the patient. The lead specialist is either the liver or colorectal surgeon. By avoiding referral to the appropriate anatomical-site specific MDT with consequent delay in decision-making and management, disease progression is minimized. This advanced multi-specialist meeting thus provides coordination, continuity of care and better patient care.[1,21,22] The main determinants of the decision-making process are the tumor statuses of both the primary tumor and metastases, the need for emergency surgery of a complicated primary tumor and, the resectability of both tumor sites.[21,22,29] The major objective and end-point are to increase resectability of the CRLM due to the impact on patient survival (40% >5 years).[1,21] The diagnosis and decision-making on the management of resectable, borderline resectable or unresectable CRLM is expedited in the advanced MDT. The utilization of protocols, appropriate preparation of patients, audit, and trial recruitments are optimized. The multidisciplinary and inter-professional approach renders optimal solutions with cost-effectiveness, decrease length of hospital stay, decrease postoperative mortality, and a trend

toward higher survival rates.[1,21,22,31] Non-adherence to MDT decisions has been shown to result in a trend toward lower survival rates.[32] A number of series with sufficient long-term follow-up indicate that the 10-year survival after resection can be expected in 20–30% of patients.[33,34] It is important to regularly evaluate the outcome of the advanced MDT meetings so as to maintain the improvements in treatment goals as compared to a general colorectal MDT meeting,[35] and compare with other centers the effect on survival.

Minimally invasive surgery

Laparoscopic surgery had been slowly introduced in surgical oncology because of the concern of inadequate margins or lymph node sampling, tumor seeding, missing small metastases, and poor pathological and oncological outcomes. The OSLO-COMET randomized controlled trial showed that in patients undergoing parenchyma-sparing liver resection for colorectal metastases, laparoscopic surgery was associated with significantly less post-operative complications compared to open surgery, was cost effective (early recovery, short hospital stay, and early return to work), and the rate of free resection margins was the same.[36] The LapOpHuva prospective randomized controlled trial comparing laparoscopic liver resection (LLR) versus open liver resection (OLR) in patients with CRLM showed LLR presenting with a lower global morbidity (11.5% vs. 23.7%), but with similar severe complications. The long-term survival outcomes were similar in both groups. LLR involved more use of the Pringle maneuver (15.5% vs. 30.2%) and a shorter hospital stay (4 vs. 6 days). There were no differences regarding surgical time, blood losses, transfusion, and mortality.[37] Thus, the study demonstrated that in selected patients with CRLM, LLR presents similar oncological outcomes to OLR with the advantages of the short-term results associated with LLR. The concerns of the rare air embolism is met by putting the patient in 15° Trendelenburg position and careful surgical technique especially when dissecting the hepatic veins.[1,21,38] In the current coronavirus disease (COVID)-19 pandemic just as with surgery in HIV/AIDS,[39] care should be taken during laparoscopy on using disposable ports with a vestibular flange to prevent splash back, and by deflating the abdomen prior to port withdrawal because any aerosol emanating from the port entry wound will harbor COVID-19.[40,41] In addition to the currently advised personal protective equipment to health-care staff in the operating theater, this simple method would further lessen the risk of occupational transmission.[41] COVID-19 patients would benefit from the reduced surgical stress of minimally invasive surgery, but it would be important to know the effect of immunosuppression from major LLR on COVID-19 disease progression.[42]

During the 1990's minor resections of two or fewer easily accessible couinaud's liver segments had been the standard of care. The posterior-superior segments (VII, VIII) and segments (SI, IVa) were excluded as they posed a higher surgical challenge from the extensive mobilization required to bring those segments to the operative field. Resections of lesions located on anterolateral segments (S II, II, IVb, V, and VI) and left lateral sectionectomy (S II, III) were performed systematically by laparoscopy in hepatobiliary centers. The posterior-superior resections had been indicated as "major operations" despite including only two segments (VII, and VIII). This was corroborated by the associated higher conversion rates, higher blood loss, prolonged operative times, and narrower surgical margins.[43] Resection of lesions located on posterior-superior segments and major liver resections were shown to be feasible but remain technically demanding and reserved for experience surgeons in high volume hepatobiliary centers. Laparoscopy-assisted and transthoracic port placement are useful strategies applied to difficult resections.[38,43] Cherqui *et al*. in 2000[44] published the feasibility study of LLR for both benign and malignant diseases of the liver including hepatocellular carcinoma in cirrhotic livers. Since then, nearly 10,000 minor and major LLRs as an alternative to open surgery have been reported in the literature showing the wide acceptance and safety.[42,45] At present, the indications for LLR do not differ from those for open surgery.[45,46] A recent meta-analytic study[47] showed LLR having better perioperative outcome than OLR for recurrent liver cancer without compromising oncological outcome. With longer overall and median survival rates following recurrent resections, the indications for surgery are increasing with R1 surgery (complete tumor resection without safe margins) being justified for patients with a response to preoperative chemotherapy.[1,21,22,25] It makes sense that minimally invasive procedures are made available to these elderly patients who may also have CASH, prior liver resections, and other comorbidities.[25,36,38] In addition, the majority of patients around 65% develop intrahepatic within 3 years, even with the addition of systemic chemotherapy and approximately 20% of these patients have liver-only recurrence and hence may be suitable for re-resection.[1,21,22,28] Although repeat hepatectomy is often more difficult than the initial procedure because of dense adhesions and more friable and fibrotic liver parenchyma,[48] reported mortality and morbidity rates after repeat liver resection of metastases are surprisingly similar to those reported after initial hepatectomy.[31,49] Adjunctive treatment such as laparoscopic RF/microwave ablation is acceptable for patients of high surgical risk for liver resection, or with small solitary CRLM may also be suitable.[1,21,22] Therefore, the favorable biology of CRLM has enabled patients to live with their disease with repeat resections for recurrence.[1,21,22,28] However, oncogenic mutations of RAS (*N-ras* and *K-ras*) genes controlling cell proliferation have been associated with worse disease-free and overall survival following CRLM resection even with adjuvant anti-epidermal growth factor *cetuximab* therapy.[50] Thus, the rationale for neoadjuvant chemotherapy even for resectable patients, and biologic agents for the *k-ras* exon *2* wild-type, is to destroy occult micrometastases and

increase progression-free survival.[1,20,21] Where CRLM are unresectable chemotherapy may downsize tumors and improve biological selection for resection. This is seen as a complete radiological response which depends on the quality and completeness of preoperative imaging, or as "missing" metastases. As complete radiological response does not signify a complete pathological response, liver resection of curative-intent would include all initial and currently known sites of disease [Figures 2 and 3].[1,21] Robotic-assisted resections are feasible as demonstrated in reported case series. The three dimensional (3-D) view and greater range of movement can be useful for complex resections.[51] The dynamic applicability of the 3-D planning to navigation during operation may also improve operative results.[52]

One stage (simultaneous) or staged procedure?

The decision as to whether the operations for the primary tumor and LM are done at the same time (simultaneous) or separately (staged) is made at the advanced MDT meeting and in discussion with the patient.[1] The advantages of a one stage (simultaneous) operation[53,54] are (a) the decreased risk of disease dissemination (transperitoneally), (c) no repeated post-operative immunosuppression causing increased tumor growth,[37,55] and (c) lower costs. A staged procedure would (1) allow assessment of biological behavior of metastases, (2) avoid operating on patients who are progressing while on chemotherapy, and (3) allow more precise selection for curative surgery.[1,21,56] Delayed hepatic resection may not impair survival but help select those patients most likely to benefit from hepatic resection, i.e., stable disease.[57,58] For mid and low rectal primary tumors, chemoradiotherapy is often needed and in addition to a difficult resection a one stage surgery is not recommended.[1,21,22] One stage surgery is not advocated for complex colonic and the upper rectal primary tumors, for high risk patients or when hepatectomy is major (>3 segments). Minor liver resections (two segments or less) may be safely performed at the same time as colorectal resection (open or laparoscopic) when both the primary tumor and the metastases are easily resectable. The outcomes are similar to sequential surgery in this scenario.[1,21]

Figure 2: Pre-operative chemotherapy computed tomography scan of colorectal liver metastases

Figure 3: Post-chemotherapy computed tomography scan of colorectal liver metastases

The four clinical scenarios of stage IV CRC

The management of the four clinical scenarios are as follows (1) for the asymptomatic CRC and resectable synchronous CRLM, chemotherapy is first with or without radiotherapy for rectal cancer, followed either by surgery in a one-stage procedure for patients with limited hepatic disease and easy to resect primary tumor, or by staged (liver-first) surgery for other patients; (2) for asymptomatic CRC and non-resectable synchronous CRLM, the consensus is for optimal chemotherapy first, with the aim of making the LM resectable. This is followed by hepatic surgery and then resection of the primary; (3) for symptomatic CRC and resectable synchronous CRLM, recommendations are for resection of the primary tumor for perforated or occlusive tumors (but not for tumors with bleeding causing anemia), followed by chemotherapy and then surgery for LM; and (4) for symptomatic CRC and non-resectable synchronous CRLM, recommendations are for resection of the primary tumor for perforated or occlusive tumors, followed by chemotherapy and then surgery for LM if tumor shrinkage is achieved. For tumors with bleeding causing anemia, induction chemotherapy is recommended to downsize both the primary and LM, followed by surgery at the site with the most significant tumor load which is usually the liver, i.e., a reverse approach.[1,21,22] Thus, although the treatment strategy depends on the clinical scenario,[59] the disease being systemic dictates for chemotherapy before surgery in most cases.[60,61]

CONCLUSION

Both proper selections of patients who will benefit from liver resection and a high experience in minimally-invasive surgery are warranted in a hepatobiliary unit. Minimally invasive approach to CRLM will be beneficial to these elderly cohort of patients with comorbidities, CASH, and prior liver resections. The major end-point of the advanced MDT meeting on Stage IV CRC management is resectability due to the impact on patient survival (40%> 5 years). Improved imaging techniques, identification of genomic markers,

advances in chemotherapy, and personalized therapy will further improve the outcome of minimally-invasive surgery in the management of stage IV CRLM.

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