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Colorectal Liver Metastases

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Abstract
Background With modern multimodality therapy, patients with resected colorectal cancer (CRC) liver metastases (CLM) can experience up to 50–60 % 5-year survival. These improved outcomes have become more commonplace via achievements in multidisciplinary care, improved definition of resectability, and advances in technical skill.
Discussion Even patients with synchronous and/or extensive bilateral disease have benefited from novel surgical strategies. Treatment sequencing of synchronous CRC with CLM can be simplified into the following three paradigms: (classic colorectal-first), simultaneous (combined), or reverse approach (liver-first). The decision of whether to treat the CLM or CRC first depends on which site dominates oncologically and symptomatically. Oxaliplatin with 5-fluorouracil/leucovorin (FOLFOX) and irinotecan with 5-fluorouracil/leucovorin (FOLFIRI) are the foundations of modern chemotherapy. Although each regimen has positively impacted survivals, both have the potential for negative effects on the non-tumor liver. Oxaliplatin is associated with vascular injury (sinusoidal ballooning, microvascular injury, nodular regenerative hyperplasia, and long-term fibrosis) but not steatosis. Irinotecan has been associated with steatohepatitis, especially in patients with obesity and diabetes. Steatohepatitis from irinotecan is the only chemotherapy-associated liver injury (CALI) associated with increased mortality from postoperative hepatic insufficiency. Extended duration of preoperative chemotherapy is also associated with CALI.
Conclusions To determine resectability and to prevent overtreatment with systemic therapy, all patients should receive high-quality cross-sectional imaging and be evaluated by a hepatobiliary surgeon before starting chemotherapy. Even as chemotherapy improves, liver surgeons will continue to play a central role in treatment planning by offering the best chance for prolonged survival—safe R0 resection with curative intent.

Keywords Colorectal cancer · Colon cancer · Rectal cancer · Liver metastases · Chemotherapy · Hepatectomy · Liver resection · Synchronous · Metachronous · Reverse approach · Chemotherapy-associated liver injury · Oxaliplatin · Irinotecan

Introduction

An estimated 143,000 Americans will be diagnosed with colorectal cancer (CRC) this year.[1] Over half will develop metastases, with most developing colorectal liver metastases (CLM). Unfortunately, many CLM will be unresectable due to the distribution of intrahepatic disease and/or extrahepatic disease. As few as 20 % of patients with CLM will be candidates for resection. However, with modern oncosurgical approaches, patients with resected CLM can experience up to 50–60 % 5-year overall survival (OS).[2–4]

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Symptoms

CLM are often asymptomatic and diagnosed with surveillance cross-sectional imaging, such as computed tomography (CT). Because 80 % of metastases are detected in the first 3 years following the primary diagnosis, for stage III and high-risk stage II patients, annual CT is recommended by the National Comprehensive Cancer Network for the first

3–5 years after primary resection.[5] Imaging is augmented by interval colonoscopy and serum carcinoembryonic antigen (CEA) measurement. Rarely, patients present with symptoms such as pain, abdominal distention, and liver insufficiency. These patients usually have advanced CLM with significant hepatic tumor burden. These symptomatic patients may be less likely to be treated due to cancer burden and performance status.[6]

Diagnosis, Staging, and Imaging

For CRC/CLM imaging, there are four main options—ultrasound (US), CT, magnetic resonance imaging (MRI), and positron emission tomography/CT (PET/CT). US is inexpensive and reliable but has been replaced by cross-sectional imaging due to limited image capture, user dependence, and lower sensitivity for small lesions. However, intraoperative US remains a critically important modality as it can detect additional tumors beyond preoperative cross-sectional imaging in up to 27 % of patients.[7]

The current standard for staging, surveillance, and preoperative planning is high-resolution, contrast-enhanced multidetector CT of the chest, abdomen, and pelvis. For enhanced liver characterization, MRI abdomen and pelvis with chest CT is an alternative. CT scan is more useful than MRI for general imaging, including chest and other abdominal structures. On CT, CLM are hypovascular and more prominent in the portovenous phase as hypodense lesions. Concerns about the risks of repetitive radiation dosing do not apply to this advanced stage cancer population, since their disease burden is their real life-limiting issue and the detail of CT clearly guides appropriate life-extending therapy. Although suboptimal for the whole body surveillance, MRI can be useful for diagnosis and staging of liver tumor burden. Using multiple contrast agents and dynamic phases, high-resolution (3-T) MRI offers increased lesion characterization, especially for subcentimeter indeterminate lesions. Whichever is chosen before chemotherapy, that modality should be repeated after preoperative treatment and before CLM resection.

Recent years have seen a dramatic increase in the use of PET/CT to identify areas of increased metabolic activity. These areas are often presumed to be metastases in cancer patients. However, they can also be nonspecific, and the accompanying non-contrast CT adds little information for equivocal areas, prompting additional workup. We reserve PET/CT for the detection of occult extrahepatic disease in patients with high pretest probability and equivocal cross-sectional imaging (e.g., elevated CEA with normal CT) when detection would change the treatment strategy.

Percutaneous needle biopsies of suspected CLM are unnecessary when imaging identifies new lesions with characteristic imaging features for CLM. Needle biopsy may be appropriate when a benign or non-CLM lesion is suspected and cannot be delineated noninvasively with MRI and if the treatment plan would change based on the result.

Radiographic evaluation of treatment response has prognostic value and frequently determines resectability. Although traditionally measured by Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST criteria,[8] change in tumor diameter may not provide the best prognostic information. Morphologic change in a treated metastasis may better reflect tumor response.[9] When tumors change from heterogeneous consistency and irregular borders to homogenous density, clearly demarcated borders, and no enhancement, this pattern strongly correlates with pathologic response, margin control, and survival.

Surgical Treatment and Scenarios

Definition of Resectability

Resectability can be defined in the following three domains: technical, physiologic, and oncologic. Technical resectability is the ability to surgically remove all CLM with R0 (negative microscopic) margins while leaving adequate future liver remnant (FLR) volume. Adequate FLR must have regenerative capacity and consist of two contiguous hepatic segments with vascular inflow/outflow and biliary drainage. Of note, tumor *resectability* should be differentiated from patient *operability*, which can be defined as a patient's physiologic and medical ability to undergo and recover from major abdominal surgery.

Oncologically, patients with limited extrahepatic disease in controllable sites (e.g., portal lymph nodes or small lung metastases) can still benefit from hepatic resection. Biologically, these patients are at higher risk of recurrence and thus require perioperative chemotherapy. Even patients with limited growth of existing CLM while on preoperative therapy, but whose tumors remain anatomically resectable, should undergo resection. However, patients who develop new CLM or interval extrahepatic disease while on therapy should not undergo resection until their systemic disease is controlled.

Synchronous Presentation of Resectable Metastases: Three Approaches

Synchronous presentation of liver metastases, occurring in up to 25 % of new CRC,[10] creates many challenges for the multidisciplinary team. With synchronous CLM and asymptomatic primary CRC, short course (≤6 cycles) preoperative systemic chemotherapy should be considered. Frequently, mild primary tumor symptoms can be palliated with

systemic chemotherapy. The natural history of unresectable CLM suggests that resection of an asymptomatic primary tumor without hepatectomy with curative intent offers poor long-term benefit (<5 % 5-year OS).[11]

Treatment sequencing can be simplified into the following three paradigms: classic (colorectal-first), simultaneous (combined), or reverse approach (liver-first).[12] The decision of whether to treat the CLM or CRC first depends on which site dominates both oncologically and symptomatically, which requires multidisciplinary discussions. Unilateral decision-making, often by the first clinician to see the patient, can potentially limit a patient's curative options.

Patients with asymptomatic primary tumors and CLM requiring major hepatectomy are candidates for the reverse approach. For patients needing minor hepatectomy, the extent of CRC resection dominates decision-making. For low-risk CRC resections, including low anterior resections, a simultaneous approach can be performed safely with minor hepatectomy, potentially decreasing length of stay, cost, and patient disability.[12–14] For more extensive CRC resections, the classic approach is safer. When indicated, patients with rectal cancer receive preoperative chemoradiation prior to proctectomy. Using this algorithm, there is a logical balance of surgical risk and oncologic benefit. The major hepatectomy rate is, as expected, lower in combined cases (35 %) compared to the classic (66 %) sequencing.[3]

In properly selected patients, the reverse approach is oncologically sound with good OS.[3,15] Treating the liver first offers the ability to control metastatic disease early before potential progression beyond resectability.[16,17] Once the metastatic disease is resected, locoregional control is the next priority. However, if the patient's disease systemically progresses after hepatectomy, then the patient is spared an unnecessary CRC resection and potential ostomy.[15] One important caveat regarding the reverse approach is the need for surveillance of the primary CRC, especially in patients with malignant strictures. Fortunately, primary site progression during systemic therapy rarely (5–7 %) requires a strategy change.[3,18]

Staged resection is recommended for the following scenarios: marginal/inadequate FLR, significant comorbidities precluding longer operative time for simultaneous resection, and/or complex operations needed at both sites (e.g., major hepatectomy plus proctectomy). When there are bleeding or obstruction concerns at the primary site, priority in sequencing goes to the CRC. If the liver resection involves <3 segments and other concerns that trigger the need for staged resection do not exist (e.g., right hemicolectomy with left lateral sectionectomy), then simultaneous resection can be considered.

Metachronous Presentation of Resectable Metastases

For anatomically resectable CLM, perioperative chemotherapy is often used, but it remains controversial among liver surgeons. Multiple studies have commented on the utility of preoperative systemic therapy in selecting patients, improving margin status, and downsizing metastases to resectable criteria.[19] The most relevant is the EORTC 40983 phase III trial that compared surgery plus perioperative oxaliplatin with 5-fluorouracil (5-FU) and leucovorin (FOLFOX) versus surgery alone for patients with one to four resectable CLM.[20] Eligible patients, randomized before treatment sequencing, had improved 3-year PFS (36.1 vs. 28.1 %, $p=0.041$) if they completed chemotherapy plus resection. There were more reversible postoperative complications in the chemotherapy patients (25 vs. 16 %, $p=0.04$), but no increase in mortality (1 % in each arm). The study highlighted both the ability of perioperative chemotherapy to limit nontherapeutic laparotomies and to decrease the 3-year PFS events by one quarter.

Metachronous Presentation of Extensive (Multifocal and Bilateral) Metastases

Similar to other malignancies, there are a significant number of patients with CLM who present with advanced disease, bordering on unresectability. With CLM, the issues that need to be addressed in this population include questionable FLR, perivascular locations, and baseline liver parenchymal function. The ability to treat extensive CLM depends on institutional resources (i.e., multidisciplinary teams and interventional radiology).

CT-based volumetrics[21] to calculate the FLR can identify patients with inadequate FLR volume and, through patient selection, lower the risk of postoperative complications. Patients with insufficient FLR are at increased risk for postoperative hepatic insufficiency (PHI), morbidity, and death. To increase the FLR volume before extended hepatectomy, portal vein embolization (PVE) can be utilized to stimulate hypertrophy of small left livers. FLR volume >20 % is the minimum for safe hepatectomy in normal livers.[22] With chemotherapy-associated liver injury (CALI), PVE should be used for FLR volumes ≤30 %. The ability to hypertrophy in response to PVE is a critical predictor of regenerative capacity following hepatectomy. As such, an absolute percentage point increase of >5 % is associated with significant reduction in the risk of PHI and death.[23] Frequently, patients with extensive liver disease require two-stage hepatectomy. Combined with perioperative chemotherapy, two-stage hepatectomy +/− PVE can result in prolonged 5-year OS of 51 %.[4]

After downsizing with chemotherapy, the surgical goal should be an R0 resection of all known sites of CLM, including original sites of any lesions which may have disappeared with complete radiographic response to preoperative therapy. Complete radiographic response is not synonymous with complete pathologic response. Approximately 60 % of "disappeared metastases" will recur if not resected.[24]

For extensive disease, a one-stage approach using multiple subsegmentectomies ("wedge resections") has been utilized, but this is associated with higher recurrence rates. Despite the high recurrence rate, proponents argue that selected patients can often undergo repeat hepatectomies to extend survival. It is our bias in patients with extensive disease that large volume anatomic resections, frequently facilitated by PVE to grow the FLR, are preferable.

Metachronous Presentation of Unresectable Metastases

When patients present with anatomically unresectable CLM, the first consideration should be the ability to downsize their lesions to resectability. Effective chemotherapy may achieve this goal in 10–20 % of initially unresectable patients, and these patients who achieve resectability share long-term survival rates that are far superior to palliative chemotherapy and approach that of patients with initially resectable CLM.[25,26]

To convert patients from unresectable to resectable, maximal tumor response is required, frequently involving the addition of targeted agents. Bevacizumab is an anti-vascular endothelial growth factor receptor (VEGFR) and anti-platelet-derived growth factor receptor (PDGFR) antibody used as targeted therapy that supplements traditional cytotoxic chemotherapy in both delaying tumor progression in unresectable cases and inducing greater pathologic response versus chemotherapy alone for resected tumors.[27] With these agents, the conversion rate from unresectability to resectability can be as high as 13–23 %.[26,28]

Cetuximab and panitumumab are antibodies which block the epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase receptor targeted in multiple carcinomas. Cetuximab is effective in a subset (57–63 %) of patients with KRAS wild-type tumors.[29] When cetuximab was combined with FOLFOX, patients with KRAS wild-type benefited from improved response rate (RR, 57 vs. 34 %, $p=0.003$) and progression-free survival (PFS, 8.3 vs. 7.2 months, $p=0.006$), compared to FOLFOX alone.[29] Similarly, when cetuximab was used with irinotecan with 5-fluorouracil and leucovorin (FOLFIRI), patients with KRAS wild-type benefited from improved RR (57 vs. 40 %, $p<0.001$), PFS (9.9 vs. 8.4 months, $p=0.001$), and OS (23.5 vs. 20.0 months, $p=0.009$), compared to FOLFIRI alone.[30] Unlike anti-EGFR agents, bevacizumab can be used for patients regardless of KRAS status.

Ablation

Radiofrequency ablation (RFA) is the most common method of thermal ablation for treatment of many types of liver tumors. Although appealing as a less invasive treatment option, RFA is associated with higher local recurrence rates, especially for tumors >3 cm, multiple tumors, and tumors close to major vessels due to the heat sink effect. RFA plays a role in surgical therapy for highly selected patients with small tumors located away from major abdominal, biliary, and vascular structures but should be considered inferior to resection in terms of local control for CLM.[31]

Risks

Update on Chemotherapy and Chemotherapy-Associated Liver Injury

The majority of CLM patients are treated with chemotherapy prior to liver resection. FOLFOX and FOLFIRI are the foundations of modern chemotherapy. Because of their efficacy, clinicians have used both regimens to increase cure rates in resectable CLM, downsize borderline resectable cases, and attempt to convert unresectability to resectability. This has led to longer systemic treatment durations before surgical referral. However, extended duration (>8 cycles) chemotherapy only increases the risk of CALI without improving pathologic response.[32] Thus, all patients with CLM should be seen by a liver surgeon before chemotherapy to implement a multidisciplinary strategy with the goal of truncating chemotherapy at the point of resectability and not treating to maximal radiographic response. Further chemotherapy can be given postoperatively.

Before the adoption of FOLFOX[33] and FOLFIRI[34] in the early 2000s, 5-FU was the drug of choice for metastatic CRC.[35] 5-FU has been implicated with hepatic steatosis, but the evidence for this finding is unclear. Theorized mechanisms of injury include increased production of free oxygen species as well as direct injury to mitochondrial membranes.[36] One study in the USA suggested that patients treated with 5-FU were twice as likely to have >30 % steatosis versus patients not treated with 5-FU, but this was not statistically significant.[37] Others have suggested that resected livers with steatosis may have been steatotic prior to initiation of chemotherapy. Supporting this hypothesis, one Swiss study showed that steatosis was present in 48 % of chemotherapy-treated livers and 50 % of livers without chemotherapy.[38]

The evidence implicating oxaliplatin in CALI is more convincing. Oxaliplatin is associated with a spectrum of vascular injuries (sinusoidal dilatation, peliosis, centrilobular necrosis, and nodular regenerative hyperplasia), phenotypically presenting as a friable "blue liver".[39] This phenotype has been associated with increased transfusions but not mortality.[39] Using immunohistochemistry and electron microscopy, the aforementioned Swiss study found that 79 % of patients treated with oxaliplatin had sinusoidal damage versus 23 % in those who had no oxaliplatin ($p<$

0.001). The aforementioned study in the USA also showed a significant increase in sinusoidal injury in patients treated with oxaliplatin. However, reliable preoperative assessment of the extent and type of oxaliplatin-induced CALI is not available. Preoperative liver biopsy, prone to sampling error, is not a reliable means to detect the sinusoidal injury pattern. Detailed post-resection pathological assessment is the only way to confirm the sinusoidal changes.

Irinotecan has been associated with both steatosis and steatohepatitis, especially in patients with clinical symptoms of metabolic syndrome (obesity and diabetes).[40] Macroscopically, a "yellow liver" is the result. Its mechanism of injury is also due to mitochondrial damage from reactive oxygen species.[36] Steatohepatitis from irinotecan is the only CALI associated with increased mortality from PHI.[37] This is a key consideration when choosing between FOLFOX and FOLFIRI.

With regard to anti-VEGFR/PDGFR therapy, surgeons have traditionally feared its association with postoperative complications. However, with a treatment break, there may be no difference in morbidity between patients using chemotherapy +/− bevacizumab.[41] The optimal break has not been prospectively analyzed, but 4–6 weeks is commonly recommended. In practice, medical oncologists often hold bevacizumab from the last cycle of preoperative chemotherapy. On a positive note, bevacizumab may decrease the risk of sinusoidal injury associated with oxaliplatin.[27] The major toxicity of anti-EGFR therapy is a severe skin rash, but it is also a marker of efficacy. While chemotherapy remains an integral part of multimodality therapy for CLM, its clinical efficacy must be balanced against its potential hepatotoxicity, especially with extended duration.

Quality and Outcomes

National Morbidity and Mortality Benchmarks in Liver Surgery

Until the most recent decade, with post-hepatectomy 30-day mortality dropping to 2.5 % nationally[42] and 1 % at referral centers,[43] hepatectomies were deemed high-risk operations[44] with frequent hemorrhagic events that impacted both short- and long-term outcomes.[45] Outcomes derived from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database have become an excellent resource for understanding 30-day morbidity and mortality. Although some argue that 90-day outcomes more accurately reflect sequelae of PHI,[37] multiple important risk factors have emerged from NSQIP.[42] As expected, the extent of hepatectomy correlates with the rate of major morbidity. Other factors predictive of major morbidity include comorbidity score, smoking, elevated alkaline phosphatase, low albumin, elevated partial thromboplastin time, intraoperative blood transfusion, operative time, and postoperative transfusion.[42] While these variables can help prepare the surgeon and patient for possible complications, ultimately, the ability to recover and to be rescued from PHI requires adequate, functional FLR volume with regenerative capacity and the limitation of infectious complications.

Margins

Before the modern era of effective chemotherapy, when surgery was our only effective treatment, 1-cm surgical margins were required. A paradigm shift in chemotherapy efficacy has changed surgeons' tolerance for subcentimeter margins, with data from multiple studies indicating that simply margin-negative resection was oncologically acceptable.[46–48] Even R1 resections may benefit patients who are good responders to chemotherapy. However, R1 resections will not benefit those with poor chemotherapy response, since they likely have poor tumor biology.[49]

Survival

Survival expectations of patients with CLM over the last decade have increased dramatically. Before modern chemotherapy, a 37 % 5-year OS was a benchmark.[50] But in modern series, patients with resected CLM can experience up to 50–60 % 5-year OS, even with two-stage hepatectomies.[2–4] The key point is that these outcomes are far superior to those of patients treated with chemotherapy alone, indicating that all patients with potentially resectable disease should be evaluated by high-quality imaging and a multidisciplinary group that includes a liver surgeon before starting chemotherapy. The multidisciplinary strategy goal should be demonstration of chemotherapy response and an R0 resection. Delaying resection until after completion of extended duration chemotherapy (to maximal response) is contraindicated because prolonged chemotherapy is associated with CALI, PHI, and postoperative mortality. Even as chemotherapy regimens improve, liver surgeons will continue to play a central role in treatment planning by offering the best chance for prolonged survival—safe R0 resection.

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Questions

1. One year after low anterior resection, your patient develops bilateral liver metastases which are potentially resectable? You and your medical oncology colleague decide to start a short course of systemic chemotherapy preoperatively. Your patient is 50 years old with BMI 35 and diabetes. Which regimen is best?

   (a) 5-FU/leucovorin
   (b) FOLFOX
   (c) FOLFIRI
   (d) Bevacizumab alone

2. After six cycles of preoperative chemotherapy, your patient's right liver metastases have partially responded. One lesion is about 1 cm from the middle hepatic vein. In deciding whether you can preserve the middle hepatic vein, what resection margin is your goal?

   (a) 2-cm margin
   (b) 1-cm margin
   (c) An R0 (negative microscopic) margin
   (d) An R1 (positive microscopic, negative gross) margin

3. In a preoperative CT for a previously planned right hepatectomy, you see a new subcentimeter lesion in segment IV that would change your operative plan and require an extended hepatectomy, leaving <20 % FLR volume. The lesion is too small to characterize according to the radiologist. What is the least invasive yet effective preoperative diagnostic modality that can be used to characterize this 5-mm lesion?

   (a) Ultrasound
   (b) Percutaneous needle biopsy
   (c) PET/CT
   (d) MRI

4. In a patient who has received preoperative FOLFOX for six cycles before referral to you, the liver surgeon, what is the minimum standardized FLR volume required for safe hepatectomy?

   (a) >10 %
   (b) >20 %
   (c) >30 %
   (d) >40 %

5. You have a patient with an asymptomatic T3 rectal cancer and bilateral liver metastases. As part of his multidisciplinary team, you decide to use the reverse approach, or liver-first, treatment sequencing. You plan on systemic chemotherapy followed by liver resection. Chemoradiation for the rectal tumor will be delivered between liver resection and low anterior resection. Since you are delaying the chemoradiation, the patient wants to know the chances that the T3 rectal cancer will become symptomatic requiring intervention while you are treating the metastatic disease.

   (a) <10 %
   (b) 10–20 %

(c) 20–30 %
(d) >30 %

6. One year after right hemicolectomy, your patient develops two 4-cm liver metastases in segments VIII and VI. The patient's performance status is excellent with no comorbidities. What is the best treatment strategy for prevention of recurrence?

(a) Definitive systemic chemotherapy until complete response
(b) Open radiofrequency ablation
(c) Perioperative chemotherapy plus hepatectomy with negative microscopic margins
(d) Hepatectomy with negative microscopic margins but no chemotherapy

7. Your patient will require an extended right hepatectomy for bilateral liver metastases (segments IV, VI, and VII). There is only one 3-cm lesion in segment IV 1 cm from the middle hepatic vein. Your patient's calculated liver volumes for segments I, II, and III add up to 25 %. Six cycles of FOLFOX have already been completed. What is the best next step toward long-term local control?

(a) More systemic chemotherapy until complete response
(b) Right hepatectomy with radiofrequency ablation of segment IV
(c) Portal vein embolization and extended right hepatectomy if FLR reaches >30 %
(d) Partial hepatectomies, or subsegmentectomies, of all three lesions with negative microscopic margins.

8. In the EORTC 40983 phase III trial which compared perioperative FOLFOX plus resection versus surgery alone for potentially resectable colorectal liver metastases, the FOLFOX plus surgery patients had the following results compared to their surgery-only control arm.

(a) More reversible complications, no difference in mortality rate, no difference in progression-free survival
(b) No difference in complications, no difference in mortality rate, better progression-free survival
(c) More reversible complications, higher mortality rate, better progression-free survival
(d) More reversible complications, no difference in mortality rate, better progression-free survival

Answers:
1. b
2. c
3. d
4. c
5. a
6. c
7. c
8. d