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REVIEW ARTICLE

Designing Liver Resections and Pushing the Envelope with Resections for Hepatic Colorectal Metastases

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Abstract Current concepts in the management of hepatic metastases have changed dramatically over the past two decades. Multidisciplinary therapies including chemotherapy, surgery, and regional therapy have alone and in combination significantly improved the survival of patients with metastatic colorectal cancer. Conditions that were previously considered hopeless and treated merely for palliation can now be approached with curative intent. In this paper, we review the surgical treatment for colorectal cancer liver metastasis (CRLM) and describe a paradigm-shift in the management of complex heretofore-considered unresectable CRLM. Utilizing advanced multidisciplinary treatment strategies has improved the prognosis of patients with stage IV colorectal cancer to the point where we may question whether CRLM are now a chronic disease.

Keywords Colorectal cancer (CRC) · metastatic colorectal cancer (mCRC) · liver resection · hepatectomy · metastasectomy · surgical management, survival

Introduction

Colorectal cancer (CRC) is a major health concern in the United States with over 140,000 new cases diagnosed in 2012 [1]. Although it is the 3rd leading cause of cancer deaths [1], over the last three decades there has been a decline in CRC death rates. This decline can be attributed, in part, to screening and prevention, improved medical therapeutics and surgical techniques, and aggressive treatment of colorectal liver metastases (CRLM). Nearly a quarter of CRC patients have metastases at the time of initial presentation and 60 % will develop hepatic metastases during the course of their disease [2]. In addition, the liver is the most common site of CRC metastases and hepatic disease accounts for two-thirds of all CRC deaths [2, 3].

For a long period of time only a few systemic therapies, mostly toxic and ineffective, were available and surgical resections were plagued by high rates of morbidity and mortality. More recently, effective chemotherapeutic and targeted agents have emerged and surgical techniques have been greatly refined. Here, we review the surgical management of CRLM and propose a paradigm shift for the future management of complex hepatic metastases. Our objectives are: (1) to review factors which correlate with the improvement in survival of patients undergoing hepatic resection for CRLM, (2) to elucidate factors which determine eligibility for surgical resection, and (3) to discuss therapies which may convert initially unresectable disease to potentially curable surgical disease.

Without any treatment, patients with CRLM have rates of median overall survival (OS) ranging from 6 to 12 months [4, 5]. With modern chemotherapy regimens, OS has increased to 20–24 months [6]. Nevertheless, resection of CRLM remains the only curative option and the rates of 5-year OS have been reported to range between 46 % and 60 % [7–9]. The relatively high rates of survival may be attributed to better patient selection, higher-quality radiographic imaging, and safer perioperative conditions.

Decision Making for Surgical Intervention

Many multimodality treatment options are available to patients with CRLM, and optimal management warrants multidisciplinary coordination of care between specialties including medical oncology, surgery, radiology, and radiation oncology. The decision to recommend resection of CRLM is dependent upon whether the disease can be completely and

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safely removed and whether resection would provide a survival benefit. The benefits must be balanced with the risks of the surgical procedure, and several prognostic scoring systems have been designed to predict outcomes after resection for CRLM and assist with the decision for surgical intervention. One such scoring system, described by Fong and colleagues, predicts long-term survival after hepatic metastasectomy using seven factors including resection margin status, detection of extrahepatic disease, lymph node positivity, disease-free interval (DFI), number and size of hepatic metastases, and carcinoembryonic antigen (CEA) level [10]. This scoring system can be used for general guidance, but none is absolute for determining resectability in today's paradigm shift.

Decision Making: Patient Evaluation and Selection for Resection

Important factors involved in determining resectability include the number and anatomic distribution of metastases throughout the liver and their proximity to critical vascular and biliary structures. The multidisciplinary team must determine whether a margin-negative resection is achievable and that an adequate amount of liver with intact vascular inflow and outflow and biliary drainage will remain post-resection in order to prevent post-operative hepatic failure. The volume of liver parenchyma that will remain after resection, i.e., the future liver remnant (FLR), is of paramount importance in hepatic resections [11–13]. Conventionally 20 % of the total liver volume has been regarded as the minimum safe FLR in a patient with normal hepatic function [7]; however, an FLR of 30–40 % is necessary if the patient has received cytotoxic chemotherapy, since chemotherapeutic agents used to treat CRC cause hepatic injury, such as steatosis and sinusoidal obstruction with oxaliplatin and steatohepatitis with irinotecan [12, 14].

Accurate pre-operative imaging studies are mandatory to delineate the anatomic location of metastases and to ascertain if any extra-hepatic disease is present. Patients should undergo high-quality contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Modern helical CT scanning with thin-cut triple-phase liver protocols has a sensitivity of detection of liver metastases of 70–95 %, with a false negative rate of 10 % for lesions less than 1 cm in diameter [15]. MRI similarly has high sensitivity for the detection of metastases [15]. CT and MRI may be equivalent regarding the detection of metastases in the liver; however MRI appears to be inferior to CT when evaluating extrahepatic disease [7]. Positron emission tomography (PET) with radiolabeled fluorodeoxyglucose (FDG) imaging also can improve patient selection by identifying patients with extrahepatic metastatic disease [16–18], and PET imaging has been shown to alter treatment plans in up to 24 % of cases due to identification of additional disease [16]. For patients with potentially resectable metastatic disease, PET imaging may be considered.

Assessment of the extent of disease and treatment options should occur in a multi-disciplinary setting. The determination of resectability mandates the input of experienced hepatic surgeons. Previous strict guidelines of resectability, e.g. 4 or fewer hepatic lesions, tumor size <5 cm, and 1 cm margins of resection [19], have been challenged and definitions of resectability have changed. Instead, eligibility for curative resection now depends on the ability to resect all disease with negative margins and to preserve adequate liver reserve [20]. There is no role for debulking procedures or incomplete resections, as these patients have survival comparable to patients not having undergone an operation [21].

Timing of Surgery and Chemotherapy in Resectable Disease

There is rationale to administer systemic chemotherapy prior to surgery for resectable CRLM. The advantages to this approach include potential downsizing of tumor, improved ability to achieve R0 resection, treatment of occult circulating tumor cells, and assessment of treatment response. In addition, the use of neoadjuvant chemotherapy before CRLM resection provides a time period to better identify patients with favorable disease biology [22], and treatment can be tailored or altered since the disease remains in situ and treatment response can be measured [23]. Since chemotherapy is associated with hepatotoxicity, neoadjuvant chemotherapy should be limited to 4–6 cycles. If the CRLM remains resectable on follow-up imaging, patients should proceed to resection in order to minimize further hepatotoxicity and reduce the risk of perioperative complications related to the use of chemotherapy [24].

Upfront hepatic resection followed by chemotherapy remains a viable option in patients who present with resectable CRLM [25, 26]. There is one randomized prospective trial examining the timing of chemotherapy relative to the resection of CRLM. In the prospective, randomized, multi-institutional EORTC Intergroup Trial 40983, patients were treated by either surgery and perioperative chemotherapy with FOLFOX4 or by surgery alone for initially resectable CRLM. The progression-free survival rate at 3 years was significantly improved in the perioperative chemotherapy/surgery group over the surgery alone group (42.4 % vs. 33.2 %, respectively) [27]. However, the trial reported a significantly increased rate of post-operative complications in the neoadjuvant chemotherapy group as compared to the surgery alone arm. Long-term follow-up recently showed no OS advantage to perioperative chemotherapy [27]. Randomized, prospective trials are needed to better define the timing and

duration of chemotherapy in relation to hepatic resection for CRLM.

Designing Strategies for Conversion to Resectable Disease

Only 15–25 % of patients with mCRC are resectable at the time of presentation [28]. In patients who present with initially unresectable CRLM, one option for treatment is simply palliative chemotherapy. Another treatment strategy for patients who present with initially unresectable CRLM is first-line treatment with conversion chemotherapy (Fig. 1a). Modern chemotherapy has allowed 12.5 % of patients who were once considered "unresectable" to be down-staged and amenable to future hepatic resection [29]. In 2000, Adam et al. reported that staged hepatectomy was feasible in 16 of 398 consecutive patients (4 %) with previously unresectable CRLM when combined with chemotherapy and other nonsurgical ablative techniques [30]. Subsequently, 13 of those 16 (81 %) were successfully resected and median OS was 44 months from the time of diagnosis of metastatic disease [30]. An update of this series in 2008 showed that 41of 59 (69 %) patients were successfully treated with two-stage hepatectomy with initially unresectable CRLM. The remaining 18 were unable to undergo the second stage resection due to disease progression. In the patient cohort that underwent both planned hepatectomies, 3-year and 5-year OS were 60 % and 42 % respectively [31]. These outcomes are comparable to patients with initially resectable CRLM. As such, patients who have conversion chemotherapy should be imaged and evaluated for surgical resection after 2 months of therapy, and every 2 months thereafter if therapy is continued [3, 32–36].

For patients without hepatic disease or injury and who are chemotherapy naïve, resection of 80 % of the liver with 20 % FLR is safe [37]. For patients who have received chemotherapy, the FLR must be approximately 30–40 % due to the aforementioned steatosis, portal sinusoidal dilation, and steatohepatitis. One strategy to increase the volume of FLR is portal vein embolization (PVE), whereby branches of the portal vein that supply hepatic segments that are candidates for resection are embolized, thus inducing hypertrophy of the remaining segments of liver (Fig. 1-b). PVE can be performed using either transileocolic portal vein embolization or percutaneous transhepatic portal vein embolization (preferred). On average, PVE produces a 25–80 % increase in the absolute volume of the non-embolized liver [11, 38–40]. PVE has also been shown to be safe and effective in patients that are currently undergoing neoadjuvant chemotherapy. Covey and colleagues at Memorial Sloan-Kettering Cancer Center retrospectively reviewed 100 patients with CRLM who underwent PVE in preparation for extended

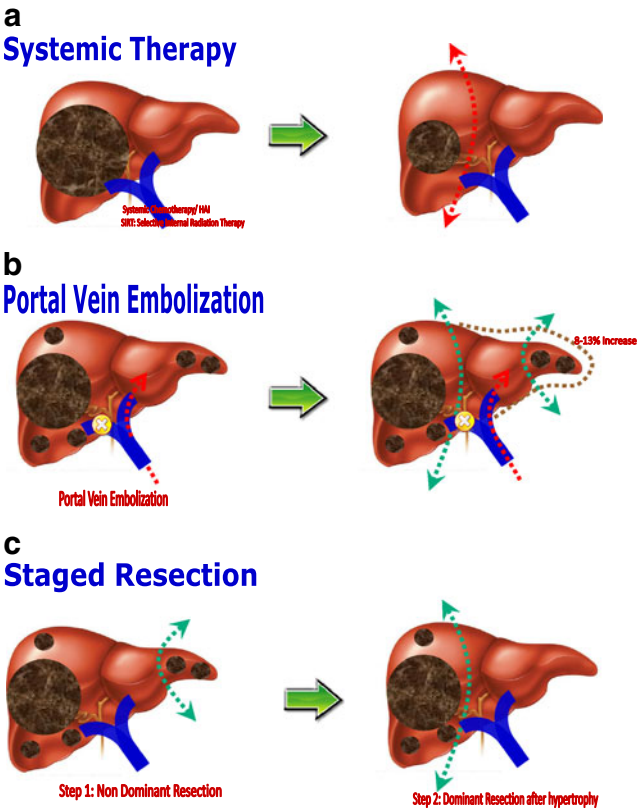

Fig. 1 Designing liver resections. **a** Size reduction following systemic chemotherapy with or without Selective Internal Radiation Therapy (SIRT). **b** Portal Vein Embolization. This allows for an average compensatory increase in the total volume ranging from 8–13 %. Following compensatory hypertrophy, elective resection is planned within 4–6-weeks. **c** Staged Resection: Usually done in two stages. The first step involves resection of the non-dominant liver metastases. This may or may not be combined with portal vein branch ligation to potentiate regeneration. Time is allowed for the liver to regenerate followed by a staged resection of the dominant liver lesions

hepatectomy; 43 patients underwent PVE during neoadjuvant chemotherapy [37]. After a median of 30 days, patients on neoadjuvant chemotherapy were found to have similar liver hypertrophy compared to patients not undergoing chemotherapy. A large meta-analysis by Abulkhir et al. identified 37 studies with 1088 patients [38]. Overall morbidity for PVE was 2.2 % and 85 % of patients underwent laparotomy with 83 % resectability in patients who underwent PVE.

Hepatectomy is normally performed 4 to 6 weeks following PVE. For patients with multiple bilobar liver metastases, there is concern that metastatic nodules may grow more rapidly than the nontumoral liver parenchyma following PVE. In these cases a two-stage hepatectomy can be combined with PVE [39]. Metastases in the FLR are first resected, and then following PVE a second-stage hepatectomy is performed, thus removing the residual disease burden in the atrophic lobe (Fig. 1c). Using PVE, previously unresectable CRLM may become resectable (Fig. 2).

Other options to decrease the size of metastases include trans-arterial chemoembolization (TACE), selective internal radiation therapy (SIRT) with yttrium-90-conjugated micro-beads, and direct hepatic artery infusion (HAI) of chemotherapeutic agents with implanted subcutaneous pumps. For patients with unresectable disease who are likely to not become candidates for resection in the future, all of these techniques along with systemic chemotherapy may be used as well, although the use of TACE, SIRT, and HAI require specific skill-sets that may differ from institution to institution and are not uniformly available. A discussion of these techniques is beyond the scope of this review.

Surgical Techniques

Removal of CRLM can be approached with a formal anatomic hepatic resection or hepatic wedge resections, since anatomic hepatectomy does not specifically confer a survival benefit [9, 41]. Preservation of hepatic parenchyma in patients is a high priority given that these patients may require more than one liver resection if their disease recurs or progresses. A stepwise approach to these complex patients is important as it ensures the capability for future repeat resections during the course of their disease. It has been shown that of those patients who have future mCRC recurrences, 30–40 % will have liver-only disease, and thus may be candidates for repeat hepatectomy [7, 10, 42, 43]. As discussed previously, for patients who initially present with less than four metastases amenable to resection, those patients should be taken to operation for resection; however for patients with more extensive disease, such as limited bilobar disease, a strategy of resection and ablation with or without PVE should be adopted for preservation of hepatic parenchyma in the case that future resections are needed.

At operation, there are several intra-operative considerations to be addressed prior to liver resection. A thorough exploration of the abdomen must be initially performed at the time of laparotomy to search for extrahepatic disease, as well as to determine that the CRLM are indeed resectable. Intra-operative hepatic ultrasound is very useful in confirming the relations of the metastases to vascular structures and should be used. Once the final decision to proceed with hepatic resection has been made, the CVP must remain low in order to minimize blood loss during the parenchymal transection. Techniques for hepatic parenchymal transection include finger-fracture technique, cavitron ultrasonic surgical aspirators (CUSA), bipolar hemostatic sealing devices (Aquamantys, Medtronic Advanced Energy, Portsmouth, NH, USA), and tissue sealing devices (LigaSure, Covidien, Mansfield, MA, USA). Regardless of the technique used, negative margin resection remains critical. There is no role for a margin-positive operation, and multiple studies have shown higher local recurrence rates and diminished survival when hepatic resection margins are positive [41, 44–50].

Although surgery remains the gold standard in the treatment of CRLM, alternatives to resection include the use of ablative techniques. Ablation is an effective option for patients who are not candidates for hepatic resection due to inadequate FLR or patient co-morbidities [51]. Other criteria for the use of ablation include fewer than 3 CRLM and hepatic tumor size less than 3 cm [52, 53]. Although the use of ablative techniques is popular and safer in some patients when compared with surgical resection, ablation results in higher local recurrence rates [8, 52–54]. Radiofrequency ablation (RFA) is the

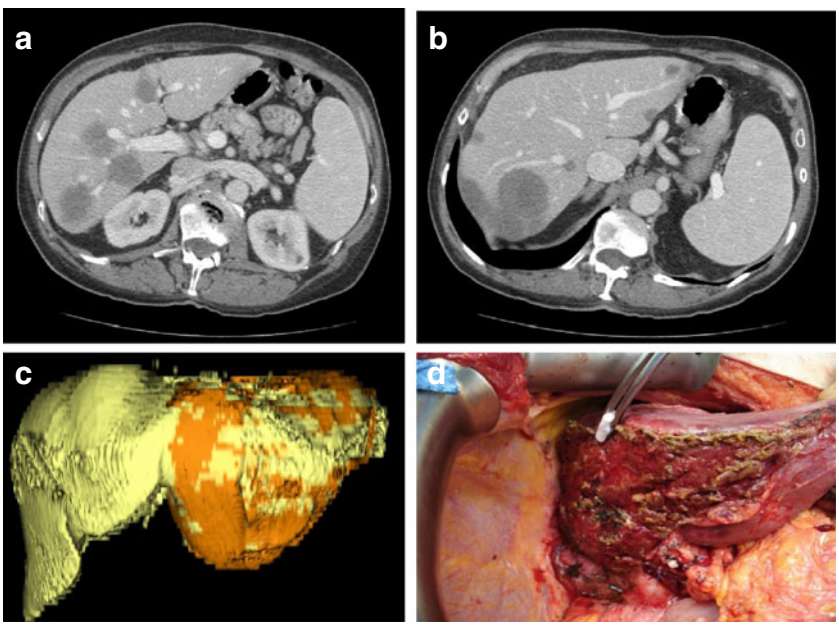

Fig. 2 Compensatory hypertrophy after PVE followed by resection. **a** and **b** CT scan images showing multiple liver metastases in the right lobe and segments II, III & IV. **c** Compensatory hypertrophy following right PVE. The image is reconstructed from CT scan images following PVE, and shows an increase of the volume of the left lateral segments by 18 %. **d** Intra-operative photograph showing the liver after the right extended hepatectomy and wedge resection of the lesions in segments II and III (not visualized)

most commonly-used ablation technique used currently and can be used to ablate residual unresectable disease as well as to treat small hepatic recurrences [8, 52, 53, 55]. Other ablation technologies include cryoablation, microwave ablation (MWA) [56], and the newest, most recent option, irreversible electroporation (NanoKnife System, AngioDynamics, Latham, NY, USA); however a detailed discussion of these techniques is outside the scope of this review.

Pushing the Envelope: Extended Resections for Extra-Hepatic Disease

With the advent of improved chemotherapy and the demonstrated safety of major hepatic resections [57, 58], combined resection of liver metastases at the time of resection of extra-hepatic disease, or in sequential fashion, has demonstrated improved long-term survival rates [59–63]. Consequently, the presence of extra-hepatic disease alone is no longer an absolute contraindication to surgical therapy; however complete resection with negative margins of both the hepatic and extra-hepatic sites must be achieved [59–62, 64]. In a meta-analysis of over 1,142 patients addressing hepatectomy for CRLM with extra-hepatic disease, median survival was 30 months (range 14–44 months), and four studies reported patients who were able to undergo R0 hepatectomy with complete removal of extra-hepatic disease with 5-year OS of 19–36 % [59]. Other published series have reported 10-year survivors who may be effectively cured of their disease [65–67]. In addition, several studies have shown that staged resection of visceral metastases from liver and lung confers similar survival benefits and results in long term survivors [63, 68–71]. The recognition of the oncologic benefits to aggressive metastasectomy has resulted in expanded criteria for resection of mCRC [6].

Conclusion

In the past two decades, the survival of patients with CRLM has dramatically increased. Multimodality treatment that includes systemic chemotherapy and regional treatments has resulted in a greater number of patients who undergo resection for CRLM. CRLM may be considered a potentially curable disease, treated chronically with systemic chemotherapy and serial resections and staged metastasectomies. Each patient must have his extent of disease carefully evaluated and a tailored approach to the management of the metastatic disease should be considered. This paradigm-shift has contributed to the improvement in overall survival in patients with mCRC and to the numbers of long-term survivors. Given the complex management of CRLM, as well as the treatment options currently available, patients with mCRC should be discussed in a multidisciplinary setting that includes all members of the treating team to create a personalized approach to surgical resection of metastatic CRC.

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