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Complex Surgical Strategies to Improve Resectability in Borderline-Resectable Disease

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Abstract

Colorectal cancer is the third most common malignancy in the USA and continues to pose a significant epidemiologic problem, despite major advances in the treatment of patients with advanced disease. Up to 50 % of patients will develop metastatic disease at some point during the course of their disease, with the liver being the most common site of metastatic disease. In this review, we address the relatively poorly defined entity of borderline-resectable colorectal liver metastases. The workup and staging of borderline-resectable disease are discussed. We then discuss management strategies, including surgical techniques and medical therapies, which are currently utilized in order to improve resectability.

Keywords

Colorectal cancer; Colorectal liver metastases; Liver resection; Hepatectomy; Two-stage hepatectomy; Borderline; Borderline-resectable; Future liver remnant; Portal veinembolization; Ablation; Systemic chemotherapy; Hepatic arterial infusion pump

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the USA. Colon and rectal tumors comprise approximately 140,000 cases per year and over 55,000 attributable deaths. Therefore, CRC still poses a significant epidemiologic problem, despite major improvements in the treatment of patients with advanced disease [1]. Up to 20 % of patients have metastatic disease at presentation and approximately 50 % will develop metastatic disease at some point during the course of their disease [2]. The liver is the most common site of metastatic disease, with involvement in 80 % of cases, either in isolation (40 %), or in combination with other sites of disease (60 %) [3].

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Unfortunately, at presentation, only approximately 20 % of disease is thought to be amenable to resection [4]. The importance of this finding is directly linked to outcome, since 5- and 10-year survival in resected liver-only metastatic CRC ranges between 25 to 74 and 9 to 50 %, respectively [5–7]. Survival in untreated, but potentially resectable, disease ranges between 6 and 12 months, with rare survivors noted at 3 years [8]. In general, modern systemic chemotherapy results in response rates of over 50 % and approximately 2-year median survival in most studies [9]. However, although 5-year survival after treatment with modern systemic chemotherapy alone occurs, it is relatively uncommon and requires chronic therapy.

Surgical intervention provides the best hope for long-term survival cure in patients with metastatic disease confined to the liver. As such, recent improvements in the treatment of metastatic disease have served to increase rates of resectability. This review discusses strategies to improve resectability in patients with “borderline-resectable” colorectal liver metastases (CRLM).

Defining Disease Resectability

Resectable CRLM disease is most commonly defined as hepatic disease that can be resected with negative margins (R0) and leaves at least 2 contiguous disease-free segments with adequate vascular inflow, outflow, and biliary drainage [10]. In addition, in patients without hepatic dysfunction, a future liver remnant (FLR) volume of at least 20 % of total liver volume is considered necessary to safely preserve a remnant capable of adequate regeneration [4, 11••, 12]. Finally, patients must be suitable operative candidates and without evidence of unresectable extrahepatic disease. This definition only addresses the technical issues related to removing liver tumors, regardless of presentation, number of tumors, and other clinical factors representative of advanced disease. As an example, 20 metastases that happen to be in the right lobe of the liver are “resectable.” However, the risk of recurrence is very high.

Defining resectability, therefore, remains very challenging. The surgeon must consider both technical and biologic issues. The presence of limited and resectable extrahepatic disease (EHD) has been considered resectable by many, including our group. However, recurrence after these operations is nearly universal, which has limited resection to highly selected patients with low-volume chemoresponsive and indolent disease. Similarly, positive margins have been associated with poor outcomes and very high recurrence rates. Unfortunately, predicting a positive margin based on preoperative imaging is not always possible. As the number of liver metastases increases, so does the rate of recurrence. Traditionally, the presence of four or more metastases was considered a contraindication to resection. Indeed, recurrence rates in these patients are high, occurring in approximately 90 % of patients. However, cure remains a possibility. It is likely that as the number of metastases increases, the curative potential of the operation diminishes. Lastly, clinical risk scores have been developed. These are based on scores related to multiple prognostic factors such as the number and/or size of tumors, pathology of the primary tumor, CEA level, and timing of presentation. While these risk scores reliably stratify outcomes, they do not preclude the possibility of cure in patients with the worst scores.

Definitions of resectable, unresectable, and borderline-resectable CRLM are, therefore, inexact and poorly defined entities. While we feel that the biologic issues related to the presentation and extent of disease are very important, if the disease is confined to the liver and technically resectable then some curative potential ultimately exists. We would like to stress, however, that as disease burden increases, curative potential significantly decreases. For the purposes of this review, we will define borderline-resectable CRLM as 2 entities. The first is the patient with grossly resectable disease with a 2 contiguous-segment FLR that is of inadequate volume. Strategies to improve resectability in this situation revolve around optimizing the FLR volume and function, in order to minimize the risk of post-operative morbidity and liver failure. The second situation is that of extensive tumor burden that compromises the likelihood of obtaining an R0 resection with an adequate FLR. In this situation, the focus is on shrinking tumors to improve the likelihood of a successful resection. Of course, there are situations that require both tumor response and optimization of the FLR. For the purposes of this review, we will not consider technically resectable but biologically high-risk disease as borderline-resectable.

Imaging of Borderline-Resectable CRLM

In the modern era, CRLM are typically asymptomatic at clinical presentation. The aim of modern imaging techniques is to accurately identify the extent of the disease, the proximity to critical structures, including inflow and outflow vessels, and bile ducts, and provide an estimation of the FLR size. Although bias exists in the choice of tests ordered in the workup of CRLM, modern imaging techniques such as multidetector computed tomography (MDCT), magnetic resonance imaging (MRI) (with or without hepatobiliary contrast agents), and fluorodeoxyglucose positron emission tomography (FDGPET) are all frequently utilized in the radiologic assessment of metastatic CRC. Overall, the difference in accuracy between MDCT, MRI, and FDG-PET in detecting CRLM ranges from 72 to 98 % in the literature for tumors larger than 1 cm [13••].

As a general principle, MDCT is considered the best initial modality for the evaluation of suspected CRLM disease, due to its wide availability, rapid image sequencing, and high resolution. MRI possesses additional advantages beyond the initial screening. In cases of borderline-resectable disease, MRI can be helpful in identifying small lesions, particularly in the setting of fatty liver change after chemotherapy. MRI can also be helpful in characterizing lesions that may not be malignant. FDG-PET scans are especially useful in the identification of occult extrahepatic disease.

MDCT has emerged as the imaging modality of choice in the detection and evaluation of CRLM disease. MDCT can quantify liver tumor burden, assess disease proximity to critical structures, evaluate operative liver anatomy, and detect extrahepatic disease. MDCT is also helpful in assessing the extent of the primary colorectal tumor. Limitations of MDCT are predominantly limited to tumors smaller than 1 cm. In a recent study by Weiring et al., the authors demonstrated a sharp decline in the sensitivity of MDCT in detecting lesions of decreasing size, with a detection rate of 97 % for lesions greater than 2 cm, 72 % for lesions 1–2 cm in size, and only 16 % in identifying lesions smaller than 1 cm [14, 15]. Another weakness of MDCT is the identification of liver tumors within fatty liver [16, 17].

MRI, while less readily available and with significantly slower scanning speed than MDCT, possesses superior sensitivity and specificity compared with MDCT. The sensitivity of MRI in detecting liver metastases, particularly with inclusion of contrast agents such as gadolinium or gadoxetate disodium, has been estimated at 91–97 % [18]. With respect to specificity, MRI is able to accurately identify malignant lesions 97.5 % of the time, compared with 77.3 % of the time with MDCT according to one study [19]. Importantly, in lesions deemed too small to characterize by MDCT, MRI is able to distinguish between benign versus malignant lesions in 91.5 % of cases, which is particularly relevant in instances where multiple liver lesions exist [13••]. Finally, MRI has a superior ability to detect tumors on a background of fatty liver change following chemotherapy. Therefore, the usefulness of MRI in borderline-resectable disease, particularly after chemotherapy treatment, cannot be underestimated [16, 17].

While FDG-PET possesses a sensitivity and accuracy of approximately 75–95 % for CRLM detection among reported studies, a recent study by Ruers et al. has shown that the predominant benefit of FDG-PET is in the identification of occult extrahepatic disease, thereby helping reduce the rate of unnecessary laparotomies in their study from 48 to 28 % [20]. In an earlier study, FDG-PETwas found to similarly alter the treatment strategy in 23 % of patients [21]. Several additional studies have confirmed the utility of FDG-PET scans in identifying occult extrahepatic disease [22, 23]. However, in a recent randomized-controlled trial comparing combined FDG-PET with computed tomography (CT) versus CT alone in patients with potentially resectable CRLM, combined FDG-PETwith CT did not significantly alter surgical management, and provided no difference in disease resectability or long-term outcomes between the 2 groups [24]. This trial only included patients with resectable CRLM at presentation, and, therefore, the use of FDG-PET in higher-risk, borderline-resectable, patients may have utility in the detection of occult extrahepatic disease. Notable disadvantages of FDG-PET include limited availability, reduced sensitivity in detecting CRLM following chemotherapy, low sensitivity in detection of lesions smaller than 1 cm, and overall high cost of utilization [25, 26].

Image-Guided Volumetric Assessment and Preoperative Planning

In order to accomplish a safe hepatic resection with an adequate FLR, preoperative assessment of liver volumes is usually carried out using MDCT. MRI has also been employed for volumetric evaluation, particularly when concern for fatty liver infiltration exists. Accurate evaluation is especially important in cases of borderline-resectability, and may affect operative planning as described below. The FLR is calculated as a proportion of total liver volume (TLV), and is measured accurately using cross-sectional volumetric analysis, given the low volume of disease burden that is often encountered within the FLR. Techniques have also been developed to “subtract” any tumors that might be present in the FLR for a more accurate estimation of the FLR volume. The TLV may be estimated based on the total body surface area (BSA), which is unaffected by disease burden (standardized TLV). Alternatively, TLV may also be directly measured using CT volumetry with subtraction of tumor volume (corrected TLV) [4, 27–29].

Surgical Staging

Historically, laparotomy was considered a diagnostic modality during which unresectable CRLM would often be diagnosed and alternative therapies would be sought in up to 70 % of cases [30]. In current practice, patients may have additional disease detected during laparotomy that may either preclude resection, or necessitate a change in strategy. However, with the advances in preoperative detection of extensive or extra-hepatic disease, rates of unresectable disease discovered intraoperatively have declined. In a recent review that assessed operative resectability in 455 patients with CRLM, only 35 patients (7.7 %) were noted to have unresectable disease at surgery, largely due to extensive liver disease or previously undetected extrahepatic disease [31]. This may, in part, have been explained by expanded resection criteria when compared with older studies. Diagnostic laparoscopy has been attempted in an effort to reduce discovery of occult extrahepatic disease during laparotomy. In the same report evaluating routine use of diagnostic laparoscopy in 55 patients with CRLM, only 4 patients were found to be unresectable during laparoscopy. Given the low yield of this intervention, diagnostic laparoscopy in the treatment of CRLM has largely been abandoned, and is likely to provide no benefit in the management of patients with borderline-resectable disease. Diagnostic laparoscopy can be valuable in patients with radiologic findings concerning for, but not diagnostic of, unresectable extrahepatic disease.

In terms of surgical staging, the use of intraoperative ultra-sound (IOUS) and contrast-enhanced intraoperative ultra-sound (CE-IOUS) are frequently utilized, and their role has been addressed in the literature. A recent report evaluated the impact of IOUS, by comparing IOUS findings in patients with CRLM who had already undergone MDCT with or without MRI imaging, in order to detect previously undiagnosed tumors that would affect the surgical strategy [32]. There were a total of 632 liver tumors among 219 patients that were diagnosed preoperatively using MDCT and MRI. IOUS successfully identified 20 additional lesions in 18 patients, of which 12 were malignant. Thus, the authors concluded that IOUS permits the identification of a few additional lesions that affect the surgical strategy in 1.4 % of patients. By helping diagnose additional lesions, showing larger or smaller than expected sizes, identifying disappearing lesions, and identifying differences in lesion appearance and characteristics, other studies have identified a change of surgical strategy in up to 43 % of patients [33]. These findings are, however, based on retrospective data.

CE-IOUS uses microbubble gas contrast agents that are stabilized by a shell, and include octafluoropropane, sulfur hexafluoride, or perfluorobutane with a phospholipid shell. CE-IOUS is not currently available in the USA, as these agents have not been licensed for use by the Food and Drug Administration. However, CE-IOUS permits real-time dynamic high-resolution imaging of the liver during arterial, portal, and delayed phases of vascular imaging. In a report by Arita et al., the authors evaluated the use of IOUS followed by CE-IOUS in CRLM patients who had already undergone gadolinium-based contrast MRI imaging, and noted that IOUS identified an additional 25 lesions to 242 nodules that were identified by MRI [34]. The addition of CE-IOUS subsequently indentified a further 22 lesions, but also confirmed the additional 25 lesions identified by IOUS alone. Of the 25 and 22 additional lesions detected by IOUS and CE-IOUS, 21 and 17 lesions were noted to be

CRLM, respectively. The authors confirmed a change of surgical strategy in 12 and 14 patients, respectively. Reported sensitivity, positive-predictive value, and accuracy of CE-IOUS were 99, 98, and 97 %, compared with 82, 99, and 83 % for gadolinium-enhanced MRI, respectively. The potential superiority of CE-IOUS over any other imaging modality has previously been proposed [35]. IOUS and CE-IOUS are additional tools that are helpful in surgical staging of borderline-resectable CRLM, where yield is likely to be high.

Strategies to Optimize FLR in Borderline-Resectable Disease

Today, hepatic resection is a safe operation in expert hands and at tertiary level referral centers. A recent study reported an associated mortality of 2.5 % and 30-day morbidity rate of 20 % for hepatic resection [36]. Interestingly, in CRLM disease, mortality rates following hepatectomy are on the order of 1 %, which is likely related to the increasing use of parenchymal preserving hepatic resection [37].

Although parenchymal preservation is not a strategy used to optimize FLR per se, its implementation, where possible, has obviated the need for extensive liver resection and subsequent FLR optimization, and is of worthy mention. Early data suggested improved outcomes with greater than 1 cm margins and anatomic resections in resection of CRLM. However, there has been a recent trend toward parenchymal-sparing liver surgery, in an attempt to preserve a larger FLR, thereby reducing the extent of resection and associated complications [38, 39, 40•, 41]. In a report by Kingham et al., the authors evaluated a cohort of 4152 liver resections over a period of 19 years carried out at our institution [40•]. Among 2476 patients with CRLM, 90-day mortality decreased from 5.0 to 1.6 %, perioperative morbidity decreased from 53 to 20 %, and transfusion rates decreased from 51 to 21 %. In a separate study of 440 CRLM patients with bilobar disease, Gold et al. were able to demonstrate a significant shift away from major hepatectomies toward parenchymal-sparing segmental and wedge resections, with a decrease in major hepatectomy rate from 90 to 75 %, along with an increase in the rate of wedge resections from 15 to 40 %. Importantly, the mortality rate dropped from approximately 6 to 1 %, without impacting disease-specific and disease-free survival [42]. The importance of parenchymal-sparing liver surgery in patients with bilobar metastases cannot be underestimated, and is often critical in patients with borderline-resectable disease. It is important to note that hemi-hepatectomy or extended hemihepatectomy is not always necessary in the treatment of extensive bilobar CRLM.

In borderline-resectable cases where a major hepatic resection is necessary and FLR volume is below a regenerative capacity threshold, there is a significant risk of postoperative liver failure and death. Arbitrary FLR volumes of 20 % (in healthy liver), 30 % (fatty liver), and 40 % (cirrhotic liver) are often quoted [4, 12, 43–47]. These volumes are typically derived from retrospective reviews of postoperative liver dysfunction and correlations with FLR volumes. The ability of the liver to regenerate may also be influenced by numerous perioperative factors and events, such as major hemorrhage and post-operative sepsis [48–50]. However, In order to determine the extent of FLR that is adequate for continued hepatic function and adequate regeneration, liver function is evaluated using objective tests, such as the Child-Pugh classification, which is based on clinical and laboratory parameters to help establish underlying severity of preexisting liver disease. Although uncommon during

treatment of CRLM, chemotherapy-induced steatohepatitis (CASH), or cirrhosis, may occur secondary to extensive chemotherapy use. Child-Pugh classes B and C, which occur uncommonly in CRLM disease, are excluded from hepatic resection, as are patients with clinically relevant portal hypertension.

Portal Vein Embolization and Two-Stage Hepatectomy

Once the underlying condition of the liver has been clinically evaluated, the determination of the FLR is primarily made with cross-sectional imaging modalities such as high-resolution CT as described above. In cases where FLR is deemed inadequate, attempts to optimize the FLR volume may be undertaken to augment resectability. The most common strategy is preoperative portal vein embolization (PVE), which was introduced in the 1980s, although data supporting findings following interruption of portal venous flow originated in the 1920s [51, 52]. The portal vein supplying the portion of liver to be resected is embolized, or surgically ligated, which results in ipsilateral atrophy and compensatory contra-lateral hypertrophy of the remnant liver lobe over a median period of approximately 4 weeks. By increasing the volume of the FLR, the risk of post-operative hepatic failure decreases. The strategy of PVE to optimize FLR is a successful strategy, and many studies have confirmed the increase in the FLR following PVE. In a recent meta-analysis of 1088 patients who underwent PVE prior to resection, an increase in FLR following PVE was confirmed in every study [53]. There were no deaths reported from the use of PVE among any of the studies. Eighty-five percent of patients included in the analysis, of whom approximately one-third included patients with CRLM disease, underwent successful hepatectomy, with a post-operative hepatic failure incidence of 2.5 %, and associated mortality of 0.8 %. The incidences of hepatic insufficiency and associated mortality, while not directly compared to non-PVE patients in this analysis, were lower than corresponding values in matched patients who did not undergo PVE in other reported series, highlighting the effectiveness of this strategy [44].

Numerous studies have validated the effectiveness of this strategy in reducing post-operative morbidity following hepatic resection [44, 54, 55]. Liver hypertrophy, as measured by absolute volume increase, ranges from approximately 8 to 27 %, and is an important predictor of outcome following resection [53]. However, recent data have also shown the rate of compensatory hypertrophy appears to be equally important in predicting outcomes following resection [56].

Importantly, the use of PVE can be extrapolated to the treatment of bilobar borderline-resectable disease in two-stage hepatectomy. In the initial stage of the strategy, minor resections of tumor-bearing liver are performed in the FLR. Subsequently, PVE is utilized in order to increase the volume of the tumor-free FLR. Once adequate hypertrophy of the FLR has occurred, the second stage is performed, often with a major resection of the portion of liver bearing the remnant disease. Oncologic outcomes associated with this specific strategy have been striking. In a report by Jaeck et al., 3-year survival in patients who underwent two-stage hepatectomy with PVE was 54 %, with a median tumor number of 8 [55]. Seventy-five percent of patients who underwent initial resection completed treatment.

While two-stage hepatectomy combined with PVE provides a useful approach in the treatment of borderline-resectable disease, ablative therapies, which are discussed in more detail below, may be employed in the first stage of the procedure, in order to treat disease within the FLR.

Associated liver partition with portal vein ligation for staged hepatectomy (ALPPS) is a novel two-step technique for optimizing FLR in patients with limited anatomic reserve, which is based on the same principles of PVE [57]. Portal venous ligation is combined with an in situ liver transection during the first stage of the procedure, which results in a pronounced short-term parenchymal hypertrophy over approximately 1 week. The underlying cause of the more pronounced hypertrophy compared with PVE is likely due to transection of bridging inflow vessels between liver segments. This further diminishes portal venous blood supply, which does not occur with standard PVE alone. Approximately 1 week following the initial operation, a second laparotomy is undertaken to remove the pre-divided liver segment. This procedure requires two laparotomies over a short period of time, and early reports note an associated morbidity and mortality that are significantly higher when compared with standard PVE and two-stage hepatectomy procedures (67 vs. 48 % morbidity and 12 % in-hospital mortality vs. 6 % 90-day mortality, respectively) [58]. As such, the benefit of ALPPS over conventional PVE is heavily debated.

Locoregional Therapies

Ablative therapies can be useful as a parenchymal-sparing strategy in patients with marginal FLR volumes. Currently, the most common ablative therapy is radiofrequency ablation (RFA), which is used to thermally ablate tumors, and is highly effective for small tumors. RFA can be delivered via percutaneous, minimally invasive, or open techniques, and involves image-guided targeted transmission of heat into tumor cells, which results in destruction of tumor cells within the metastatic focus. Local recurrence following RFA occurs more commonly than following surgical resection with negative margins. In a recent report, recurrence range was noted to range from 10 to 50 % [59••]. A recent meta-analysis noted that tumor size exceeding 3 cm and percutaneous approaches were ultimately responsible for the highest recurrence rates on multivariate analysis [60]. We recently reported our results with intraoperative ablation and found excellent local control for tumors less than 1 cm in size [61•]. In a review of 158 patients, a total of 315 tumors were ablated, with 53 % of tumors being smaller than 1 cm. RFA was used to treat the majority of ablated tumors (70 %). The 2-year ablation zone recurrence-free survival was 92 % for tumors less than 1 cm and 81 % for tumors greater than 1 cm in size. On multivariate analysis, tumors greater than 1 cm in size, the lack of post-operative chemotherapy use, and use of cryotherapy were significantly associated with increased recurrence rates in the analysis.

Thermal ablation may be used in combination with resection in order to optimize FLR while serving to eradicate all metastatic foci, and is particularly helpful to the surgeon in the treatment of bilobar hepatic disease. In a recent report of 141 patients treated with multiple resections who were compared with 95 patients treated with a combination of ablation-resection techniques, ablation-resection performed similarly to multiple resections. However, the combined ablation-resection strategy allowed incorporation of patients with higher

severity of illness clinical scores, who would otherwise have been poor surgical candidates for repeat resection [62]. While 5-year overall survival was statistically similar between ablation-resection (56 %) and multiple resection (49 %) patients, estimated blood loss and length of stay were significantly improved in the combined ablation-resection group, despite inclusion of higher-risk patients. Combining resection and ablation is a strategy that is utilized by many liver surgeons in specialized centers, and provides an effective option in the treatment of high-risk borderline-resectable CRLM disease. A notable disadvantage of RFA includes limited application in tumors with close proximity to vascular structures due to the heat sink effect that limits the ability of the treatment to achieve effective necrosis. Complications related to RFA include the development of liver abscesses, major vascular and biliary injuries, as well as injury to nearby organs such as the diaphragm or stomach.

Alternative ablation techniques for CRLM include use of microwave ablation and cryotherapy. Cryotherapy has not been used in recent years, largely due to higher reported rates of morbidity. Microwave ablation use appears to be increasing substantially. Similar to RFA, patients with tumors greater than 3 cm have high recurrence-free survival when treated with microwave ablation [63]. In a recent retrospective review of 176 patients with a total number of 416 tumors treated with intraoperative microwave ablation, there were 33 (7.9 %) local tumor recurrences among 31 (17.6 %) patients predominantly with CRLM [64]. In a recent retrospective comparison of RFA with microwave ablation, a lower local recurrence rate was noted with microwave ablation (6 % compared with 20 % in RFA), with an estimated 2-year Kaplan-Meier recurrence of 7 % with microwave ablation compared with 18 % with RFA [65].

Finally, irreversible electroporation (IRE), a soft tissue ablation technique that uses short electrical pulses to disrupt cell membranes and induce cellular apoptosis rather than necrosis, has emerged as a novel percutaneous therapeutic modality in the treatment of a variety of hepatic malignancies. Long-term data regarding efficacy and long-term safety of this modality are, as yet, limited. However, local control, especially around large hepatic vessels, appears to be promising [66,67].

Strategies to Shrink Tumor Burden in Borderline-Resectable Disease

Systemic Therapy

With response rates reaching above 50 % for most modern systemic regimens, the use of systemic therapy for borderline-resectable disease has permitted R0 resection with curative intent in a significant proportion of patients [68••, 69–71]. As discussed above, approximately 10 to 20 % of patients with CRLM are initially considered candidates for hepatic resection of disease [72]. When patients with unresectable or borderline-resectable disease are downstaged to complete resection, long-term data appear to support 5- and 10-year survival figures that are similar to upfront resectable patients, with 5-year survivals in the 40–50 % range [73, 74]. In a report by Adam et al., the authors were able to downstage 12.5 % of patients to resectability in initially unresectable patients, of whom 33 % were survivors at 5 years and 23 % alive at 10 years [75].

Common regimens utilizing 5-fluorouracil (5-FU), oxaliplatin, and irinotecan in a variety of combinations (FOLFOX, FOLFIRI, and FOLFIRINOX) are approved as first-line therapy in patients with unresectable or borderline-resectable disease [76–78]. While conversion to resectability and shrinkage of tumor burden in borderline-resectable disease provides the only hope for significant long-term survival and cure, it is important to note that second-line systemic options are, unfortunately, largely unhelpful in inducing significant responses in the majority of non-responders, with response in this patient population generally occurring in fewer than 15 % of patients [79].

The addition of molecular-targeting agents such as bevacizumab and cetuximab in systemic combinations appear to be associated with modest improvements in response rates, with conversion to resectability achieved in only a small proportion (12 to 18 %) of patients [80–84].

Interestingly, in addition to absolute response rates to modern systemic therapy, a recent report by Cauchy et al. stratified patient outcomes based on response kinetics, and noted that in patients who required less than 12 cycles of chemotherapy (termed “fast responders”), outcome was significantly improved when compared with “slow responders” [85]. Mortality in fast responders versus slow responders was 0 and 19 %, respectively, morbidity was 20 and 55 %, respectively, and all slow responders recurred within 3 years.

Hepatic Arterial Infusion Pump Therapy

The rationale for hepatic arterial infusion pump (HAIP) therapy, which is a strategy utilized in the treatment of borderline-resectable liver disease, is based upon pharmacologic and anatomic and principles. Pharmacologically, hepatic arterial infusion of agents such as floxuridine (FUDR), which is largely extracted by the liver during first-pass metabolism, results in high intrahepatic concentrations with minimal systemic spill-over. Anatomically, liver metastases are perfused almost exclusively by the hepatic artery, whereas normal hepatocytes derive their blood supply from the portal vein and the hepatic artery [86]. As such, regional infusional therapies via the hepatic artery allow for effective administration of chemotherapeutic agents with minimal systemic toxicity.

In the context of borderline-resectable or unresectable disease secondary to metastatic CRC localized to the liver, a recent phase II trial published by our group evaluated the conversion rate of patients with unresectable CRLM with combined HAIP therapy and systemic chemotherapy including bevacizumab [87•]. Forty-nine patients with unresectable disease were included and conversion to resection was the primary outcome. Patients included suffered from advanced CRLM, with a median tumor number of 14. Sixty-five percent had received prior systemic chemotherapy. Impressively, overall response rates were 76 % with 4 complete responses. Twenty-three patients (47 %) underwent conversion to complete resection at a median of 6 months from treatment initiation. Median overall survival was 38 months and progression-free survival was 13 months. Conversion was the only factor that was associated with prolonged overall survival and progression-free survival on multivariate analysis. Three-year overall survival was 80 % in resected patients compared with 26 % who did not undergo resection. Incorporation of bevacizumab was associated with a higher biliary toxicity rate and was discontinued during the study period. Ten of 49 (20 %) patients

had no evidence of disease at a median follow-up of 39 months. The use of HAIP, where feasible, is a strategy that is associated with impressive outcomes that may be utilized in the treatment of borderline-resectable disease.

Conclusion

Borderline-resectable CRLM remains a poorly defined entity. When one restricts this definition to patients with extensive tumor burden resulting in the requirement of a major hepatectomy and an inadequate FLR, or tumor burden simply precluding complete resection, there are two basic strategies. The first is to optimize the FLR, most commonly by PVE techniques. The second is to shrink tumors with systemic chemo-therapy, regional infusional chemotherapy, or both. Of course, both of these strategies may be simultaneously necessary. Fortunately, these strategies are generally safe and effective, and have likely increased the number of patients who can undergo complete resection.

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