Current Treatment of Colorectal Liver Metastasis as a Chronic Disease

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Abstract. *Background/Aim:* The treatment of colorectal liver metastases is challenging and requires multidisciplinary strategies. Unfortunately, only 25% of patients with colorectal liver metastases are eligible for liver resection. Due to the variety of therapeutic approaches, this percentage has increased; however, at the same time, the definition of resectability has become complex. The aim of this review was to provide an overview of current surgical therapies for colorectal liver metastases. *Materials and Methods:* Relevant studies published before June 2019 were identified using PubMed. A comprehensive review of the current literature regarding the impact of and innovations in the therapy of colorectal liver metastases was carried out. *Results:* The major advances in the resectability of colorectal liver metastases were effective chemotherapy regimens and preoperative liver volume modulation techniques. In addition, health professionals face rapid technical developments in interventional local therapies, minimally invasive surgery, robot-assisted surgery and even liver transplantation. *Conclusion:* Currently, liver metastases from colorectal cancer are considered a chronic disease. In cases of advanced colorectal liver metastases, the definition of resectability and the indications for surgical treatment should be exclusively determined by experienced hepatobiliary surgeons.

Colorectal cancer (CRC) is the third most frequent type of cancer and the fourth leading cause of cancer-related death worldwide. About 15-42% of patients with CRC have or develop liver metastases (1-4). Despite the high prevalence

of liver metastasis, therapy for colorectal liver metastases (CRLMs) is still challenging and requires multidisciplinary strategies. Extensive achievements have been made in the systemic therapy for CRC as well as in local therapies for liver metastasis, such as ablation procedures (radiofrequency ablation, and microwave ablation) (5), regional hepatic intraarterial chemotherapy (6), chemoembolization (7), radioembolization (8), and radiation therapy, including stereotactic radiation therapy (9). Unfortunately, only 25% of patients with CRLM are eligible for liver resection (10, 11). Thus, the main question is how to define the resectability of metastasis (12-14). The aim of this review was to provide an overview of the current therapeutic options for CRLM by redefining surgical resectability.

Materials and Methods

Relevant and recent studies that focused on the treatment of CRLM and were published before June 2019 were identified using PubMed by searching for journal articles and colorectal liver metastases. A comprehensive review of the current literature regarding the impact of and innovations in therapy for colorectal liver metastases was carried out to provide guidelines for health professionals.

Results

Metachronous metastasis. The incidence of CRLM is approximately 12.8% in the five years following the diagnosis of primary CRC (4, 15). Primary surgery for liver metastasis, which ranges from a single subsegment resection to extensive bilateral resections, should still be considered as the primary therapy. Apart from the co-morbidities of the patients, the limitations of resection in most cases are the future of the remnant liver volume and poor liver function. Thus, when there is a disseminated pattern of metastases in the liver, it is challenging to perform extensive resection.

Since Adam *et al.* published their first series of two-stage hepatectomy (TSH) in 2000, TSH has been the most common curative approach for the surgical treatment of bilobar disease. TSH involves the surgical clearance of CRLM in one hemiliver during the first stage, followed by

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a second stage that includes the clearance of the contralateral hemiliver after hypertrophy to maintain a sufficient volume of the future liver remnant (16).

A systematic review showed that TSH is safe and effective in selected patients with primarily unresectable CRLM (17). TSH leads to significantly fewer complications and better overall survival (OS) than one-stage hepatectomy, which involves major hepatectomy and contralateral resection/ablation for bilobar disease (18). However, dropout rates after the first stage remain high due to poor liver regeneration and disease progression. Factors that are independently associated with poor OS following TSH are rectal primary tumors, more than five hepatic lesions, chemotherapy between the two stages and RAS mutations. RAS mutations are linked to worse long-term survival and are the only factor independently associated with OS and progression-free survival (PFS) for patients who underwent second-stage resection. Nevertheless, RAS mutations are not associated with dropout after the first stage (19).

A minimum of 25% of the liver volume has been considered as the minimum remnant volume for liver resection in healthy livers. However, functionality should also be considered (20). In cases with prior systemic chemotherapy, the remnant volume should be 30%, and in cases with liver disease such as steatosis, at least 40% of the liver should be preserved after surgery (21). To induce growth of the future liver remnant, portal vein embolization (PVE) is a well-established intervention. PVE is considered the standard procedure prior to extended liver resection, which can otherwise jeopardize the remnant liver volume (22). The limitation of hypertrophy following PVE is mostly due to cholestatic disease or liver fibrosis (22). Seventy percent of patients could undergo surgery five weeks after PVE. Unfortunately, the progress of oncological disease is the predominant reason for dropout, followed by insufficient liver hypertrophy (23, 24). Additional hepatic vein embolization combined with PVE could be a safe alternative to induce faster hypertrophy in the future remnant liver; however, to date, the evidence for this procedure is weak (25).

Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) was introduced first as a rescue strategy in patients with biliary carcinoma. Later, ALPPS was evaluated in metastatic liver disease (26). ALPPS allows extended liver resection for bilateral diseases in shorter term compared to classical TSH, with a 90-day mortality rate of 8.8% (27) and a morbidity rate of 56.3% (28). The first stage consists of tumor clearing in the left lateral liver segments, right portal vein ligation (PVL) and a so-called “*in situ* splitting”, which is a complete parenchymal dissection while preserving the right hepatic artery, the right bile duct and the right hepatic vein. A major right hepatectomy is performed during the second stage (29). The advantage of this approach is the rapid hypertrophy of 74% (range=21%-192%) of the

left lateral lobe in a median period of 9 days (range=5-28 days) (30). While there are high dropout rates after the first stage of TSH, in ALPPS, completion rates of 100% have been reported (31). The first prospective multicenter randomized controlled trial showed significantly higher resection rates for ALPPS than TSH, with similar mortality and morbidity (32). Thus, ALPPS can be considered an additional strategy for the treatment of advanced CRLM in patients with a very extensive tumor burden who are otherwise being considered for palliative treatment and as an intraoperative rescue strategy for cases with intraoperatively diagnosed advanced disease.

Synchronous metastasis. Patients with advanced synchronous CRLM with locally advanced rectal cancer are at risk for a poor outcome because liver disease may progress during the treatment of the primary CRC, especially if complications occur due to colorectal resection (33). The liver-first approach allows most patients with locally advanced rectal cancer and synchronous liver metastases to undergo curative resections of both metastatic and primary disease (34). As shown in small study groups, patients treated with the liver-first approach have a considerable OS and PFS, although disease-free survival (DFS) remains relatively low (35-37). The development of surgical techniques and the ability to perform liver and primary CRC resections with little blood loss, combined with advances in anesthesia and perioperative care, have made the synchronous approach an additional treatment option (38). However, the synchronous approach is still linked to postoperative morbidity and has a negative impact on PFS (39).

Minimally invasive liver resection. Since the introduction of laparoscopic liver surgery in 1992, this technique has become increasingly important for the operative management of CRLM (40). A systematic review of 4,967 patients indicated that laparoscopic liver resection had higher rates of clear surgical margin without significant differences in disease recurrence, OS and DFS compared to the open approach. Laparoscopic liver resection was associated with less intraoperative blood loss and fewer blood transfusions but also with longer operation times. Less overall morbidity and shorter postoperative hospital stays were observed for patients who underwent laparoscopic liver resection, while there was no significant difference in mortality (41). Even challenging surgical procedures such as laparoscopic posterior resections are associated with shorter hospital stays with similar oncological results (42). Recently, a study by Fretland *et al.* has shown that patients had a better life quality after the laparoscopic resection of CRLM than after the open approach in terms of both their physical and social recovery (43).

The limitation of laparoscopic liver surgery is mostly related to the experience of the surgeon. While left and anterior segment resections can be performed by surgeons with low and intermediate experience levels, the resection of the posterior, especially the right superior sections, is highly advanced. Furthermore, obesity and thrombocytopenia can complicate the procedure (44). Robot-assisted liver resection might be a suitable option for surgically advanced cases (45).

Primary unresectable CRLM. While surgery is the only curative treatment approach for CRLM, only 25% of CRLMs are considered primarily resectable (46). Multifocal intrahepatic tumor spread in both liver lobes, extensive tumor burden or diffuse extrahepatic metastases result in either technical or functional unresectability or make the potential for curative treatment unlikely. Although bilateral CRLM was a contraindication for surgery in the past, over the past three decades, the therapy for advanced CRLM has changed and steadily improved; thus, the definition of resectability has changed. The most significant development in terms of resectability is the definition of the surgical margin in liver metastasis. Miller *et al.* have shown in a retrospective analysis that a minimum 1-mm surgical margin is sufficient for oncological clearance (47). On the other hand, significant developments have been made in chemotherapy regimens with the intention to downsize the metastases and achieve secondary resectability. Furthermore, surgical techniques for preoperative liver volume modulation, such as PVE, PVE in combination with left vein embolization (48, 49), TSH and ALPPS, have improved resectability, as described above (48).

Total vascular exclusion of the liver, vascular reconstruction (including hepatic veins), even *ex situ* hepatic resection and autologous transplantation, can be considered as surgical approaches for otherwise unresectable CRLM (30, 50). However, these techniques should be performed at experienced hepatobiliary units with a transplant background and should be considered only if no neoadjuvant options are available.

Perioperative chemotherapy. Neoadjuvant oxaliplatin- and irinotecan-based chemotherapy regimens in combination with 5-fluorouracil or leucovorin are currently first-line treatments for unresectable CRLM (51). Furthermore, classical regimens are combined with biologic agents such as bevacizumab and cetuximab and panitumumab for KRAS wild-type patients. The use of biologic agents combined with doublet chemotherapy regimens (FOLFOX or FOLFIRI) increases the resectability rate for initially unresectable CRLM. Furthermore, successful conversion results in outcomes similar to initially resectable CRLM (52-54). Due to downsizing by chemotherapy, between 13% and 54% of unresectable patients become resectable (51). On the other

hand, nonresponse to neoadjuvant chemotherapy may be a contraindication for major hepatectomy in combination with ablation because of high local recurrence rates (55).

Findings by Lim *et al.* have shown an increase in OS with bevacizumab-based chemotherapy compared with conventional chemotherapy in a neoadjuvant setting for patients who underwent liver resection for synchronous CRLM. This benefit was shown in those who underwent primary tumor resection first. Bevacizumab had no impact on the liver-first approach (56). García-Alfonso *et al.* have retrospectively reviewed 74 patients treated with neoadjuvant or conversion chemotherapy plus bevacizumab. The authors emphasized that the OS was longer and that there was a trend for prolonged PFS and RFS in patients with a complete or major pathological response (57). However, in the patients who underwent staged surgical approaches, interval chemotherapy did not prevent disease progression or dropout rates before the second stage (58).

There is no clear evidence for additive chemotherapy following margin-negative liver resection; thus, there is no clear recommendation for the routine administration of chemotherapy (59, 60). However, a randomized controlled trial of 364 patients comparing perioperative chemotherapy with FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) before and after the surgical treatment of resectable CRLM to surgery alone showed no significant difference in OS between the two groups but a better PFS following preoperative chemotherapy. In contrast, the administration of perioperative chemotherapy has been associated with serious parenchymal liver damage and an increase in the postoperative morbidity-mortality rate (61). In cases of margin-positive resection, adjuvant chemotherapy should be considered since 54% OS can be achieved (47).

Transplant oncology. Currently, there is an increasing emphasis on liver transplantation (LTx) as a treatment for CRLM (62). Because of poor OS before 1995, LTx was abandoned for otherwise unresectable CRLM (63, 64). The systemic spread of metastatic disease and LTx-associated postoperative immunosuppressive therapy may lead to increased recurrence in CRLM. Moreover, it is crucial to implement CRLM as an indication for LTx in light of the current donor shortage, since the prognosis of CRLM patients following LTx is not clear. However, advances in the treatment of CRLM and immunosuppression have led to a re-evaluation of this approach as a treatment option for unresectable CRLM (65).

Hagness *et al.* have published a prospective pilot study on 21 LTx cases with unresectable liver-only metastases (the SECA study). This study showed that the hepatic tumor load before LTx, time between primary surgery and transplantation, and progression despite chemotherapy were

prognostic factors. The DFS after one year was 35% (66). Two years later, Dueland *et al.* compared the results of the SECA study with first-line chemotherapy. The 5-year OS rate was 56% in patients undergoing LTx compared with 9% in patients starting first-line chemotherapy (67). A retrospectively collected cohort by Toso *et al.* with 12 selected patients attained similar results regarding OS (68).

In the course of the SECA study, 19 of the 21 patients experienced recurrence. Consequently, pulmonary recurrence appeared frequently and early but was relatively indolent. In contrast, patients who developed metastases to the transplanted liver had poor outcomes. In the SECA study, metastases to the transplanted liver appeared exclusively as a part of disseminated disease. Six of the seven patients who developed metastases to the transplanted liver died from metastatic disease. There were no first-site liver-only recurrences (69). According to Grut *et al.*, patients treated by LTx for unresectable CRLM with pulmonary recurrence have a good prognosis following the resection of pulmonary metastases (70). Strict selection criteria for LTx in cases of unresectable CRLM have not yet been well defined, but tumor load, response to chemotherapy, pretransplant CEA level, and time interval from resection of the primary tumor to transplant are all related to outcome (62).

Finally, a fundamental limitation of this approach is the scarcity of liver grafts. A potential donor source is donation after cardiac death (DCD) or marginal grafts.

A possible strategy to address this scarcity could also be the so-called RAPID-Concept (Resection and Partial Liver Segment 2/3 Transplantation with Delayed Total Hepatectomy). The first stage of this strategy consists of liver resection of the left liver combined with transplantation of a left lateral section graft, usually from a living donor, and modulation of the graft portal inflow. This technique induces the fast regeneration of the transplanted graft during the course of two-three weeks. During the second stage, delayed total hepatectomy of the liver remnant is performed (71, 72). Currently, several worldwide studies are recruiting patients for the evaluation of LTx in the treatment of CRLM. More recently, a German group has launched a study based on the RAPID-Concept, which includes patients with unresectable CRLM, with stable disease or tumor regression after at least 8 weeks of systemic chemotherapy and without extrahepatic tumor growth (73).

Conclusion

The major advances in the resectability of CRLM are effective chemotherapy regimens with the intention to downsize the tumor and preoperative liver volume modulation techniques that affect the hypertrophy of the future remnant liver. Due to these developments, patients with CRLM commonly undergo various operations and interventions combined with chemotherapy during the course of their therapy. Thus, CRLM

treatment has been transformed from being predominantly palliative to the management of a chronic disease. In addition to chemotherapy regimens and volume modulation, especially new surgical techniques, laparoscopy and even liver transplantation, are of crucial importance. Because of the technical developments in minimally invasive surgery, laparoscopic and robot-assisted surgery are pushing the boundaries of the resectability of liver metastasis in fatty livers following chemotherapy (74). Downsizing the metastases using preoperative chemotherapy and parenchyma-sparing surgery with the margins of 1-mm allow a wide spectrum of therapeutic options for patients with CRLM. Thus, surgical and oncological improvements might dramatically increase the OS of those patients. Due to the variety of approaches, the assessment of resectability with modern surgical indications for the resection of CRLM has large disparities (13). Therefore, especially in cases of advanced CRLM, the definition of resectability and the indications for surgical treatment must be determined by experienced hepatobiliary surgeons.

Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding this study.

Authors' Contributions

All Authors conceived of the presented idea. N.M.D. and M.H.M. conducted the review of the literature. M.B. and M.H.M. verified the method. M.B. encouraged N.M.D. to investigate transplantation for colorectal metastasis and supervised the findings of this work. All Authors discussed the results and contributed to the final manuscript.

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