review

Eur Surg (2023) 55:94–99
https://doi.org/10.1007/s10353-023-00796-w

european surgery
ACA Acta Chirurgica Austriaca

Surgical management of colorectal liver metastases—a practical clinical approach

Yawen Dong · Thomas Gruenberger

Received: 12 February 2023 / Accepted: 14 February 2023 / Published online: 8 March 2023

Summary
Background Despite the remarkable advances that have been made in the management of colorectal cancer over recent years, the optimal treatment for colorectal liver metastases (CRLM) remains a controversial matter. Undoubtedly, such a complex disease requires a multidisciplinary approach, in which close collaboration between all specialists involved in its management is of utmost importance.
Methods A literature search was conducted in PubMed. There was no limit set to the date of publication. The main focus of the literature review is to provide a comprehensive summary of the current multidisciplinary management of CRLM while highlighting the surgical approach.
Results Assessment of resectability, evaluation of the patient's fitness, and discussion of clinicopathological features all play a vital role in finding the most suitable treatment strategy for CRLM patients, who should all be timely discussed in the multidisciplinary tumor board, in order to decide upon the optimal therapy sequence, operative time window, and postoperative treatment.
Conclusion Although hepatic resection remains the only potentially curative treatment strategy for patients with CRLM, a multidisciplinary approach is essential for optimal treatment. A clear definition of treatment goal (curative vs. palliative) at the time of disease diagnosis determines the further therapeutic course. Preoperative estimation of liver functional reserve is a key factor in the decision-making process for CRLM resectability.

Keywords Clinicopathological features · Multidisciplinary approach · Treatment sequence · Resectability criteria · Future liver remnant

Introduction

In recent years, considerable progress has been achieved in the management of colorectal cancer. However, metastatic disease remains a challenge and is often considered incurable. For patients with colorectal liver metastases (CRLM), current treatment approaches include various systemic therapeutic options (chemotherapy and targeted therapy) in combination with surgical resection. Constant improvements in the field of liver surgery as well as the development of more effective systemic therapies have made a wider application of surgery in the treatment of CRLM possible. Therefore, this multimodal approach has been established as the gold standard for CRLM treatment, as it can improve clinical outcomes of patients with metastatic colorectal cancer and poses the only option for cure. Nevertheless, the real issue at hand remains the fact that oftentimes, the evaluation of factors that determine whether the liver metastases are resectable or not can be very complex. Each CRLM patient should be discussed within a multidisciplinary tumor board, in order to decide upon the optimal treatment sequence, operative time window, and postoperative treatment. The objective of this review is to provide an outline of current surgical strategies for CRLM with the focus on patient selection, disease resectability, and the integration of surgery and systemic therapy in the treatment of CRLM patients.

Y. Dong (✉) · T. Gruenberger
Department of Surgery, Clinic Favoriten, HPB Center, Health Network Vienna, Kundratstr. 3, 1100 Vienna, Austria
yawen-dong@hotmail.com

T. Gruenberger
tgruenberger@icloud.com

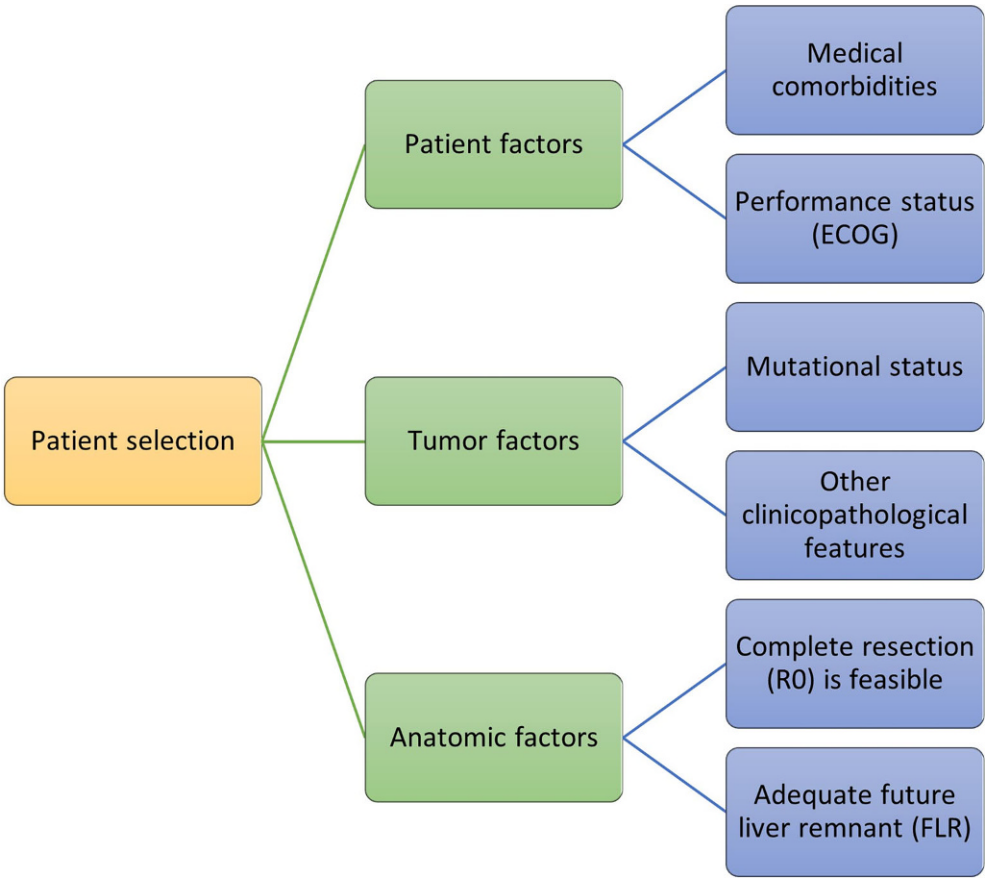

Fig. 1 Meticulous patient selection as a key component in facilitating the best perioperative and long-term oncologic outcomes

Methods

A literature search was performed in the PubMed database up until September 2022. There was no limitation set on the date of publication. As the main purpose for the literature review was to summarize the multidisciplinary management of CRLM, keywords used for the PubMed search included colorectal metastases, resectability criteria, surgical management, systemic therapy, treatment sequence, and future liver remnant. No statistical analysis was applied due to the narrative nature of the present review.

Results

Patient selection

Although surgery poses the only potential treatment strategy for long-term survival and cure in patients with CRLM, not every patient is amenable for surgical resection [1]. Thorough patient selection within the multidisciplinary conference as early as at the time of disease diagnosis is crucial (Fig. 1). The following key components should be taken into account during the evaluation process:

- *Patient-related* factors: patients undergoing liver resection should be carefully assessed preoperatively for their underlying medical comorbidities, especially with regards to preexisting liver disease, severe cardiopulmonary conditions, and other chronic illnesses. Consequently, a poor general performance status can prohibit a patient with resectable CRLM from receiving liver surgery, as the perioperative risk may be too high.
- *Tumor-related* factors: most patients with liver metastases should receive a short course of induction chemotherapy combined with an anti-EGFR antibody (if initially unresectable) or anti-VEGF antibody, partly with the intention to determine, whether the tumor is responsive to systemic therapy. This in turn allows clinicians to allocate the tumor into a group with a "more favorable" or "less favorable" tumor biology. Based on clinicopathological features such as mutational status (RAS and BRAF, MSS/MSI) and sidedness of the primary tumor, several clinical prognostic scores have been established so far, which should guide clinicians through the question of whether the patient might benefit from perioperative chemotherapy or if he is more prone to developing recurrent disease [2, 3].
- *Anatomy-related* factors: previous guidelines were more restrictive regarding the definition of "resectable disease" and placed limits on the number, size, and distribution of the tumor lesions. Conversely, nowadays patients with CRLM are deemed resectable if a complete resection/ablation of all hepatic metastases can be accomplished while

Table 1 Classifications of conventional colorectal liver metastases resectability criteria

Upfront resectable (10%)	Borderline resectable (20%)	Unresectable (70%)
Sufficient future remnant liver (at least 20% of healthy liver volume)	CRLM can potentially be completely resected but there may be technical challenges	Multiple disease sites (intra- and extrahepatic disease)
Possibility of upfront R0 resection	Requirement of tumor downsizing to achieve resectability	All liver segments infiltrated by metastases
Adequate vascular inflow/outflow and biliary drainage can be preserved	Invasion or contact of metastases with preservable vascular structures	Poor patient performance status
± Neoadjuvant therapy	Conversion therapy	Palliative therapy
CRLM colorectal liver metastases		

maintaining a sufficient functional residual liver volume [4]. Furthermore, the presence of extrahepatic metastases is no longer considered to be an absolute contraindication to hepatic resection, only under the premise that a margin-negative resection of both intra- and extrahepatic disease is feasible [5].

Resectability criteria for CRLM

In general, colorectal liver metastases can be divided into three subgroups: *resectable, borderline* or *potentially resectable (after downsizing)*, and *unresectable*. Of note, a patient's resectability should always be defined by the purposes of treatment planning, as surgery for CRLM is always performed with curative intent. As already mentioned earlier, the surgical strategizing eventually revolves around the question of whether complete removal of the metastatic lesions is achievable while preserving a functional future liver remnant (FLR). In case the FLR is not sufficient, the patient might develop post-hepatectomy liver failure (PHLF), a serious postoperative complication associated with high morbidity and mortality [6]. In addition, the following aspects should also be kept in mind when assessing resectability: *disease burden* (size, number, location of CRLM) [7, 8], *disease biology* (progression during systemic therapy, suspected extrahepatic metastases, primary tumor sidedness, metachronous vs. synchronous CRLM development, mutational status, presence of microsatellite instability) [9, 10], and *technical considerations* such as relationship to the vascular inflow/outflow and biliary system [11].

Importantly, several factors such as liver cirrhosis, steatosis hepatis, and chemotherapy-associated liver injuries (CALI) might diminish the liver's regenerative capacity. Therefore, the target FLR is directly dependent on the quality of the non-metastatic liver parenchyma. Current guidelines propose an FLR of minimum 20–25% in healthy hepatic tissue, 30% in patients with chemotherapy-associated liver injury, and 40% in cirrhotic liver [12].

Only 10% of CRLM cases are deemed resectable upfront, where sufficient remnant liver can be left behind after complete removal of all liver metastases (Table 1). 20% of CRLM patients have borderline resectable disease, in which a conversion therapy (5-fluorouracil-based triplet or doublet chemotherapy in combination with a targeted agent) is indicated due to metastatic invasion into preservable vascular structures, thus making tumor downsizing necessary first, in order to achieve negative margins following surgery. The remaining 70% of CRLM patients suffer from unresectable disease, where factors such as multiple disease sites, infiltration of metastases into all liver segments, or a poor patient performance status render resection unfeasible. As a result, the patient will initially undergo so-called palliative systemic therapy but should be reevaluated for potential resectability after 2–3 months [13].

Timing and treatment sequencing for CRLM

The optimal timing and treatment sequencing when treating patients with synchronous colorectal liver metastases must be discussed in a multidisciplinary setting involving chemotherapy/chemoradiotherapy (for patients with primary rectal cancer), surgery, and maybe other forms of locoregional treatment. Depending on the acuity of symptoms and disease burden, the sequence of surgical resection of the primary tumor and liver metastases can vary [14]. For instance, patients who present with symptoms from the primary colorectal cancer (i.e., bowel obstruction, bleeding, and perforation) will require resection of the primary tumor first. In contrast, if the patient is asymptomatic from his primary tumor and suffers from multiple bilobar metastases, then the liver-first approach is the gold standard, as it is associated with a more favorable prognosis [15]. Finally, the simultaneous approach, which involves resection of the primary tumor and liver metastases during one surgical procedure, should be reserved for patients with a good performance status and limited hepatic disease. Major hepatic surgery combined with removal of the primary tumor may be prone to postoperative complications such as anastomotic leakage [15, 16]. Figure 2 provides an outline of a possible treatment algorithm for synchronous CRLM.

Surgical strategies of CRLM resection

With the development of various novel operative techniques, several surgical strategies can currently be followed for treatment of CRLM. The main goal of resec-

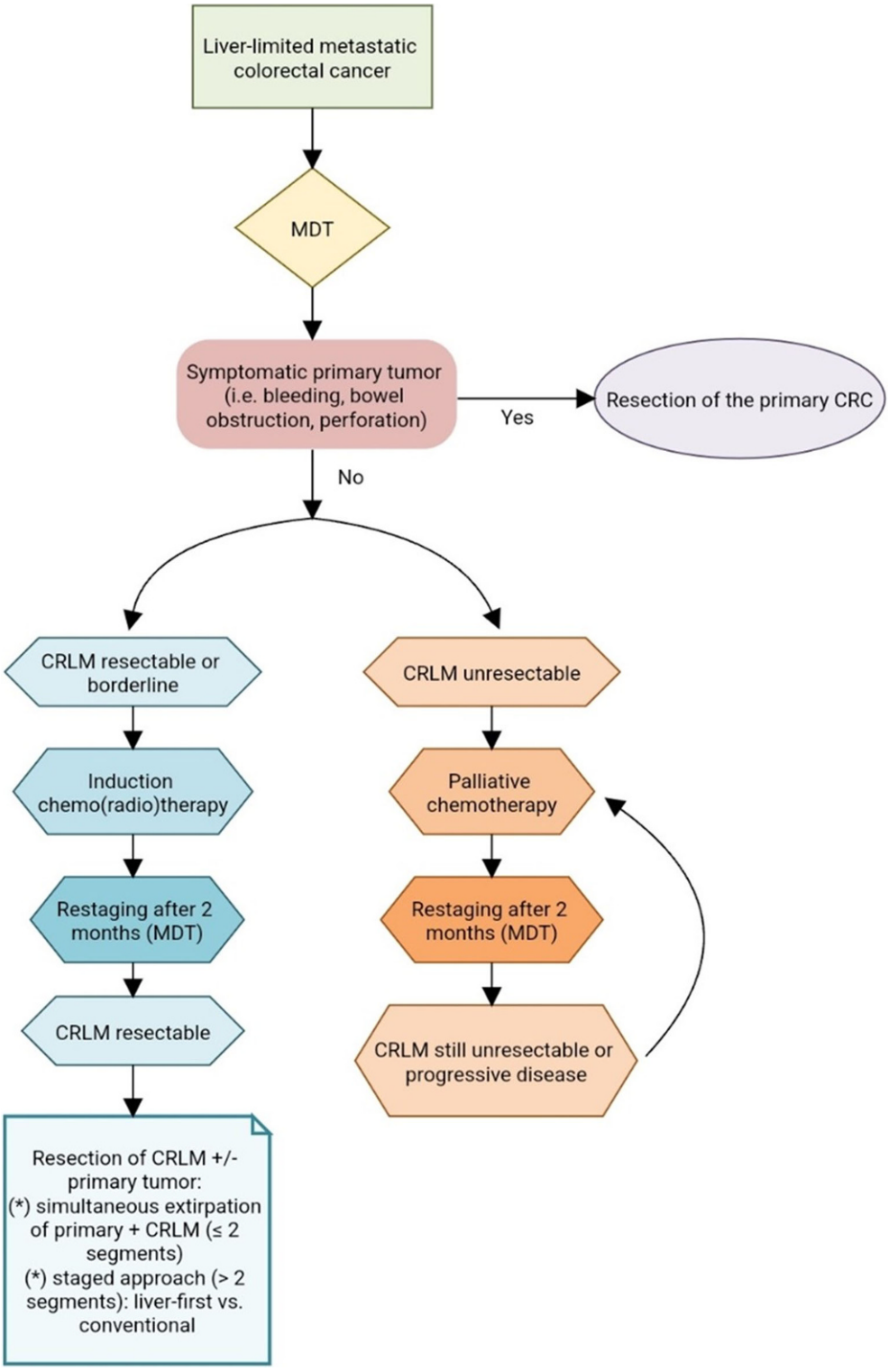

Fig. 2 Exemplary treatment algorithm for synchronous colorectal liver metastases (*CRLM*). *MDT* multidisciplinary tumor board, *CRC* colorectal cancer

tion remains the complete removal of all macroscopic hepatic metastases, while leaving a sufficient FLR behind. In this regard, the following surgical interventions should be mentioned:

1. parenchymal-sparing hepatectomy (i.e., non-anatomic liver resection),
2. portal vein and hepatic vein embolization,
3. two-stage hepatectomy, and
4. associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [17].

While parenchymal-sparing hepatectomy follows the idea of preserving as much non-tumorous liver tissue as possible, it is still considered to be oncologically equivalent to anatomic liver resections [18]. The con-

cept of preoperative double-vein embolization (portal vein and hepatic vein embolization) is based on the induction of hypertrophy in the future liver remnant (FLR). Especially in patients with a small FLR, double-vein embolization of the diseased lobe can result in augmentation of the FLR, thus facilitating curative resection at a later timepoint (usually 2–6 weeks) [19]. In addition, the principle of two-stage hepatectomy consists of two liver resections, where during the first surgery a tumor clearance from the planned FLR is performed. Subsequently, the contralateral portal vein is ligated or embolized, in order to induce hypertrophy of the FLR. Once this has been achieved, the remaining tumor burden will be resected during the second surgery [20]. Lastly, the so-called ALPPS procedure is a variant of two-stage hepatectomy. Similar to the conventional strategy, the first operation aims at clearing all tumor mass from the FLR. Following this, the contralateral portal vein is ligated and the liver is divided along the intended transection line without destroying the remaining vascular and biliary pedicles of the FLR. After sufficient FLR augmentation has been accomplished, the remaining hepatic metastases are removed during the second stage, mostly extended liver resection [21].

Conclusion

In summary, patients with CRLM should be discussed in detail in a multidisciplinary conference and evaluated for an operative approach at the first opportunity, as surgery poses the only potential option for cure. Previously, resectability revolved around the size, number, and distribution of the liver metastases, whereas nowadays the most important technical consideration is the feasibility of complete resection of all hepatic metastases while preserving a sufficient and functional liver volume.

Main novel aspects

- Hepatic resection is the only potentially curative therapeutic approach for patients with CRLM. However, a multidisciplinary approach is crucial in the treatment of CRLM.
- Preoperative estimation of liver functional reserve plays an essential role in the decision-making process of CRLM resectability.
- Clear definition of treatment goal (curative vs. palliative) at the time of disease diagnosis determines further therapy course.
- Restaging examination and rediscussion within the tumor board should be performed on a regular basis to assess a potential change of treatment strategy.

Conflict of interest Y. Dong and T. Gruenberger declare that they have no competing interests.

References

1. Loree JM, Kopetz S. Why a one size fits all approach to RAS might not fit colorectal cancer. J Natl Compr Cancer Netw. 2017;15(4):545–7.
2. Roberts KJ, White A, Cockbain A, et al. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. Br J Surg. 2014;101(7):856–66.
3. Wimmer K, Schwarz C, Szabo C, et al. Impact of neoadjuvant chemotherapy on clinical risk scores and survival in patients with colorectal liver metastases. Ann Surg Oncol. 2017;24(1):236–43.
4. Eadens MJ, Grothey A. Curable metastatic colorectal cancer. Curr Oncol Rep. 2011;13(3):168–76.
5. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1261–8.
6. Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF)—Recent advances in prevention and clinical management. Eur J Surg Oncol. 2021;47(2):216–24.
7. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–21.
8. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Cancer. 1996;77(7):1254–62.
9. Dijkstra M, Nieuwenhuizen S, Puijk RS, et al. Primary tumor sidedness, ras and braf mutations and msi status as prognostic factors in patients with colorectal liver metastases treated with surgery and thermal ablation: Results from the amsterdam colorectal liver met registry (amcore). Biomedicines. 2021;9(8):962.
10. Brudvik KW, Passot G, Vauthey JN. Colorectal liver metastases: a changing treatment landscape. J Oncol Pract. 2016;12(1):40–1.
11. Mohammad WM, Martel G, Mimeault R, et al. Evaluating agreement regarding the resectability of colorectal liver metastases: a national case-based survey of hepatic surgeons. HPB. 2012;14(5):291–7.
12. Khan AS, Garcia-Aroz S, Ansari MA, et al. Assessment and optimization of liver volume before major hepatic resection: current guidelines and a narrative review. Int J Surg. 2018;52:74–81.
13. Nordlinger B, Van Cutsem E, Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: Recommendations from an expert panel. Ann Oncol. 2009;20(6):985–92.

14. Modest DP, Pant S, Sartore-Bianchi A. Treatment sequencing in metastatic colorectal cancer. Eur J Cancer. 2019;109:70–83.
15. Gavriilidis P, Katsanos K, Sutcliffe RP, et al. Simultaneous, delayed and liver-first hepatic resections for synchronous colorectal liver metastases: a systematic review and network meta-analysis. J Clin Med Res. 2019;11(8):572–82.
16. Hajibandeh S, Hajibandeh S, Sultana A, et al. Simultaneous versus staged colorectal and hepatic resections for colorectal cancer with synchronous hepatic metastases: a meta-analysis of outcomes and clinical characteristics. Int J Colorectal Dis. 2020;35(9):1629–50.
17. Ivey GD, Johnston FM, Azad NS, et al. Current surgical management strategies for colorectal cancer liver metastases. Cancers. 2022;14(4). https://doi.org/10.3390/cancers14041063
18. Andreou A, Gloor S, Inglin J, et al. Parenchymal-sparing hepatectomy for colorectal liver metastases reduces postoperative morbidity while maintaining equivalent oncologic outcomes compared to non-parenchymal-sparing resection. Br J Surg. 2021;108(Supplement_4). https://doi.org/10.1016/j.suronc.2021.101631
19. Heil J, Schadde E. Simultaneous portal and hepatic vein embolization before major liver resection. Langenbecks Arch Surg. 2021;406(5):1295–305.
20. Chavez MI, Gholami S, Kim BJ, et al. Two-stage hepatectomy for bilateral colorectal liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2021;28(3):1457–65.
21. Hasselgren K, Røsok BI, Larsen PN, et al. ALPPS improves survival compared with TSH in patients affected of CRLM—Survival analysis from the randomized controlled trial LIGRO. Int J Surg. 2020;75:S1.