Review

Overview of the Surgical Management of Oligometastatic Disease in Colorectal Cancer

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Article

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Abstract: Oligometastatic colorectal cancer (CRC) refers to a state in which distant metastatic spread is limited to a few sites, offering the potential for curative treatment with aggressive local therapies. The surgical management of oligometastatic CRC has gained increasing attention due to its potential to improve survival. This review explores the evolving role of surgery in the treatment of oligometastatic disease, focusing on the criteria for selecting patients, surgical techniques, and outcomes. While systemic therapy remains essential, surgery can offer long-term survival benefits for appropriately selected patients with limited metastatic disease, particularly those with metastases confined to the liver, lungs, or isolated sites in other organs. Advances in imaging technologies, minimally invasive surgical techniques, and perioperative care have enhanced the safety and efficacy of these procedures. The integration of multimodal therapies, such as chemotherapy, targeted therapy, and immunotherapy, in conjunction with surgery, is also discussed, with a focus on optimizing outcomes. This review aims to clarify how and when liver resection first can be chosen, when preoperative systemic treatment is needed and if this is chosen, what is the best approach.

Keywords: colorectal cancer; mCRC; oligometastatic; hepatic metastases

Introduction

The liver is the most common anatomic site where metastases occur in colorectal cancer, and one-third of metastatic patients have lesions located only at this level. Some patients with liver-only metastases may be candidates for surgical intervention, but their initial approach is essential for a good long-term outcome. The option of liver resection is the standard treatment for patients with liver-only disease. This approach improves survival considerably (5-year survival of 40%). When it is feasible it is done with intent to cure [1]. Chemotherapy is also essential in patients with resectable metastases and is usually administered postoperatively. However, it is possible to opt for preoperative systemic treatment to check the tumor biology in a patient in whom such a complex intervention may not be curative or in patients with metastases initially considered unresectable due to their size [2,3].

This review aims to clarify how and when liver resection per primam is chosen when preoperative systemic treatment is needed and if this is chosen, what is the best approach.

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Methods: Literature Search

The present narrative review aims to describe the surgical and systemic treatment options for patients with liver metastases originating from colon cancer. The analyzed literature was selected according to exclusion and inclusion criteria. Peer reviewed articles and clinical trials published over a period of 20 years (from 2004 to 2024) were taken into account, and the ones published after 2015 were preferred. For this, 2 databases, the Cochrane Library and the PubMed database, were used, both accessed on 27th of December The keywords were: *colorectal cancer, mCRC, oligometastatic, hepatic metastases, resectable, borderline resectable*. Only articles in English were included. The initial search resulted in 2367 publications, whose titles and abstracts were evaluated one by one by the authors, and 68 of them were finally selected, considered relevant due to the period of publication and the quality of the information. The information was structured into 6 paragraphs.

Results and Discussion

Presurgery Evaluation

Preoperative imaging evaluation is essential in the decision on surgical treatment. This not only informs on the number, anatomical distribution, and resectability of liver metastases but also on the possible extrahepatic extension. Usually, the first proposed imaging investigation is computed tomography with contrast. This has a specificity of 96 percent for the detection of liver metastases. Still, it must be taken into account that the ability to identify those under 1 cm is reduced and that the false negative rate in this case is 10 percent. However, this investigation is useful in estimating the liver volume before resection and determining if portal embolization is necessary in advance [3–6].

Magnetic resonance imaging is preferable to computed tomography, especially to detect infracentrimetric liver metastases. It is of choice in the case of patients with hepatic steatosis, having a specificity and sensitivity of up to 97 percent when used with contrast enhancement. It is also more efficient than computed tomography in the detection of metastases at the peritoneal level or at the level of the porta hepatis [7–9].

The NCCN guideline recommends that any patient with metastatic colorectal cancer with potentially curable disease should be evaluated with positron emission tomography [10].

The data related to the usefulness of PET CT in this clinical situation come from a clinical trial that demonstrated the reduction in the number of futile laparotomies, preventing unnecessary surgery in 1 out of 6 cases [11,12]. However, it is ideal for the patient to have both PET and contrast-enhanced CT acquisitions simultaneously for the best specificity [13,14].

Simultaneous Versus Staged Resection

The decision on the type of surgical intervention is fundamentally influenced by the time of appearance of liver metastases. Those that appear up to 12 months after the identification of the primary tumor are called synchronous metastases and those that appear after this interval are metachronous [15,16]

The biggest challenge is dealing with synchronous metastases, most of the time requiring complex surgical interventions. Other important aspects to consider in the choice of surgical intervention are severe symptoms and tumor burden. If the symptoms deriving from the primary tumor are disabling (obstruction, perforation, or bleeding), the primary tumor should be operated on first [17,18]. If the patient is asymptomatic, simultaneous hepatic and colonic resection is ideal, depending on how extensive the disease is in the liver.

The algorithm for management of patients with hepatic metastases originating from colon cancer is illustrated in Figure 1.

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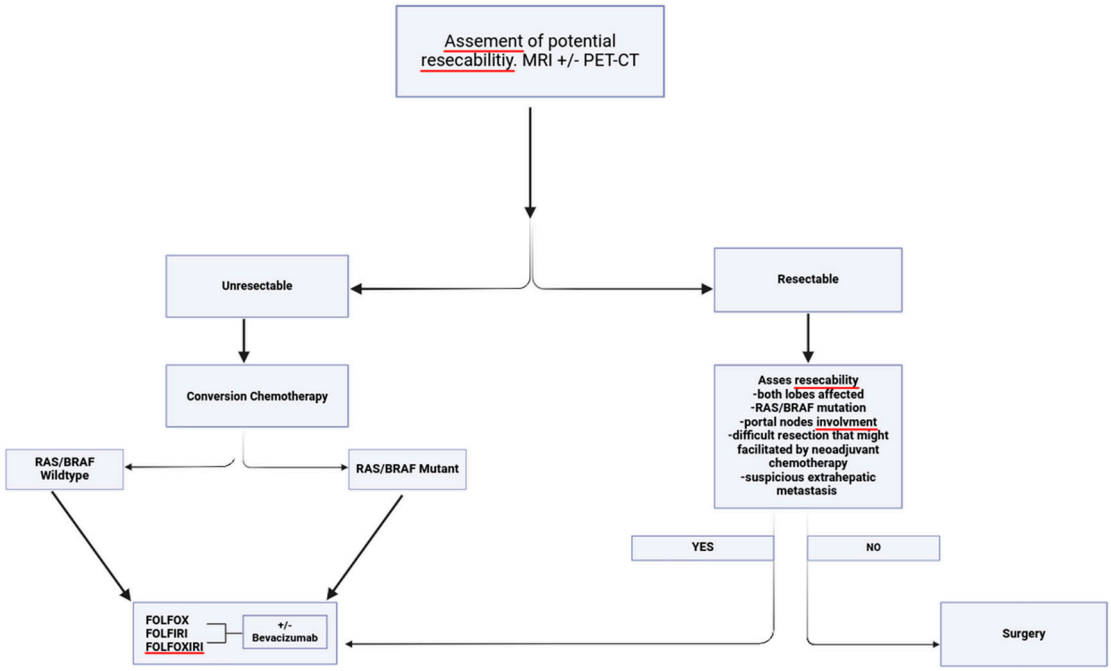

Figure 1. Algorithm for management of hepatic metastases originating from colorectal cancer.

Patients with a favorable location of the primary tumor (right colon) and a limited number of liver metastases are ideal candidates for simultaneous surgical intervention.

In patients with extensive bilobar disease, the treatment decision is more controversial from several points of view. First of all, technically, only a two-time resection is feasible. This involves the initial maximum resection first with multiple partial hepatectomies and postponing the anatomical liver resection for the second surgical step. In some cases, portal embolization may also be necessary, which targets the hypertrophy of the remaining liver [19,20].

However, although extensive liver resection at first has the advantage of the absence of changes at the parenchymal level that chemotherapy gives, it also has the disadvantage of a long postoperative recovery time, in which the patient is deprived of systemic treatment. In this interval, the disease can evolve and these aspects must be carefully weighed by the multidisciplinary team [21–23].

Even in the desired situation in which the patient has a complete clinical response, resection of the respective liver segment is necessary because only 4 to 9 percent have a complete pathological response after neoadjuvant chemotherapy [24,25]. There is evidence that up to 83 percent of lesions with complete clinical response still have viable tumors present [26,27]. These are the reasons why lesions with the highest probability of imaging disappearance (those below 2 cm) and which due to their location are easily accessible (subcapsular lesions) must be marked with a fiducial marker before the initiation of treatment [28,29].

Hepatic Metastases Defined as Unresectable

The decision on treatment in patients with initially unresectable liver metastases depends on the RAS-RAF status, the side tumor and on the general condition of the patient (ability to tolerate aggressive treatment or not). The treatment used in this situation is called conversion therapy. It can be used in patients who are expected to have a sufficient objective response to allow R0 rejection of liver lesions [30,31].

The most important trials that made significant contributions to understanding and improving the efficacy of perioperative chemotherapy in patients with colorectal cancer and hepatic metastases have beed summarized in Table 1 Some of this trials also included patients with upfront resectable hepatic disease.

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Table 1. The most important trials that made significant contributions to understanding and improving the efficacy of perioperative chemotherapy in patients with colorectal cancer and hepatic metastases.

Trial Name	Authors	Publication Year	Key Findings/Important Data
New EPOC	Bridgewater JA, et al. [32]	2020	The multicenter, open label, randomized study found a detrimental effect on overall survival in patients with metastatic colorectal cancer, RAS wild type with resectable or suboptimal resectable liver metastases who received perioperative cetuximab.
FIRE-3	Stintzing S, et al. [33]	2015	Comparison of FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab in mCRC. The study highlighted that cetuximab significantly increased the rate of conversion to resectability compared to bevacizumab, especially in patients with RAS wild-type tumors.
COIN (Chemotherapy versus Chemotherapy plus Cetuximab)	Seymour MT, et al. [34]	2007	This trial assessed the addition of cetuximab to standard chemotherapy (FOLFOX) in mCRC patients. It demonstrated an improvement in progression-free survival (PFS) but did not show a major increase in resection rates for liver metastases. It highlighted the challenge in using cetuximab for conversion.
CRISTAL	Van Cutsem, et al. [35]	2010	Studied FOLFIRI plus cetuximab in RAS wild-type mCRC patients. It found that cetuximab improved overall survival and response rates and supported its role in conversion strategies for patients with limited metastatic spread.
OPTIMOX	Tournigand C, et al. [36]	2006	Investigated the use of oxaliplatin-based chemotherapy in mCRC, showing that alternating chemotherapy (OXALIPLATIN/FOLFOX) regimens led to significant tumor reduction, aiding in conversion to resectability in some patients.
PEAK	Schwartzberg LS, et al. [37]	2014	Focused on the combination of FOLFOX and bevacizumab in patients with liver-limited mCRC. It demonstrated that a high response rate with this regimen increased the likelihood of achieving resectability, especially in patients with isolated liver metastases.

The most significant conversion rates reported were with triplet chemotherapy or the combination of chemotherapy with epidermal growth factor receptor inhibitors [38–40].

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Patients who become resectable and undergo surgery have a substantial benefit in overall survival (improvement from 20 percent to 30-35%) [41,42].

The maximum duration of preoperative treatment until resection is 4 months, after this interval, changes in the liver due to chemotherapy make resection very difficult. Also, if the patient becomes resectable during the 4 months, he will be offered adjuvant treatment for a duration that completes the administration up to 6 months.

RAS/RAF Mutated Tumors

In patients with RAS-RAF mutations, the most effective possible option is FOLFOXIRI (irinotecan 165 mg-m2, oxaliplatin 85 mg/m2, fluorouracil 2400mg-3400mg/m2 continuous infusion of 46 hours, leucovorin 200 mg/m2) with or without bevacizumab. This regimen was compared in the CAIRO5 study, a phase III study that enrolled 294 patients with RAS/BRAF V600E mutations or primary location in the right colon. They were randomized to FOLFOXIRI+ bevcizumab or FOLFOX/FOLFIRI+ bevacizumab. They were re-evaluated by imaging at 8-9 weeks for resectability, and if this was feasible, they received up to 12 postoperative treatments. If resection was not possible, the patients received maintenance with 5-fluorouracil and bevacizumab after 6 months of initial treatment. 51 percent of the FOLFIRINOX arm underwent complete local treatment (R0 liver resection or R1/ combined with ablative treatment) versus 33 in the doublet arm. This result translated into a survival benefit (progression-free survival 10.6 versus 9 months, HR 0.76, 95%CI 0.6-0.98) and a higher response rate (objective response rate 54 versus 33 percent). Toxicity was, as expected, greater in the triplet arm [43].

The addition of bevacizumab to chemotherapy in patients with induction treatment is controversial because of its toxicity profile (impaired wound healing) and because of the need for a 6-8 week break from the last administration to the intervention, which can postpone surgery. However, retrospective data suggest that the rate of bleeding and functional recovery after bevacizumab is comparable to chemotherapy regimens without bevacizumab. [46–51] There is, however, the hypothesis that the use of bevacizumab after portal embolization would be detrimental because of liver regeneration impairment [52,53].

RAS/RAF Wild-Type Tumors

In RAS/RAF wild-type tumors, the regimens with the highest response rate are preferred, as there is an important correlation between this, the resection rate, and overall survival [54,55].

The triplet (FOLFOXIRI regimen) is thus preferred for all patients who can tolerate this more aggressive approach irrespective of RAS status. [56,57] Doublets with irinotecan or oxaliplatin and 5-fluorouracil are options for patients in whom triple treatment is not an option. They are equally effective and the choice between them should only be based on the different toxicity profiles [58–60].

In patients in whom liver resection is considered, the regimen based on oxaliplatin (FOLFOX-oxaliplatin 85 mg/m2, 5-FU bolus administration 400mg/m2, 5-FU 2400 mg/m2 46-hour continuous administration, every 2 weeks) is preferred, irinotecan being associated with more important liver changes. However, if metachronous liver metastases and the patient has received oxaliplatin in the last 12 months, FOLFIRI (irinotecan 180 mg/m2, 5-FU bolus administration 400mg/m2, 5-FU 2400 mg/m2 46-hour continuous administration, every 2 weeks) is the best option. [10]

Targeting EGFR in patients receiving conversion therapy is an option with modest benefits. In the CRISTAL and OPUS trials, the resection rate improved from 3.7% to 7% and from 2.4 to 4.7 when chemotherapy doublet (either with oxaliplatin or irinotecan) was compared with doublet plus cetuximab or panitumumab [35,61,62].

However, the experts do not recommend the combination of the oxaliplatin-based regimen with anti-EGFR, considering the inferior outcomes demonstrated in the NewEPOC trial. The trial studies the addition of cetuximab to FOLFOX perioperatively in patients with potentially resectable liver metastases. They received FOLFOX with or without cetuximab 12 weeks pre- and 12 weeks postoperatively, those with anti-EGFR treatment had significantly lower survival (14.5 versus 24.5

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months). A possible explanation of this result would be that the oxaliplatin - cetuximab combination is detrimental in the first line even in patients with RAS-RAF wild-type left colon tumors [32,63,64].

Therefore, the administration of FOLFIRI and cetuximab remains an option to improve the resection rate, but at the price of possibly more difficult hepatic resections after irinotecan.

Hepatic Metastases Are Defined as Resectable

Several trials demonstrated that the use of perioperative chemotherapy in patients with primary resectable metastases does not improve survival and that it has the disadvantage of a more difficult rejection (due to changes after chemotherapy, especially after irinotecan) and of a greater possibility of postoperative complications.

The EORTC 40983 trial enrolled 364 patients with up to 4 resectable liver metastases who were randomized to receive or not perioperative treatment with FOLFOX (12 weeks pre- and 12 weeks postoperative). The resection rate was similar in the group with primary surgery versus the one with perioperative chemotherapy (84 versus 83 percent). However, the use of preoperative chemotherapy reduced the rate of failed laparotomy (11 percent in the primary rejection group versus 5 percent in the study group). A higher rate of postoperative complications was reported in the chemotherapy group (25 versus 16 percent, OR 1.58 percent, 95% CI 1.02-2.45), but postoperative mortality was the same. Among the present complications were biliary fistulas, intra-abdominal infections, and reversible hepatocellular insufficiency [65,66].

The study also demonstrated, after a follow-up of 8.5 years, a trend of favorable survival in the group that received chemotherapy (38 versus 30 percent, OR=0.71) which was statistically significant only when stratified for truly resectable patients [66].

These data led to the indication from the guidelines for surgery first in all patients who do not have more than 4 liver metastases and whose metastases are limited to one liver lobe, who do not have radiological suspicion of portal nodes involvement, with no suspicion of non-hepatic metastases and no BRAF or RAS mutation [66].

In patients treated with surgery first, the guidelines recommend 6 months of adjuvant oxaliplatin-based chemotherapy, except for those with metachronous metastases who received oxaliplatin in the last 12 months. This recommendation is extrapolated from the indications in non-metastatic patients. However, the data studying this particular clinical situation are contradictory [10].

A study that enrolled patients with initially resectable disease who received 6 preoperative and 6 postoperative chemotherapy administrations did not demonstrate a benefit for overall survival (survival at 5 years 52 in the chemotherapy group versus 48 percent HR 0.88, 95% CI 0.68 - 1.14), nor for colorectal cancer related deaths. However, it should be taken into account that survival was not the main endpoint of this trial [66,67].

Another trial that included the Japanese population randomized patients to observation versus 6 months of FOLFOX type chemotherapy after resection with R0 hepatectomy. It demonstrated a substantial benefit in progression-free survival (5-year DFS 50 versus 39 percent, HR0.67, 95% CI 0.5-0.92), but failed to demonstrate a benefit in overall survival. It can be speculated that the use of regimens based on oxaliplatin would have a greater effect of selecting resistant cells in this particular clinical situation [68].

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Conclusion

In patients with liver metastases and colorectal cancer, liver resection, when feasible, significantly improves survival. The ideal way to determine resectability preoperatively is an abdominal MRI. Even for patients in whom this investigation reveals unresectable disease, conversion treatment can be considered, which consists of double or triple chemotherapy. Adding targeted treatment increases the response rate, but also the rate of postoperative complications, and there is evidence that EGFR treatment combined with oxaliplatin-based chemotherapy is detrimental. Conversion chemotherapy can last a maximum of 4 months, and response assessment must be done at a maximum of 2 months. In patients with primary resectable liver metastases, surgery is preferred, followed by postoperative chemotherapy. Therapeutic decisions both in resectable and unresectable situations are complex and require a multidisciplinary team with experience in this clinical situation.

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