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How to treat liver metastases in colorectal cancer: A review

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Abstract

Over 50% of colorectal cancer experience the development of liver metastases during the disease, impacting, annually, around of 900,000 cases. Regarding this setting of disease, the treatment, consisting in the integration of locoregional therapy with systemic therapy, it has achieved the agreement among clinicians and surgeons. Nevertheless, the diversity of pattern of disease in patients diagnosed with Colorectal Cancer Liver Metastases (CRCLM) poses difficult decisions on which treatments to use and how to integrate chemotherapy with locoregional treatments.

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Introduction

At least 50% of Colorectal Cancer (CRC) develop liver metastasis, and the number of individuals globally who experience Colorectal Cancer Liver Metastases (CRCLM) is thought to be at least 900,000.

The treatment of CRCLM has generated a lot of debate among medical oncology and surgeons. The role of surgical resection in the management of colorectal cancer liver metastases was not established until the 1980s. Only a small percentage (about 15-20%) of liver metastases found at the time of diagnosis may be removed, and a significant number will return following surgery. It is evident that a surgical approach alone is unable to better treat the complex nature of CRCLM. The effectiveness of systemic therapy and surgical skill have both improved over the last 20 years, and this has significantly enhanced the prognosis for CRCLM. The aim of having No Evidence of Disease (NED) is being reached by a growing number of patients; nevertheless, choosing the right treatment for the right patient still presents a effort. To clarify future research, this review offers a overview of CRCLM therapy choices

Methods

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles from 2017 to May 31, 2023, using the keywords colon, liver, metastasis, surgery, neoadjuvant. The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and October 2023 were examined.

Pretreatment patients' assessment

Enhanced colorectal cancer liver metastases locoregional therapy: The notion of oligometastasis was initially minted in 1995 and is present in a number of guidelines and clinical trials. The term "oligometastasis" describes a stage of tumor where only a small number of localized secondary metastases, typically inferior to 5, are detected by conventional TAC scan, PET o RMN. The idea was first presented in the 2015 ESMO (European Society of Medical Oncology) guidelines for the management of colorectal cancer. It was used to distinguish between two types of metastatic Colorectal Cancer (mCRC): oligometastatic disease and diffuse disease, which has the presence of liver and

lung metastases. Patients classified as oligometastatic are seen to be a group with long-term survival and opportunity for good prognosis. While extensive disease is characterized by more systemic distribution. In each one, the primary goal is to achieve a tumor-free state with curative intent with No Evidence of Disease (NED). The underlying principle of treatment is to highlight locoregional treatment based on effective systemic therapy. But because to technological advancements, technically tolerable liver metastases are no longer just oligometastases.

Surgical resection isn't the only method used to treat intrahepatic lesions; instead, a combination of surgical resection, ablation, and radiation therapy are employed. In terms of concept, it has also changed from R0 resection to NED, indicating that there is no longer any sign of a tumor based on current clinical exams. The only requirements state by the NED criteria for locoregional treatment of CRCLM are that the patient's overall state be able to withstand surgery, the residual liver volume be greater than thirty to forty percent, and all lesions must be totally eradicated by various means. The quantity and extent of the lesions are no longer strictly limited. Parenchyma-Sparing Hepatectomy (PSH) has largely replaced classic anatomical hepatectomy techniques including segmentectomy and lobectomy.

Intrahepatic lesions should be treated except for the following cases: (1) the tumor is located in a special position (e.g., invasion of large blood vessels that cannot ensure inflow or outflow of the liver); (2) the tumor surgery cannot reach NED status; (3) there is insufficient postoperative residual liver volume; and (4) the patient's general condition makes the procedure intolerable. Transarterial Chemoembolization (TACE), local chemotherapy, and selective internal radiation therapy (SIRT) have all been used to treat liver metastases in relation to initial liver cancer treatment methods. High-level evidence has not been provided to support the role of these technologies. The boundaries of the restricted zone of liver resection have been frequently broken by the ongoing advancement of surgical procedures. The most advanced surgical procedure for treating CRCLM, liver transplantation, is now being investigated by practitioners [1]. Patients with nonresectable CRCLM had a 100%, 83%, and 83% survival rate after liver transplantation at 1, 3, and 5 years, respectively, in the prospective research SECA-II. In contrast, patients receiving palliative treatment had a 5-year OS of roughly 10%. There was a 53, 44, and 35% disease-free survival at 1, 2, and 3 years. The longest OS is achieved by liver transplantation in carefully chosen patients [2]. Another cutting-edge technique in liver surgery is the linking of portal vein ligation and liver partition for phased hepatectomy (ALPPS). In a group of 510 CRCLM patients, the first long-term oncologic outcomes of APLLS revealed a 90-day mortality rate of 4.9%, a median Overall Survival (OS) of 39 months, and a Recurrence-Free Survival (RFS) of 15 months. According to the data, patients treated with ALPPS for CRCLM that was predominantly incurable had favourable long-term outcomes [3].

An effective treatment plan is based primarily on biological behaviour: Patients' general health and the state of their tumors have to assessed before to treatment. Various items are advised about the pretreatment assessment imaging study. Rectal ultrasonography and enhanced Computer Tomography (CT) are less effective than enhanced nuclear Magnetic Resonance Imaging (MRI) in the detection of rectal cancer. Better CT scans are recommended for colon cancer. The most effective test for assessing intrahepatic metastases is Magnetic Resonance Imaging (MRI); other options include enhanced computed tomography and contrast-enhanced ultrasound. Additionally optional are bone testing, brain MRI, chest CT, and PET/CT to rule out extrahepatic metastases.

To evaluate if surgery is necessary, another criterion called the oncological/biological behavior criterion must be met. The likelihood of recurrence or the biological behavior of the tumor has a greater impact on the oncological prognosis of patients following surgery of liver metastases. The Clinical Risk Factor (CRS) score system, which Fong introduced in 1999 [4], is the most widely utilized approach for evaluating tumor biology, albeit there isn't a set gold standard. It comprises five indicators: A positive primary tumor lymph node is the first: (2) a 12-month period between the primary tumor excision and metastasis; (3) more than one liver metastasis; (4) the largest metastases are larger than 5 cm; and (5) the CEA level is greater than 200 ng/mL. Patients with a CRS score of 0 had a 5-year survival rate of up to 60%, compared with just 14% for those with a score of 5. One point was recorded for each point. Despite its shortcomings, the CRS scoring system remains the most significant prognostic scoring method in use. Furthermore, a previous retrospective study by Adam, revealed that the prognosis following surgical resection, is also influenced by the patients' responsiveness to preoperative chemotherapy. Patients who progressed on preoperative chemotherapy had a 5-year survival rate of only 8% after surgical resection, compared to 37% and 30% for patients with Partial Response (PR) and Stable Disease (SD), respectively. In this paper, however, also note that tumor development following chemotherapy is not a strict absolute controindication [5]. The prognosis following surgical excision is also influenced by the genetic status of the tumor; the RAS and BRAF genes have been the subject of the most research [6-8]. Tumor growth pattern, pathological grading of tumor regression following treatment, and molecular subtypes are additional markers of biological activities. It is evident that a variety of factors influencing the biological behavior of individuals with CRCLM may need to be combined. A new scoring system called GAME (Genetic and Morphological Evaluation) was proposed in a recent study [9]. It combined the genotyping of CRCLM with clinical factors and included six risk factors: high tumor burden (calculated from the maximum diameter and number of metastases), presence of extrahepatic metastases, positive primary tumor lymph nodes, and CEA level ≥20 ng/mg. In two sizable CRCLM cohorts at Johns Hopkins Hospital and New York Memorial Hospital (MSKCC), the study validated both the GAME and CRS scores. It also demonstrated that GAME scores were superior to CRS scores and could eventually take his place. This demonstrates how difficult and ambiguous it is to evaluate tumor biology. To be clear, we classified CRCLM, in the following discussion, in two groups depending on the technical viability of locoregional therapy in order to attain the objective of NED: "patients initially NED-eligible" and "patients initial non-NED-eligible". Neoadjuvant therapy, which is explained below, is systemic therapy given to CRCLM patients who are initially NED-eligible before surgery, or not initially NED-eligible before possible locoregional treatment.

Strategies of treatment in resectable patients

Everyone agrees that effective systemic therapy and local treatment are essential for CRCLM that are initially eligible for NED. The EPOC study was the first phase III Randomized Controlled Trial (RCT) to show that, in patients with resectable CRCLM, liver surgery plus perioperative chemotherapy improved survival when compared to surgery alone. The 3-year

Disease-Free Survival (DFS) increased to 42.2% from 33.2% after perioperative chemotherapy [10,11]. Resectable CRCLM can be considered for resection and neoadjuvant treatment FOLFOX and CAPEOX are preferred. It is possible also to perform primary CRC resection followed by chemotherapy and liver resection, with adjuvant chemotherapy recommended postoperatively, according to the 2001 National Comprehensive Cancer Network (NCCN) guidelines [12]. Determining which patients need neoadjuvant therapy is the first of many details that remain unclear when creating a treatment plan for a particular patient.

Patients with resectable liver metastasis and good biological behaviour: Neoadjuvant therapy contains benefits and drawbacks. It's crucial to determine which patients are best suited for a surgery-first approach or neoadjuvant chemotherapy. In 2015, Ayez et al. conducted a multicentre retrospective analysis with 364 resectable CRCLM patients [13]. The results indicated that neoadjuvant chemotherapy significantly increased survival in the group with a high CRS score (3-5), while patients with a low CRS score (0-2) did not demonstrate any improvement in survival. In 2021, the first prospective randomized controlled trial on surgical sequence was published on Annals of Surgery. The colon-first approach was inferior to the simultaneous excision of the primary and metastatic lesions, according to the results. However, it is important to note that 27% of patients in this study had two liver lesions, compared to more than 41.2% who had just one [14]. The biological behaviour of these patients' tumors is somewhat good. Consequently, for patients with a low CRS score (0-2) who are technically straightforward to resect, it is agreeable that surgery must be performed first, followed by adjuvant chemotherapy.

Neoadjuvant treatment in patients with high-risk characteristics: In 2009 Reddy et al. conducted at three US medical centres, a retrospective analysis in 499 CRCLM cases, in that were initially resectable [15]. In comparison to the 297 neoadjuvant patients, the 202 individuals that underwent surgery first had a median overall survival of 76 months. However, there was a notable bias in the treatment selection process: the neoadjuvant group tended to have a greater proportion of combined radiofrequency, more difficult liver resections, more liver metastases, and more positive lymph nodes. In 2012 a study conducted by Marques et al. examined data from 676 CRCLM with liver metastasis reectable d'emblee, produced similar findings [16]. According to a survey conducted by Professor Adam's, the LiverMetSurvey, the largest CRCLM database in the world [17], neoadjuvant treatment was found to provide a survival advantage when the diameter was greater than 5 cm or the metastatic number was greater than 3. More detailed guidelines were provided by an expert consensus from Europe in 2009 [18], indicating that neoadjuvant chemotherapy with surgical resection was advised if the patient had a CRS score of >2. The 2012 ESMO recommendations [19] state that surgery should only be done first for CRCLM that is initially resectable if there is a solitary metastasis that is less than 2 cm in size. According to the 2016 ESMO guidelines [20], it is advised that when start an initial decision making for CRCLM, it should be taken into account the tumor's biological behaviour and surgical approach of tumor excision. In this instance, patients who exhibit technical difficulties or poor prognostic signs are advised to get neoadjuvant therapy.

FOLFOX; the preferred neoadjuvant regimen: FOLFOX, employed in the EPOC study, is the only RCT-validated neoadjuvant chemotherapy for resectable CRCLM, it has become the standard in this setting. Clinical practice also frequently employs the CAPOX regimen because it has been demonstrated to be equally effective as FOLFOX in treating advanced colorectal cancer. More debatable is the combination of targeted therapy. The ESMO recommendations and the NCCN guidelines have differing opinions. Furthermore, both ESMO and NCCN guidelines were modified owing to the results of randomize phase III trial NEW EPOC [21], the only significant RCT in this field. The purpose of the NEW EPOC trial was to determine if three months of preoperative FOLFOX plus Cetuximab had a greater efficacy on initial resectable CRCLM than FOLFOX alone. The median PFS was 14.8 in the experimental arm, versus 24.2 months in the control arm and was considerably shorter in the Cetuximab (Cet) group. Bevacizumab (Bev), another targeted therapy that acts on neo angiogenesis, has not yet been investigated in an phase III RCT in the context of neoadjuvant therapy. The current literature consists only of phase II studies that demonstrate the good Objective Response Rates (ORR) when FOLFOX/CAPOX or FOLFXIRI are combined with Bevacizumab. Nevertheless, from 2017, NCCN guidelines edition eliminated all targeted therapies from the neoadjuvant setting for in resectable CRCLM due to the unfavorable outcomes of NEW EPOC. However, from 2016 ESMO recommendations [20] did not rule out targeted agents, noting that the optimal preoperative treatment for CRCLM that is technically resectable but linked to one or more poor prognostic variables is still up for debate. However, a more robust regimen, such as doublet cytotoxic chemotherapy plus a targeted drug or FOLFOXIRI triplet chemotherapy alone or in conjunction with Bevacizumab, may be taken into account when these patients have a far reduced chance of cure. The ESMO panel assigned a level of evidence of V to this proposal; nonetheless, the panel consensus was greater than 75%, suggesting that clinical practice has reached a broad consensus on this matter. Furthermore, in RCTs and clinical practice, we must be mindful of the criteria for resectable liver metastases. 77% of the patients in the NEW EPOC trial had one to three intrahepatic metastases; only 53% had a maximal lesion larger than three centimetres; and only 25% had a CEA greater than thirty ng/ml. The bulk of CRCLM included in the NEW EPOC trial were found to have rather good tumor biology and to be technically easy to resect. Considering this, we do not, in our practice, advise targeted therapy for patients who satisfy the NEW EPOC study's inclusion criteria; however, targeted agents shouldn't be disregarded in cases of complex surgical resection and poor tumor biological behaviour (such as the presence of more than five metastasis or a high risk of CRS score). RCT, on the other hand, should offer stronger trials.

Treatment for patients not resetable

According to NCCN guidelines, patients who are no candidate for surgery or potentially resectable, should receive chemotherapy in addition to targeted therapy. Every two months, the disease's status would be evaluated, and if it is determined to be NED-eligible, locoregional therapy could be performed; postoperative adjuvant therapy is also necessary [12]. Furthermore, for patients with mCRC, the guidelines strongly advise routine testing for the presence of the RAS, Braf gene mutation. Triplet chemotherapy regimens have been shown to produce better results in several clinical trials when used as neoadjuvant therapy; additionally, the combination of targeted therapy may increase the effects. The FOLFOXIRI regimen increased the conversion rate of R0 resection in CRCLM patients when compared to the FOLFIRI regimen: 36% versus 12%, while also extending

median OS: 23.4 versus 16.7 months, according to the results of GONO, a phase III RCT [22]. In the first-line treatment of patients with CRCLM, the TRIBE study compared FOLFOXIRI with Bevacizumab versus FOLFIRI and Bevacizumab [23]. The median OS was 29.8 months in the experimental arm compared to 25 months in the control arm.

In OLIVIA study, a phase II randomized controlled trial, bevacizumab plus FOLFOXIRI was compared to mFOLFOX6 plus bevacizumab. The results showed that the FOLFOXIRI bevacizumab group, had higher rates of resection and R0 resection (61% versus 49% and 49% versus 23%), with corresponding median PFSs of 18.6 months and 11.5 months [24]. A comparable outcome was reported by the 2020 TRIBE2 research [25]. Therefore, the triplet regimen offers better oncological outcome: better PFS, better OS, and Overall Response Rate (ORR), which would translate to better likelihood of conversion, either with chemotherapy alone or in combination with targeted therapy. The consensus now is to add a targeted therapy in order to increase the conversion rate. In patients with KRAS wild type, FOLFIRI plus Cetuximab produced better outcomes than FOLFIRI alone, according to the CRYSTAL research [26]. While several studies have expressed differing opinions regarding the best targeted drug, some have recommended cetuximab [27]. On the other hand, some other studies did not find a statistically significant difference between them [28]. Two months after starting systemic therapy, MDT should reevaluate whether liver metastases are NED-eligible, and as soon as they are, they should offer locoregional treatment, including surgical excision. It is advised to modify the regimen in an effort to further attempt conversion if NED is not achieved after 6-8 months of chemotherapy. Patients who are intolerant, unwilling to accept a change in treatment, or who have no response to treatment, are referred to palliative care. In the clinical setting, we occasionally observer individuals whose intrahepatic metastases were diffuses at the time of diagnosis; nevertheless, following neo adjuvant systemic chemotherapy , most of the metastases vanished, allowing them to receive locoregional treatment and ultimately achieve NED status.

Individualized treatment is an important focus in the future

Since the limits of liver surgery have reduced and many patients can be brought to the operating table, the surgeon within the MDT, in addition to having a great technical skill, must know and share the different biological characteristics of each individual case proposed to liver surgery.

The fundamental principles of surgical oncology are still those of oncology. The current absolute contraindications for liver surgery are estimated in residual liver volume less than 30% and intrahepatic lesions unable to reach NED. Intrahepatic lesions that need to be transformed through intricate methods in order to achieve R0 surgical resection are the related contraindications.

Adam [29] defined the following oncologic criteria as relative contraindications: tumor number ≥5, tumor growth after treatment, technically resectable but judged to be at high risk of recurrence after resection, along with extrahepatic metastases. To pursue technological advancements and to follow the current standards, we should choose the best course of action for each patient based on the biology of their disease. To investigate the limit of surgical NED, a significant number of carefully planned studies that demonstrate clinical management are still required.

Conclusion

In summary, there is a great deal of variation among patients with colon cancer and liver metastases. Most patients who benefit from locoregional therapy are those who are both technically and physiologically eligible for NED. The patient's risk factors are taken into consideration when choosing both postoperative adjuvant therapy and neoadjuvant therapy. To generate the best possible prognosis for every patient, it is imperative in the MDT to integrate locoregional treatment with systemic treatment, and it is thanks to the multidisciplinary approach that better outcomes can be obtained as demonstrated by various publications which highlight statistically significant improvements when the tumor is approached in a multidisciplinary team compared to an individual approach.

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