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Colorectal Liver Metastases

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Abstract

The adenocarcinoma of the colon and rectum (CRC) affects more than 1.3 million patients each year, being the third most common malignancy in the world. Approximately, 30–50% of these patients will present with liver metastasis at the time of diagnosis or will develop metastasis later. The incidence of metastatic CRC (mCRC) is approximately 4.3% at 1 year, 8.7% at 2 years, 12% at 3 years, and 16.5% at 5 years after resection. Recently, the clinical outcome for patients with mCRC has improved, with a median overall survival (OS) for patients with mCRC is approximately 30 months, more than twice of that observed 20 years ago. The treatment approach for patients with colorectal liver metastases should be focused toward complete resection whenever possible, with both oncological and technical criteria being considered. Considering the fact that nearly 80% of patients with mCRC are not candidates for resection at diagnosis, initial treatment options include chemotherapy and locoregional therapies. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has emerged as modification on classic two-staged hepatectomy (TSH) with portal vein embolization. In experienced hepatobiliary centers and in well-selected patients, ALPPS can be performed with low morbidity and minimal mortality, resulting in good intermediate-term survival and excellent quality of life. Multidisciplinary tumor boards should critically scrutinize the best treatment options.

Keywords: colorectal cancer, liver, liver cancer, liver metastasis

1. Introduction

The adenocarcinoma of the colon and rectum (CRC) affect more than 1.3 million patients each year, being the third most common malignancy in the world [1]. Approximately, 30–50% of these patients will present with liver metastasis at the time of diagnosis or will develop metastasis later [2, 3].

Due to the fact that venous drainage of the intestinal tract is via the portal system, the first site of hematogenous spreading is usually the liver. The most common site of metastatic CRC is the liver, occurring in 80% of cases, representing nearly half of all patients with CRC. It is also the single site of metastasis in 20–50% of the cases [2]. The majority of metastatic CRC liver disease will be potentially resectable at the time of diagnosis, approximately 75–80% of cases [3]. Recurrence after resection of the primary lesion depends on the stage. The overall recurrence rate ranges from 9% in stage 1–56% in stage 3 CRC tumors [3].

A majority of CRC metastases (mCRC) occurs within the first 3 years. The incidence of mCRC is approximately 4.3% at 1 year, 8.7% at 2 years, 12% at

3 years, and 16.5% at 5 years after resection [2]. The frequency of metachronous CRC metastases is highly variable in the literature, arising from database differences and diversity of definitions. Metachronous CRC metastases are restricted to the liver in 44% of patients with distant recurrence following potentially curative resection of the primary lesion. In prospective and retrospective studies of referral centers, this rate reaches 35% [4]. In prospective observational studies and population studies, this frequency is lower, ranging from 5.7 to 16.3% [5]. In population studies, the frequency of synchronous liver metastases from CRC varies from 14.5 to 24% [2]. Patients presenting with stage 4 disease at the time of the diagnosis will have liver-confined metastases (synchronous metastases) in 77% of the cases [6].

Recently, the clinical outcome for patients with mCRC has improved. Nowadays, the median overall survival (OS) for patients with mCRC is approximately 30 months, more than twice of that observed 20 years ago [7]. It is not clear which improvements and/or strategic changes in the treatment and management of patients with mCRC in recent years have been responsible for the improved treatment outcomes for these patients. Some changes that might have contributed for this gain in OS are (i) changes in the clinical presentation of patients, before the commencement of treatment, due to closer follow-up after resection of the primary tumor and earlier detection of metastatic disease; (ii) improvements in the efficacy of systemic therapies in terms of regimens used, sequence of administration, number of lines of therapy administered, and biomarker-based patient selection; (iii) an increase in the number of patients being treated with a view to facilitating resection of their metastases, offering an increased number of patients the chance of cure and/or durable relapse-free survival and, more recently, the utilization of other ablative therapy techniques with the aim of achieving the same outcome; and (iv) implementation of “continuum of care” treatment strategies coupled with the early integration of optimal supportive care measures [7].

The best treatment strategies for patients with mCRC are evolving rapidly. Superior clinical outcomes are reached when the treatment approaches for individual patients are discussed within a multidisciplinary team (MDT) of experts, meeting regularly as a tumor board to review mCRC cases [8]. The responsibility of the MDT is to define the initial diagnostic workup and then the treatment focus, based on the best diagnostic and therapeutic decision-making available. Initially, the MDT member should critically define whether or not a patient has clearly resectable or initially unresectable metastatic disease. Contrariwise, for patients whose disease is believed “never to be resectable,” the discussion may be left to the treating medical oncologist (after discussion with the MDT) and patient as to the pros and cons of various approaches and sequences based on the perceived aims (e.g., duration of disease control versus quality of life and toxicity profiles, etc.) [7].

2. Imaging

The preferred method for the diagnosis of extrahepatic disease is computed tomography (CT) [9–11]. It is the method of choice for staging and follow-up of patients with colorectal cancer, as imaging methods are widespread in our environment, familiar to oncologists, radiologists, and surgeons, with good cost/benefit. Therefore, the use of CT is recommended as the initial method in the diagnosis of extrahepatic metastases.

Magnetic resonance imaging (MRI) is the most accurate imaging technique for the detection and characterization of focal liver lesions. However, costs are

higher and it has restricted availability. Other limitations include magnetic field exposure and gadolinium use restrictions in patients with renal insufficiency. Retrospective and meta-analyses have shown that MRI has a superior sensitivity to TC both in analysis per patient (81.1–88.2% vs. 74.8–83.6%) and in analysis per lesion (80.3–86.3% vs. 74.4–82.6%); such superiority is related to higher detection of lesions smaller than 1 cm [12, 13]. MRI with hepatobiliary contrast has demonstrated to have greater accuracy than FDG-PET/CT in detection of small liver metastases (92 vs. 60%) [14]. In a multicenter randomized prospective study, the performance of MRI with hepatobiliary contrast was superior to CT with iodinated contrast and MRI with extracellular gadolinium as first-line method in the initial evaluation of liver mCRC [14].

PET/CT have shown to be of great value in the evaluation of extrahepatic sites of metastases undetected by other methods in patients eligible for surgical resection of liver mCRC, altering the therapeutic plan [15, 16].

Since cross-sectional imaging modalities have improved sensitivity of the diagnosis of mCRC, diagnostic laparoscopy is no longer standard for evaluating patients with mCRC. Instead, it is only used in patients with a suspicion of small-volume carcinomatosis on radiographic imaging studies or who are at particularly high risk for harboring unresectable diseases [17].

3. Prognostic determinants

The pathologic stage at presentation is the most important indicator of outcome after treatment in general, followed by the presence of extramural tumor deposits, lymphovascular and perineural invasion, histologic grade of differentiation, the preoperative level of serum carcinoembryonic antigen (CEA), microsatellite instability (MSI), and RAS and BRAF mutations [18, 19].

Microsatellite instability (MSI) status or mismatch repair deficiency (MMR-D) has been the biomarker for adjuvant 5-FU monotherapy and immune checkpoint inhibitor. Hematogenous and lymphogenous metastasis-dominant CRC with high-frequency MSI (MSI-H) are reported to have poor prognosis. However, the validity as the prognostic factor of MMR is still to be confirmed, and it should thus be used cautiously [20, 21].

On the other hand, it is also known that RAS and BRAF mutations are of prognostic and predictive value in mCRC [21]. The pathogenesis of CRC involves the accumulation of genetic and epigenetic modifications within pathways that regulate proliferation, apoptosis, and angiogenesis.

KRAS mutations involving either codon 12 or 13 can be identified in 12–75% of tumors, and they have been individually correlated with a worse prognosis in most studies [22]. BRAF V600E mutations are present in 8–10% of patients, are consistently associated with poor prognosis, and result in possible patient ineligibility for resection of mCRC [23]. Recently, a small single-center cohort study showed that 21 of 52 patients with BRAF V600E mutant who underwent metastasectomy had longer OS (29.1 vs. 22.7 months) and progression-free survival (13.6 vs. 6.2 months) than the non-metastasectomy cohort. The authors concluded that multimodality therapy incorporating metastasectomy for BRAF V600E metastatic CRC should be considered and might be associated with improved OS in selected patients [24]. Meanwhile, BRAF V600E can be a biomarker for selecting the appropriate chemotherapy regimen [21].

Another feature that also appears to affect the prognosis of patients who develop liver metastases is the embryonic origin of the primary colon cancer. In an analysis

of 727 patients who were submitted to chemotherapy followed by resection, mCRC from midgut origin (right colon tumors) was associated with worse pathologic response to chemotherapy and worse survival after resection than mCRC from hindgut origin (left/sigmoid colon tumors) [25]. This effect was independent of the RAS mutation status. Primary tumor from right-sided colon might be more prone to recur. Therefore, palliative resection might not be done since these patients showed no benefit from resection [26].

4. Patient selection

The treatment approach for patients with colorectal liver metastases should be focused toward complete resection whenever possible, with both “oncological” (prognostic) and “technical” (surgical) criteria being considered when evaluating patients for surgery [27, 28].

The “technical” definitions of resectable mCRC have evolved over time, with the current consensus proposing that disease should be considered technically resectable as long as complete macroscopic resection is feasible while maintaining at least a 30% future liver remnant (FLR) or a remnant liver to body weight ratio >0.5 (e.g., >350 g of the liver per 70 kg patient) [29]. Nevertheless, not all patients with technically resectable liver-limited metastases benefit from surgery; approximately half of the patients submitted to resection of mCRC will present widespread systemic disease within 3 years of the resection [30].

Prognostic information that predicts a longer disease-free survival (DFS) or a higher probability of cure is provided by the “oncological” criteria. Strong parameters for the oncological criteria are the number of lesions; the presence, or suspicion, of extrahepatic disease; and numerous other criteria used in retrospective studies. Fong et al. proposed a score based on the following parameters: nodal status of primary tumor, disease-free interval from the primary to discovery of the liver metastases of <12 months, number of tumors >1 , preoperative CEA level >200 ng/ml, and size of the largest tumor >5 cm (**Table 1**) [31]. Thus, for some patients, neoadjuvant chemotherapy may be a better option than upfront surgery.

In practice, the patients can be categorized, based upon the criteria above, whether or not they are eligible for resection, as proposed by Adam et al. (**Table 2**) [28]. The disease can be categorized as resectable, not optimally resectable, or unresectable. The not optimally resectable disease is defined as difficult to resect for technical reasons (proximity to hepatic vein and portal vein branches) or technically

Survival (%)						
Score	1 year	2 year	3 year	4 year	5 year	Median (mo)
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumor, size >5 cm, CEA >200 ng/ml.

Table 1.
Clinical risk score for tumor recurrence proposed by Fong et al. [31].

Category	Contraindication
Technical	
1. Absolute	Impossibility of R0 resection and functional residual liver volume preserved ($\geq 25\text{--}30\%$ liver remnant) Presence of unresectable extrahepatic disease
2. Relative	R0 resection possible only with complex procedure (portal vein embolization, two-stage hepatectomy, hepatectomy combined with ablation ^a) R1 resection
Oncological	
1.	Concomitant extrahepatic disease (unresectable)
2.	Number of lesion ≥ 5
3.	Tumor progression

Any patient should be categorized as A1 or A2/B1, B2, or B3. This classification may help to clearly define the type of unresectable patients included in all clinical trials.

^aIncludes all methods, including radiofrequency ablation.

Table 2.
 Contraindications to hepatic resection in patients with CRC liver metastases (adapted from Adam et al. [28]).

possible to resect, but oncologically problematic (number of liver metastases greater than 4, maximum diameter 5 cm or more, synchronous liver metastases, primary lymph node metastasis positive, and high levels of tumor markers) [32].

5. Treatment options

Considering the fact that nearly 80% of patients with mCRC are not candidates for resection at diagnosis [33], initial treatment options include chemotherapy and several locoregional therapies. In these cases, chemotherapy in combination with molecular targeted drugs is recommended, followed by curative resection if a response is achieved.

5.1 Chemotherapy

In patients with “favorable oncological” criteria (i.e., $>50\%$ likelihood of cure based on various factors including long-term metachronous disease) and “favorable surgical” criteria (no massive disease infiltration), both upfront surgery and perioperative chemotherapy are options. The EPOC study with perioperative chemotherapy has shown no clear predilection for one option over the other, since the 5-year OS rate reported for the perioperative chemotherapy group was 51% (95% CI 45–58) versus 48% (95% CI 40–55) in the surgery-only group [34].

However, in cases with disease that is not technically challenging to resect but where the prognostic situation is unclear, perioperative chemotherapy should be the preferable treatment strategy. These patients should undergo perioperative chemotherapy, 3 months before surgery and 3 months after surgery. The preferred treatment in this situation should be FOLFOX (or alternatively capecitabine with oxaliplatin—CAPOX) as reported for the EPOC trial [34]. EGFR-targeting monoclonal antibodies (cetuximab and panitumumab) are not to be used in this setting, based on the data from the New EPOC trial [35]. No data with bevacizumab are available for this specific patient group; thus, bevacizumab is not indicated [7]. Hence, especially in the case of synchronous metastatic disease, neoadjuvant chemotherapy preceding liver resection is often undertaken as a way of assessing the natural history of metastatic disease prior to resection.

The use of conversion chemotherapy in clinical practice is based on the fact that initially unresectable tumors that are judged resectable after responding to chemotherapy and that undergo surgery display better long-term result than those treated with chemotherapy only [7, 36]. It is reported that up to 33% of patients with “initially unresectable” hepatic metastases have a sufficient objective response to conversion therapy to permit a subsequent complete (R0) resection [17, 37]. However, it has also been reported that the probability of downstaging a truly unresectable disease to the point of resectability is only up to 15 [38].

Another important aspect that has to be studied when considering conversion therapy is that longer durations of chemotherapy increase the possibility of liver toxicity and postoperative complications. Evaluation of the response through imaging tests should be made each 6–8-week gap, and the resection should be made as soon as the metastases are considered undoubtedly resectable [38].

In this scenario the response of the disease to the systemic treatment is also very important. If a growth of the disease is perceived while on chemotherapy or even the development of extrahepatic disease appears in this period, it may indicate that the tumor is biologically aggressive and it would not benefit from resection [17].

After complete resection of mCRC, the best postoperative strategy is debatable as well. Due to the lack of published randomized trials to conduct clinical practice, some suggest completion of a 6-month course of systemic chemotherapy (including courses administered as neoadjuvant therapy), as also suggested by updated guidelines from the National Comprehensive Cancer Network (NCCN) [38].

The strong tumor responses for mCRC with the new agents in chemotherapy can even reach a complete response status. The tumors with less than 2 cm in diameter and more than 1 cm deep in the hepatic parenchyma are the ones with greater risk of vanishing [39]. Nevertheless, the resection is still needed considering that true pathologic complete response or clinical long-term response is, after chemotherapy alone, present in only 17% of the patients [40]. Therefore, those at risk of disappearing with the neoadjuvant treatment should be marked with a fiducial marker such as a coil before chemotherapy [41].

5.2 Radiofrequency ablation therapy

Though resection is considered the gold standard care of mCRC, sometimes there are contraindications due to anatomical reasons. Additionally, there may be comorbidities or liver dysfunction associated which grades the patient as ineligible for major surgery. In these cases, radiofrequency ablation (RFA) represents a great alternative [21].

Considered as a parenchymal-sparing approach, the ablation therapy has been used for managing tumors that can vary from small to unresectable. It can be used as part of a combined ablation/resection tactic in cases of borderline resectable tumors or cases with risk of insufficient future liver remnant [17]. In a multicenter study of 288 patients who underwent combined intraoperative ablation and resection of mCRC, the 5-year overall survival was 37%, and local recurrence-free survival from ablated lesions was 78%. Postoperative mortality was 1%, and the overall complication rate was 35% [42].

5.3 ALPPS

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has emerged as modification on classic two-staged hepatectomy (TSH) with portal vein embolization. This new concept of liver resection, ALPPS, was first described in 2011 [43]. The main advantage of ALPPS is its ability to generate

extensive and accelerated hypertrophy of the future liver remnant (FLR), achieving adequate volume for completion of the second stage of the ALPPS in as short as 1 week. This method for hepatic resection has also been described to treat various hepatic tumors in children [44]. ALPPS brings solution to a major flaw of classic TSH, where a considerable percentage ($\approx 30\%$) of patients are unable to complete the second stage due to insufficient future liver remnant (FLR) growth and short-interval progression of the disease [45].

In the initial study, 68% of the patients experienced complications, and the surgical mortality rate was 12% [43]. Since the first description of ALPPS, there has been a great deal of interest in this treatment. However, criticism of the approach has been raised mainly regarding surgical morbidity and mortality [46].

Recently, Wanis et al. [47] reported a cohort of 58 patients who underwent ALPPS for colorectal liver metastases. They observed no perioperative mortalities and a rate of severe complications of 21%. The 3-year post-ALPPS overall survival was 50%, while the disease-free survival was 13%. The most common site of first recurrence was the liver alone (38%). Patient-reported quality of life after ALPPS was similar to reference values for general population

Additionally, the Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial) comparing ALPPS with TSH [48], showed a much higher resection rate for ALPPS, 92% (44/48), than TSH, 57% (28/49) ($P < 0.0001$). Considering other parameters, such as complications [43% (19/44) vs. 43% (12/28)] and 90-day mortality [8.3% (4/48) vs. 6.1% (3/49)] or RO RRs [77% (34/44) vs. 57% (16/28)], no differences were observed.

In experienced hepatobiliary centers and in well-selected patients, ALPPS can be performed with low perioperative morbidity and minimal to no mortality, resulting in good intermediate-term survival and excellent quality of life [47].

Although many centers have been using ALPPS associated with right hepatectomy with good results to treat liver mCRC, indications for ALPPS should continue to be scrutinized critically by multidisciplinary tumor boards based on accepted criteria of remnant liver volume, number of prior cycles of chemotherapy, and histologic criteria of the presence or absence of underlying parenchymal hepatic damage based on at the least a fresh frozen section during stage 1, when considering ALPPS [49].

The technique consists of a bilateral subcostal laparotomy using an adult subcostal retractor. A thorough inspection of the abdominal cavity is carried out in order to detect any previously missed metastases. A cholecystectomy and hepatic hilum dissection are then performed. The right and left hepatic arteries, as well as the arteries for segment 4, were dissected and identified. The common bile duct was dissected. The left or right portal vein is ligated. When the tumor is located on the right hemi-liver with involvement of segment 4, the portal branch for segment 4 is ligated and divided. Full mobilization of the liver is obtained by sectioning the falciform, coronary, and right and left triangular ligaments of the liver. The right or left hepatic vein of the liver to be resected is dissected and encircled with a vessel loop, as seen in **Figure 1**. An intraoperative ultrasound is performed to verify a tumor-free parenchymal transection line.

The liver parenchyma is transected using combined ultrasonic energy (Ultracision®), monopolar and bipolar electrocautery, and ligation of the blood vessels and bile ducts. Biologic fibrin sealant can be used in both surfaces of the spitted liver. Closed drainage is placed in the liver hilum. We do not use any plastic film, mesh, or plastic bag to separate both surfaces of the liver. Metastases located in the future remnant liver (FRL) can be treated either by local resection or radiofrequency tumor ablation (RFA).

During the second operation, the hepatic artery and the bile duct of the diseased liver are ligated and transected. A clamp is applied at the right or left hepatic vein,

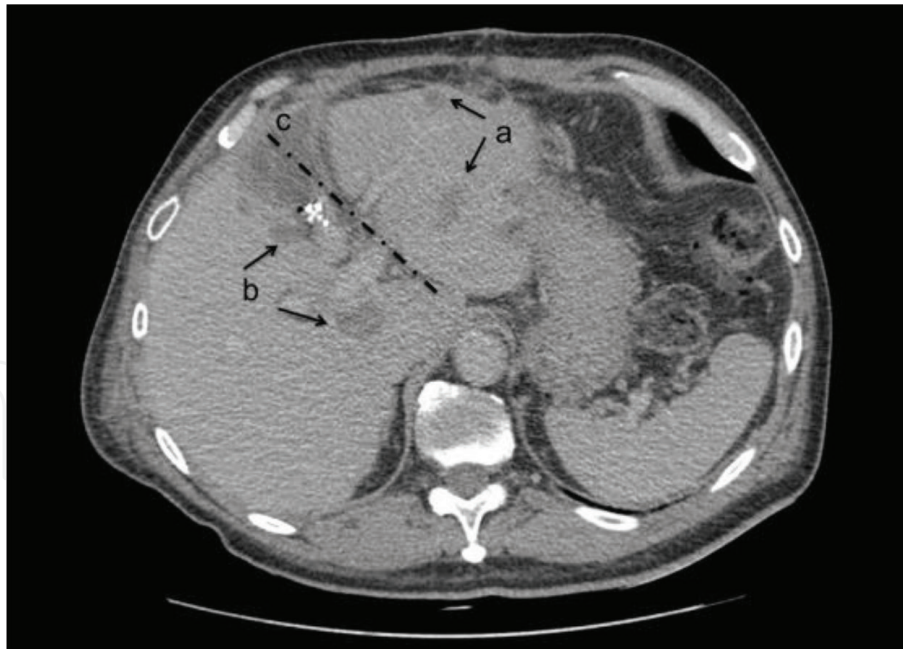


Figure 1. Postoperative CT image of a patient who underwent portal vein ligation and staged hepatectomy: (a) treated liver metastases of the FRL, (b) metastases on liver to be resected, and (c) line of liver bipartition.

and the vein is then transected. A 4–0 Prolene[®] running suture is applied to the stump of the hepatic vein. Liver segment 1 is usually preserved [46].

6. Timing for surgical approach

When facing a situation of synchronous disease, with both primary tumor and hepatic metastases, the timing for surgical approach of the hepatic lesions is still a topic of discussion.

The lesions can be accessed simultaneously in one procedure, or they can be treated with a staged resection. In the staged manner, there is the classic approach, which means accessing the primary tumor first; and there is the reverse approach, also known as liver-first approach. No difference has been shown by various studies, regardless of which method is used [50].

Therefore, the decision should be established on a case-by-case basis, considering the symptoms presented by the patient, location, size, and possible complications of each one such as bowel perforation, risk of liver failure, whether the patient underwent chemotherapy or not, performance status, and the surgeon expertise [17, 51].

7. Surgical resection

The surgical approach of the mCRC in the liver can be performed through an anatomic resection or a nonanatomic/parenchymal-sparing resection (PSR). Since the type of resection has not been associated with significant differences in rates of positive margin, recurrence, or survival [50], and considering that the PSR preserves greater hepatic reserve, recent studies are leaning toward the nonanatomic method, particularly when chemotherapy-induced liver injury is a concern [17].

Keeping in mind that recurrences after initial resection of mCRC can occur in up to 57% of cases and the most common site of recurrences is the liver [52] and considering that repeat liver resection in a second recurrence, with satisfactory

morbidity and perioperative mortality, has been associated with a 5-year survival up to 43% [38], the PSR becomes an even more attractive option.

Considering the width of the resection margin, a 2017 meta-analysis reported that margins greater than 10 mm were related with superior 5-year OS [53]. Still, numerous retrospective studies revealed that less than 10 mm but negative margin is not related with poorer survival [54]. In a multicenter study of 551 patients, surgical margins were classified as positive or negative with 1–4, 5–9, and >10 mm of tumor-free parenchyma. The positive margins were associated with a greater risk of recurrence, and the width of negative margins did not affect survival, recurrence, or site of recurrences [54].

There is one situation where anatomic resection and/or a wider surgical margin (>10 mm) may be indicated which is before a RAS-mutated mCRC as it constitutes a more aggressive tumor biology group and has been associated with more positive margins and worse survival after surgery [55]. Others reported that even a wider resection margin might not be sufficient to overcome the aggressive tumor biology associated with a RAS mutation. In a study of 411 patients who underwent resection for mCRC at Johns Hopkins University, a 1–4-mm margin was associated with improved survival compared with a positive margin (<1 mm or R1) for wild-type KRAS tumors, with which a wider resection margin did not further improve survival. In KRAS-mutated tumors, however, negative margin status, which included a 1-cm margin, did not improve survival [56].

8. Follow-up after resection

According to the consensus-based guidelines from the National Comprehensive Cancer Network (NCCN), the recommendation is carcinoembryonic antigen (CEA) testing every 3–6 months for 2 years followed by every 6 months for 3 years; computed tomography (CT) of the chest/abdomen and pelvis every 3–6 months for 2 years and then every 6–12 months up to a total of 5 years; colonoscopy in 1 year; if negative, repeat in 3 years and then every 5 years; and if advanced adenoma is found, repeat in 1 year [38].

An important point is that posttreatment follow-up should only be performed for those patients considered candidate for a second potentially curative surgical procedure [38].

9. Repeat resection for colorectal liver metastases

Re-resection for recurrence of mCRC is a safe and viable option in properly selected patients. In order to prevent post-hepatectomy liver failure, sufficient future liver reserve is paramount, as well as no evidence of extrahepatic disease and good performance status [57–59].

Although randomized trials have not been conducted to prove benefit, several reported series have demonstrated perioperative mortality rates lower than 5%, and overall survival rates ranged from 20 to 43% at 2–5 years [57–59].

Patients with a relapse-free interval of longer than 1 year appear to have a more favorable outcome from re-resection. Factors associated with a poor outcome include synchronous resection for the first liver metastases and the presence of multiple lesions at second hepatectomy [60, 61].

Interestingly, recurrences at the margin are uncommon [62, 63]. Some studies have reported 5-year overall survival rates after re-resection of 33–73% with no perioperative mortality [64, 65].

10. Conclusion

It is known that the majority of metastatic CRC liver disease will be potentially resectable at the time of diagnosis. Considering that hepatic resection is the only curative option for these patients, the parameters of resectability have expanded through the years due to a wider knowledge of the disease, improving diagnostic techniques, new drugs, and technical surgical advances. It is safe to say that the treatment strategies have advanced rapidly enough to change dramatically the natural history of the mCRC.

ALPPS has been recently introduced as an option to the treatment of mCRC. It has been shown to increase drastically the resection rates, with complications rates not different from standard two-staged hepatectomy.

Several treatment options are available to treat patients with mCRC. It is important to have in mind that the treatment approach must be established for each case. Not only the patient and anatomic factors are important, but also the tumor factors must be considered. Best results are obtained when the treatment approaches for individual patients are discussed within a multidisciplinary team (MDT) of experts, meeting regularly as a tumor board to review mCRC cases.

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