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CLINICAL GUIDES IN ONCOLOGY

# Multidisciplinary management of liver metastases in patients with colorectal cancer: a consensus of SEOM, AEC, SEOR, SERVEI, and SEMNIM

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## Abstract

Colorectal cancer (CRC) has the second-highest tumor incidence and is a leading cause of death by cancer. Nearly 20% of patients with CRC will have metastases at the time of diagnosis, and more than 50% of patients with CRC develop metastatic disease during the course of their disease. A group of experts from the Spanish Society of Medical Oncology, the Spanish Association of Surgeons, the Spanish Society of Radiation Oncology, the Spanish Society of Vascular and Interventional Radiology, and the Spanish Society of Nuclear Medicine and Molecular Imaging met to discuss and provide a multidisciplinary consensus on the management of liver metastases in patients with CRC. The group defined the different scenarios in which the disease can present: fit or unfit patients with resectable liver metastases, patients with potential resectable liver metastases, and patients with unresectable liver metastases. Within each scenario, the different strategies and therapeutic approaches are discussed.

**Keywords** Colorectal cancer · Liver metastases · Surgery · Chemotherapy · Locoregional therapies · Consensus

## Introduction

Colorectal cancer (CRC) has the second-highest tumor incidence and is a leading cause of death by cancer [1, 2]. Nearly 20% of patients with CRC will have metastases at the time of diagnosis, and more than 50% of patients with CRC develop metastatic disease during the course of their disease (15–25% synchronously and 50–60% metachronously) [3].

In the past, palliative chemotherapy showed dismal 5-year survival rates of less than 5% in these patients, but clinical advances with new chemotherapeutic and targeted biological agents have reached median survival of almost 30 months [4]. Although metastases are generally widely disseminated, a minimal metastatic disease described as an "oligometastatic or oligo-recurrence state" [5] is relatively common in these patients, showing a clinical scenario in which the combination of systemic and local therapies improves overall survival. Although the number of metastases accepted as oligometastases that would benefit from local treatment is not well established, the change in prognosis of these patients has been reflected in the 8th AJCC staging (M1a: metastases at one site, M1b: metastases at two or more sites).

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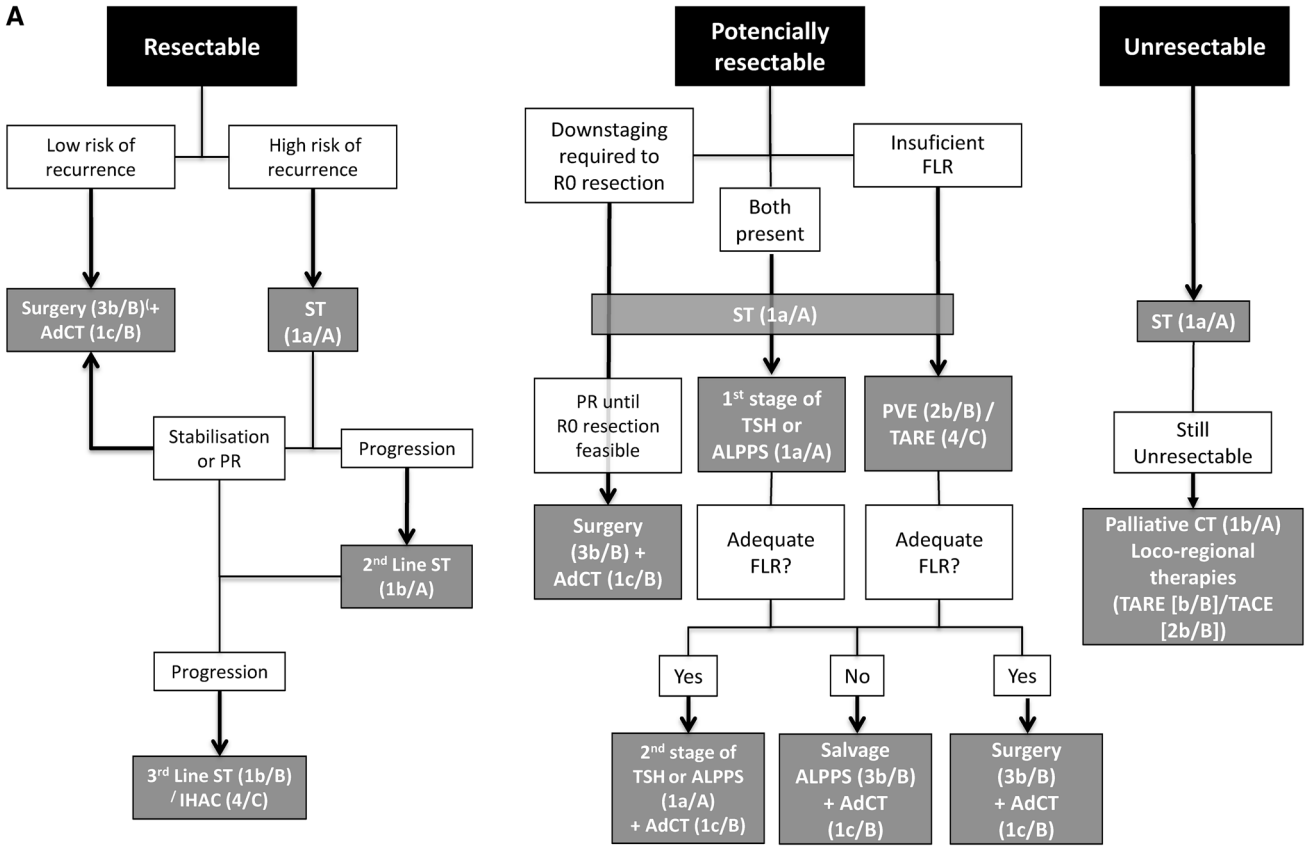
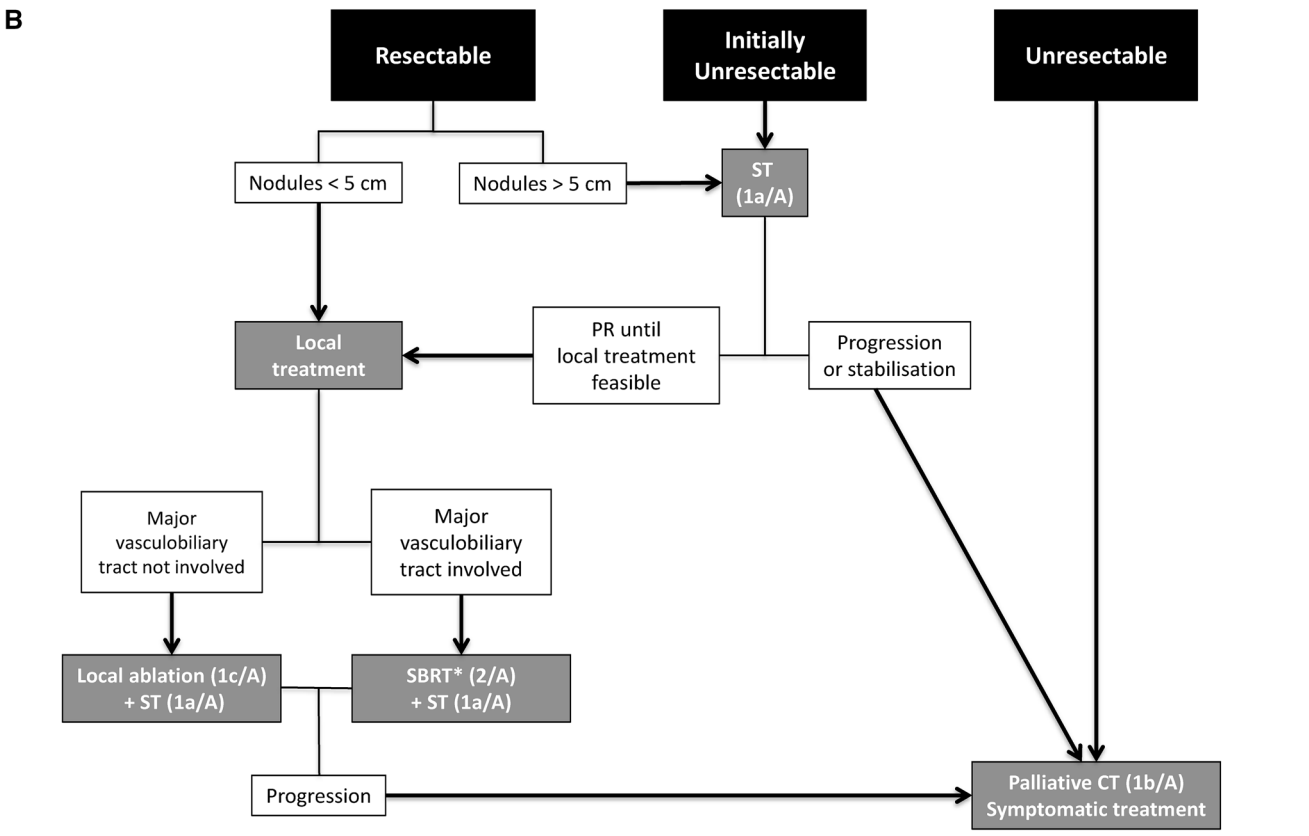

A
Resectable
Low risk of recurrence
High risk of recurrence
Surgery (3b/B)[] + AdCT (1c/B)
ST (1a/A)
Stabilisation or PR
Progression
2nd Line ST (1b/A)
Progression
3rd Line ST (1b/B) / IHAC (4/C)
Potencially resectable
Downstaging required to R0 resection
Insuficient FLR
Both present
ST (1a/A)
PR until R0 resection feasible
1st stage of TSH or ALPPS (1a/A)
PVE (2b/B) / TARE (4/C)
Surgery (3b/B) + AdCT (1c/B)
Adequate FLR?
Adequate FLR?
Yes
No
Yes
2nd stage of TSH or ALPPS (1a/A) + AdCT (1c/B)
Salvage ALPPS (3b/B) + AdCT (1c/B)
Surgery (3b/B) + AdCT (1c/B)
Unresectable
ST (1a/A)
Still Unresectable
Palliative CT (1b/A) Loco-regional therapies (TARE [b/B]/TACE [2b/B])


B
Resectable
Initially Unresectable
Unresectable
Nodules < 5 cm
Nodules > 5 cm
ST (1a/A)
Local treatment
PR until local treatment feasible
Progression or stabilisation
Major vasculobiliary tract not involved
Major vasculobiliary tract involved
Local ablation (1c/A) + ST (1a/A)
SBRT* (2/A) + ST (1a/A)
Progression
Palliative CT (1b/A) Symptomatic treatment

◂**Fig. 1** Algorithm for the management of liver metastases in patients with colorectal cancer. **a** Fit patients. **b** Unfit patients. *AdCT* adjuvant chemotherapy, *ALPPS* associated liver partition and portal vein ligation for stage hepatectomy, *FLR* future liver remnant, *NCT* neoadjuvant chemotherapy, *PR* partial response, *SBRT* stereotactic body radiation therapy, *ST* systemic therapy, *TACE* transarterial chemoembolization, *TARE* transarterial radioembolization, *TSH* two-stage hepatectomy. Between brackets appear the level of evidence/grade of recommendation according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009): level of evidence: (1a) SR (with homogeneity) of RCTs; (1b) individual RCT (with narrow confidence interval); 1c, all or none§; (2a) SR (with homogeneity) of cohort studies; (2b) individual cohort study (including low-quality RCT; e.g., < 80% follow-up); (2c) "Outcomes" research or ecological studies; (3a) SR (with homogeneity) of case–control studies; (3b) individual case–control study; (4) case-series (and poor quality cohort and case–control studies); (5) expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles". Grade of the recommendation: (A) consistent level 1 studies; (B) consistent level 2 or 3 studies or extrapolations from level 1 studies; (C) level 4 studies or extrapolations from level 2 or 3 studies; (D) level 5 evidence or troublingly inconsistent or inconclusive studies of any level

In selected favorable patients who are medically operable and who have resectable liver metastases, surgery with curative intent has reached high rates of local control and prolonged survival [5-year overall survival (OS) > 50%] [6]. This is why the approach to patients with liver metastatic CRC is a highly important challenge. Multidisciplinary committee implementation has been one of the most relevant aspects. The first step in the treatment of these patients is to clearly define if we are dealing with a resectable disease or if it would be resectable after systemic treatment, as well as primary tumor management in cases of synchronous metastatic. Based on these findings, first-line treatment will be defined. If, conversely, the disease is clearly unresectable, the choice of treatment remains in the hands of the medical oncologist.

A group of experts from the Spanish Society of Medical Oncology (SEOM), the Spanish Association of Surgeons (AEC), the Spanish Society of Radiation Oncology (SEOR), the Spanish Society of Vascular and Interventional Radiology (SERVEI), and the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) met to discuss and provide a multidisciplinary consensus on the management of liver metastases in patients with CRC. In this consensus, we will define the different scenarios in which the disease can present, as well as the different strategies and therapeutic approaches that can be offered to these patients.

## Colorectal liver metastases detection

Knowing the number, size, and location, as well as the main biliary and vessel relationships, of CRC liver metastases (CRCLm) is mandatory before treatment planning. Additionally, presurgical neoadjuvant responses and liver volumetry must be taken into account. Imaging techniques include computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET) and ultrasound. The best methods for CRCLm detection are CT and MR [7]. CT with a multiphasic technique and optimal scanning parameters providing high contrast and spatial resolution should be the initial imaging tests. On CT, liver metastases are hypodense on portal and delayed phases. CT is indicated for the detection of lung metastases. Preoperatively, both CT and MR are indistinct [8]. For subcentimetric liver nodules and after neoadjuvant chemotherapy, MR is superior to CT [9]. T2 gradient echo, diffusion sequences and hepatobiliary-specific MR contrast medium are useful in the characterization of small size lesions and to make differential diagnoses. Ultrasound improves disease detection sensitivity with ultrasound contrast introduction. US is useful to guide percutaneous ablations and is also an important tool during surgical removal [10]. PET-CT compared with CT alone does not result in frequent changes in surgical management [11]. The role of PET/CT in CRCLm detection is to rule out extrahepatic disease, thus allowing the evaluation of the resectability of a given metastatic lesion and consequently modifying the management of approximately 24% of patients in this setting [12–16].

## Resectable liver metastases

### Fit patients (Fig. 1a)

Surgical resection is widely recognized as the gold standard treatment of resectable CRCLm. However, this one lacks a high level of evidence, because it was considered unethical to design randomized studies with a non-surgical patient arm. Resectable CRCLm are defined as metastatic liver disease in which a R0 resection can be performed, leaving at least 20–25% of total liver volume with adequate inflow, outflow and biliary drainage [17]. This definition encompasses a wide range of patients. From those with peripheral single metastases that are easily resectable to those with high tumor burden or even those with single metastasis but located hepatic-center that require a major hepatectomy.

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those with high tumor burden or even those with a single metastasis that is located at the hepatic center and requires a major hepatectomy.

Several authors have tried to identify preoperative factors of poor prognosis to predict survival or even use them as a tool for treatment selection. These factors include tumor at stage T3–T4, tumor burden ($\geq 3$ liver metastases or the largest liver metastasis is $\geq 5$ cm in diameter), and synchronous CRLM and serum CEA level $\geq 5$ ng/ml [18, 19]. According to these factors, Zhu et al. [18] divided resectable patients into high- and low-risk patients. Among the high-risk patients, those who had received neoadjuvant chemotherapy (NCT) had a longer median overall survival (38.9 m vs. 28.4 m) and a better 5-year OS (39% vs. 33%; $p=0.028$) than those of patients who had not received NCT. These differences regarding NCT were not observed among low-risk patients. Therefore, this classification allows the identification of resectable patients who benefit from NCT.

Previously, Fong et al. [20] established a clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer based on clinical and morphological criteria (size and number of liver metastases), as well as CEA levels. More recently, Margonis et al. [21] developed the GAME score, which presents some advantages over the FONG score. First, it is the first score to include a genetic criterion (K-RAS status). Furthermore, the GAME score incorporates the tumor burden score (TBS) as a morphological criterion; compared with the size and number of liver metastases, TBS has proved to be a powerful tool to calculate the impact of tumor morphology on long-term survival among patients with CRClm. In addition, while previous scores have been imprecise in identifying patients with poor prognosis, patients with a GAME score of 6–7 (high risk) had an expected 5-year survival rate of 0%. Finally, when patients were classified as low, intermediate, and high risk by the GAME score, significant differences were found in the 5-year OS rate among the three groups of patients. However, when the FONG score was applied to the same cohort of patients, significant differences were found between patients with low and intermediate risks but not between those with intermediate and high risks. Therefore, the GAME score outperforms other scores to identify and discriminate between patients with intermediate- and high-risk CRClm.

### Low-risk resectable patients

As mentioned earlier, NCT has not demonstrated a benefit; thus, these patients must directly undergo liver surgery. In most cases, low-risk patients are those with less tumor burden. So, the type of liver resection to perform will be minor hepatectomy (defined as less than 4-segment hepatectomy) [22] or limited parenchymal sparing hepatectomy (PSH). The better prognosis of these cases is due to two main reasons:

- *R0 resection is easily performed* To reach a R0 resection is considered the most important factor associated with better prognosis in terms of 5-year OS: 55% in R0 patients vs 26% in R1 patients; $p=0.017$ [23]. Multivariate analysis identified R1 resection ($p=0.03$) as a factor independently associated with worse survival [24].
- *Low-burden tumor* The number and size of liver metastases negatively influence patient survival [18]. Most of these patients will undergo the following two types of liver resection:

Mainly due to the location of the lesions, a few low-risk patients will require major hepatectomies. These are associated with a higher risk (OR 1.642, CI 95% 1.281–2.104, $p<0.001$) and rate (36.9% vs 24.3%, $p<0.001$) of severe morbidity as well as a higher risk (OR 2.561, CI 95% 1.424–4.606, $p=0.002$) and rate (7.4% vs 2.6%, $p<0.001$) of mortality than minor hepatectomy.

Strategies based on PSH were initially described by Gold et al. [25], who demonstrated that multiple uni- or bilobar liver resections (wedge resections) respecting the uninvolved liver parenchyma have no negative impact on oncological outcomes if R0 resection is completed. Similar results were subsequently obtained by several authors in terms of disease-free survival (DFS) and OS with lower rates of general complications (25 vs. 34%; $p=0.03$) and type Dindo–Clavien III-IV (10 vs. 16%, $p=0.04$) when compared with standard or extent hepatectomies [26].

Other benefits of PSH include low liver failure and short intensive care unit-stays, a high rate of patients who receive adjuvant chemotherapy, and great preservation of uninvolved liver parenchyma to perform salvage re-hepatectomy in cases of liver recurrence.

### High-risk resectable patients

These patients commonly have a high tumor burden, which is why these patients usually require a major hepatectomy (four or more segments) or an extensive bilobar PSH to obtain a R0 resection.

Although R0 resection could be initially performed, several authors have demonstrated that NCT improves 5-year overall survival. The benefits of NCT in this group of patients include the following:

- The size of CRClm is reduced, thus making liver resection easier.
- Chemotherapy is better tolerated in this setting.
- Micrometastatic disease is eradicated.

- Chemosensitivity and patient tolerance is assessed preoperatively, providing valuable information on which postoperative regimen to use [27].
- Those patients who benefit from liver metastases surgery are identified. Five-year OS and disease-free survival are significantly worse in patients with progression after NCT even when a R0 resection is obtained (5-year OS in progression-patients reached 8% vs 30% in stabilization-patients or 37% in partial-response-patients) [28]. Therefore, most groups consider that progression after NCT is a contraindication criterion for liver surgery.

A meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic therapy [29]. The analysis showed a benefit of chemotherapy in progression-free survival (PFS) and DFS but not in OS. Another meta-analysis combined data on 1896 patients and found that perioperative chemotherapy improved DFS but not OS. Additional recent meta-analyses have also failed to observe an OS benefit with AT [30].

In low-risk resectable patients who have not received perioperative chemotherapy, there is no strong evidence to support the use of AT, whereas high-risk resectable patients may benefit from adjuvant therapy (AT). The international guidelines recommend AT after surgical resection of CRClm despite the low level of evidence. However, there is still no standard treatment, and the effectiveness of AT remains controversial. The preferred perioperative chemotherapy in resectable patients should be the combination of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) [or alternatively capecitabine with oxaliplatin (CAPOX)], as reported for the EPOC trial [31]. Biologics are not recommended in resectable liver metastases. EGFR-targeting monoclonal antibodies (cetuximab and panitumumab) are not to be used in this setting, based on the data from the new EPOC trial [32]. No data with bevacizumab are available for this specific patient group; therefore, bevacizumab should not be used.

## Unfit patients (Fig. 1b)

Ablative treatments are a good alternative for patients who are technically resectable but inoperable due to poor clinical conditions or comorbidities. Percutaneous ablation should be reserved for patients who are not optimal candidates for resection or who are not willing to undergo surgery [33]. The objective of ablation in resectable patients is to achieve complete local control A0, equivalent to R0. A remarkable aspect of the ablative techniques is that they can be used together with any chemotherapy regimen or surgery without impending any pre, post or concomitant oncologic treatment [34]. Patients with a limited number of liver metastases can be treated with other less-invasive local treatments. Ablation treatment is performed by placing a probe under the image guide inside the tumor nodule. CT, ultrasound or cone beam CT can be used to precisely guide the puncture inside the tumor. Energy will be delivered locally through the probe to cause a predictable and controllable volume of tissue necrosis [35]. There are several ablative technologies available, including heat radiofrequency (RF) or microwaves (MW), cold (cryoablation) or electric pulses (irreversible electroporation [IRE]) [36] (Table 1). The common factor among ablation therapies is that they are less invasive than surgery, have a shorter recovery time and have fewer major complications [37]. RF, MW ablation, and more recently stereotactic body radiation therapy (SBRT) [38] are ablation therapies with minimal toxicity and good clinical results, providing an opportunity for curative intent to nonoperative patients. Currently, there are different ablation technologies available that can be applied percutaneously or intraoperatively that have demonstrated at least good local tumor control (LC) (Tables 2 and 3).

Although less invasive than surgery, normal liver function is required for all ablation techniques. Unlike surgery with ablation, it is impossible to have pathological confirmation of the results and to know in advance if the whole nodule has been effectively treated. Under general conditions, liver resection is superior to ablation in survival outcomes. Radiofrequency is the most commonly used thermal ablation therapy since the late 90s and has shown as much

**Table 1** Types of ablation therapies for colorectal liver metastases

| Treatment | Application | Energy | Image guide | Probes |
|---|---|---|---|---|
| Radiofrequency | Percutaneous, open, laparoscopic | Heat | US, TC, CBCT | Single needle |
| Microwaves | Percutaneous, open, laparoscopic | Heat | US, TC, CBCT | Single needle |
| Cryotherapy | Percutaneous | Cold | CT | ≥ 3 needles |
| Irreversible electroporation | Percutaneous open | Nonthermal | CT, US | ≥ 3 needles |
| Stereotactic body radiotherapy | Percutaneous | Radiotherapy | CT | Fiducial/s |
| High-intensity focused ultrasound | Percutaneous | Ultrasound | MR | No needles |

*CT* computed tomography, *CBCT* cone beam CT, *MR* magnetic resonance; *US* ultrasound

**Table 2** Evidence of ablation therapies for colorectal liver metastases

| Treatment | Invasive | Anesthesia | Histologic validation | Evidence |
|---|---|---|---|---|
| Radiofrequency | Yes | Yes | Yes | Overall survival |
| Microwaves | Yes | Yes | No | Local control |
| Cryotherapy | Yes | Yes | No | No |
| Irreversible electroporation | Yes | Yes | No | No |
| Stereotactic body radiotherapy | No | No | No | Local control |
| High-intensity focused ultrasound | No | No | No | No |

**Table 3** Comparative safety and survival for ablation therapies

| Treatment | Indication/contraindication[a] | Safety[b] | Survival |
|---|---|---|---|
| Radiofrequency | Number of lesions is not an absolute contraindication. Size ≤ 3 cm. Contraindicated if central or less than 1 cm to colon | ≥ 6% grade 3 complications | 5 years 48.7–56% |
| Microwaves | Number of lesions is not an absolute contraindication. Size ≤ 5 cm. Contraindicated if central or less than 1 cm to colon | Similar to radiofrequency ablation | 3 years up to 78% |
| Cryotherapy | 3 nodules ≤ 3 cm | 5.8% grade 3 complications | 3 years up to 60% |
| Irreversible electroporation | Central/hilar nodule ≤ 3 cm | 15–18% grade 3 complications | Not clearly reported |
| Stereotactic body radiotherapy | Depended on tumor volume | Not reported grade ≥ 3 toxicity | 2 years up to 75% |
| High-intensity focused ultrasound | Lesions size more than 3 cm. Pain control | Limited experience | Not available |

[a]Normal liver function is required for all ablation techniques. Br < 2 mg/dl is a relative contraindication, and Br > 3 mg/dl is an absolute contraindication for any ablation technique in colorectal liver metastases

[b]Safety: Memorial Sloan-Kettering Cancer Complication Classification (see references). Based on the references [36, 37, 40, 87, 102–108]

as 94% of local control and 31% 5-year OS when treated tumors are ≤ 3 cm, centrally located and with ablation margins greater than 5 mm [39]. MW is a promising technology with some advantages over RF [40]. The indications for RF and MW are well-located tumors less than 5 cm. Tumor number is not an absolute contraindication, but in most centers, the consensus is to treat up to five nodules [34, 41]. Br levels lower than 3 mg/dl and induced necrosis less than the volume equivalent to two segments are general rules to indicate RF or MW ablation. Factors that influence ablation success are size, location, visibility of the target tumor and RAS mutation. Evidence suggests that metastases > 3 cm are more likely to undergo incomplete ablation. Local tumor progression-free survival after ablation in mutant-RAS was significantly worse than wild type [39–42]. Blood vessels > 3 mm may cause dispersion in tissue heating. This is known as the 'heat-sink effect', and it is a limitation of RF that is overcome using MW. Centrally located metastases contraindicated RF or MW because of concern for main biliary tree complications. In those cases, IRE could be an option because this technology does not damage biliary or vascular structures [43].

Historically, radiation therapy has had a limited role in the treatment of liver metastases because of the risk of liver toxicity induced by high doses delivered to normal liver tissue. However, recent technological advances have contributed to the development of SBRT as a precise tightly focused radiation technique that allows the treatment of hepatic metastases with an ablative intent while significantly limiting the dose to the healthy liver and surrounding tissues. Liver SBRT requires the integration of imaging (CT, MRI, PET-CT) to properly define the metastases, highly conformed dosimetry to further minimize radiation dose in healthy tissues, and intrafraction control of the liver motion to deliver the dose to the metastases with accuracy [44]. The safety and effectiveness of SBRT have been evaluated with encouraging results in retrospective and prospective clinical studies of liver metastases, showing minimal toxicity, high rates of LC [45–53] and promising OS [52, 53].

The first results of SBRT published in 1995 showed the feasibility of the technique and 50% LC [45]. Phase I studies reported the dose escalation benefit in a single fraction (14–26 Gy), reaching 66% LC at 18-month [46]. A multicenter phase I/II study demonstrated the safety and efficacy of high doses of SBRT, 60 Gy in patients with 1–3 metastases, with a 2-year LC of 92% (100% in lesions < 3 cm) and 2% of grade 3 toxicity [48]. LC seems mainly influenced by size (< 5 cm) and radiation dose (BED > 100 Gy),

and dose escalation appears to be particularly important in CRClm [48, 50]. When only dose-escalated regimens are analyzed, 1- and 2-year LC range from 90–100% and 81–100%, respectively [47–49]; recent phase II studies with even higher doses (75 Gy in 3 fractions) have reported 91% 2-year LC and high OS (2-year OS of 70%) [50].

SBRT is a very well-tolerated treatment with a low toxicity profile (G1-2 of 0–28%), exceptionally severe toxicity and grade 3 late complications < 5%. Long-term results with SBRT have also shown low toxicity (grade 3 < 5%) and long survival times (3-year OS of 4%) [52]. Although most of the studies have treated a limited number of liver metastases (1–3 lesions), patients with multiple liver metastases can be treated safely and can benefit from sequential SBRT with high LC (80.6% and 65% at 2 and 4 years) and prolonged survival (5-year OS of 57.6%) [53].

A major limitation of SBRT for liver metastases is the lack of randomized studies comparing SBRT with other local techniques; however, retrospective and prospective studies show durable LC (Table 4). SBRT offers an alternative, noninvasive approach to the treatment of limited CRClm in inoperable patients or those with unresectable metastases, especially in metastases greater than 3 cm or central lesions close to the main biliary tree or vascular structures that are not amenable to thermal ablation and have the fewest local therapeutic options. SBRT should also be studied in a multi-institutional setting in oligometastatic patients in combination with systemic therapies to improve overall survival.

## Potentially resectable liver metastases

### Surgical strategy

New surgical strategies and pharmacological agents have allowed an increase in the resectability of CRClm patients from 1–2% to 15–30%.

These patients are defined as those who present the following situations.

**Table 4** Outcomes of stereotactic body radiotherapy for liver metastases in prospective and retrospective studies

| Author | Number of patients/number of lesions | Number of metastases per patient/size | Type of metastases | Follow-up (months) | Total dose (Gy) number of fractions (fx) BED | Toxicity grade (G) | LC | Survival OS median *S* |
|---|---|---|---|---|---|---|---|---|
| Herfarth et al. [46] Phase I–II | 37/ 56 | 1–3 ≤ 6 cm | NR | 15.1 | 14–26 Gy (1 fx) BED 34–94 Gy | No late ≥ G3 | $71\%_{1y}$ $67\%_{18\,m}$ | $72\%_{1y}$ $55\%_{2y}$ OS $27_{m}$ |
| Romero et al. [47] Phase I–II | 25/34 | 1–3 < 7 cm | Mixed majority $CRC_{14}$ | 12.9 | 30–37.5 Gy (3fx) | 2% Acute ≥ G3 1% Late G3 | $100\%_{1y}$ $86\%_{2y}$ | $85\%_{1y}$ $62\%_{2y}$ |
| Rusthoven et al. [48] Phase I–II | 47/63 | 1–3 < 6 cm | Mixed majority $CRC_{15}$ | 16 | 36–60 Gy (3 fx) BED 79–180 Gy | < 2% Late G3/4 | $95\%_{1y}$ $92\%_{2y}$ | $30\%_{2y}$ OS $20.5_{m}$ |
| Chang et al. [49] Phase I/pool | 65/102 | 1–4 | $CRC_{65}$ | 14 | 46–52 Gy (1–6 fx) BED 82–100 Gy | Acute G3/4 3% 2 late G3 | $90\%_{1y}$ $43\%_{2y}$ | NR |
| Scorsetti et al. [50] Phase II | 42 | 1–3 ≤ 6 cm | Mixed majority $CRC_{42}$ | 24 | 75 Gy (3 fx) BED 263 Gy | No ≥ G3 | $91\%_{2y}$ | $65\%_{2y}$ OS $29.2_{ms}$ |
| Andratschke et al. [51] Retrospective | 74/91 | 1–4 | Mixed majority $CRC_{37}$ | 15 | 15–62.5 Gy (3–5 fx) | No acute G3/5 No late G4/5 | $74.7\%_{1y}$ $48.3\%_{2y}$ $48.3\%_{3y}$ | $77\%_{1y}$ $30\%_{2y}$ $27\%_{3y}$ OS $27_{m}$ |
| Goodman et al. [52] Retrospective | 81/106 | 1–3 ≤ 6 cm | Mixed majority $CRC_{67\%}$ | 33 | 54 Gy (3–5 fx) BED 112–151 Gy | 4.9% G3 | $96\%_{1y}$ $91\%_{4y}$ | $69\%_{2y}$ $44\%_{3y}$ $28\%_{4y}$ OS $33.6_{m}$ |
| Rubio et al. [53] Retrospective | 21/101 | 3–14 < 8 cm | Mixed majority $CRC_{13}$ | 23.2 | 36–60 Gy (3–5 fx) | No > G3 | $94.4\%_{1y}$ $80.6\%_{2y}$ $65\%_{4y}$ | $57.6\%_{5y}$ OS $62_{m}$ |

*BED* biologically equivalent dose, *CRC* colorectal cancer (subscript figures correspond to the number or proportion (%) of patients exhibiting metastases, *fx* fraction, *G* grade, *Gy* gray, *LC* local tumor control, *m* month/s, *NR* not reported, *OS* overall survival, *y* year/s

### R0 resection is feasible, but FLR is inadequate in volume or quality

Treatment is focused on improving the volume and function of FLR [54]. FLR of 25% is considered the minimum safe volume needed after hepatic resection in patients with a normal liver. However, in cases with sinusoidal obstruction syndrome (SOS), cholestasic, steatotic or cirrhotic liver, an FLR of 40% is required.

Percutaneous transhepatic portal vein embolization (PVE) is the gold standard to obtain adequate FLR hypertrophy. This procedure is performed by permanent occlusion of all right portal vein branches using different embolic agents. It is safe and effective and requires 3–5 weeks to achieve left lobe liver hypertrophy after embolization. According to a recent systematic review, the mean increase in the FRL volume was 37.9% ± 0.1% (20.5–69.4%) [55]. Adequate hypertrophy (that allows liver resection) was obtained in 96.1% of the procedures. Despite the good results of PVE, in approximately 15–20% of cases, planned liver resection is not performed. The main causes of these cancellations are extrahepatic tumor spread (8.1%), local intrahepatic tumor progression or newly developed metastases in the FRL (6.1%), and other causes (4.5%).

### R0 resection is compromised as a result of a large tumor burden, but the volume, outflow, inflow and biliary drainage of FLR are adequate

In such cases, patients require downstaging to obtain negative margin resection. These patients must undergo NCT and/or locoregional therapies, which target presurgical tumor shrinkage.

Transarterial radioembolization (TARE) with microspheres impregnated with yttrium-90 ($Y^{90}$), a high-energy β emitter with 2.5 mm tissue penetration, is a type of intraarterial brachytherapy targeted to hypervascular nodules in which neovascularization and the preference of arterial over portal perfusion determine a selective distribution of the device. This allows the safe administration of high doses of radiation to the tumor (tissue penetration range of 2,5 mm). Standard TARE indication is palliative for patients with multifocal, unresectable liver-only or liver-dominant CRClm.

It is intended to make inoperable patients candidates for surgical resection or to simply facilitate the procedure by making lesions smaller, reducing their proximity to delicate vasculature, and preserving adjoining healthy liver tissue [56, 57]. The REsect study, a blinded analysis of the patients included in the SIRFLOX trial, demonstrated that the combination of chemotherapy and TARE in patients with unresectable CRClm was associated with a statistically significant increase in the potentially curative resectability of the liver [58]. Currently, $Y^{90}$ microspheres may also be a reasonable alternative in patients who are potential candidates for resection but display a small FLR [14]. Although PVE is the gold-standard modality for inducing hypertrophy of the FLR [59], Garlipp et al. [60] showed a lesser, but still pronounced, benefit of $Y^{90}$ particles with regard to contralateral liver hypertrophy after TARE. Moreover, TARE minimizes the risk of tumor progression in the treated lobe, possibly making it a suitable modality for selected patients. An interval of 6 weeks between RE and follow-up imaging is considered appropriate, although the time to hypertrophy is heterogeneous, ranging in published studies from 44 days to 9 months.

### Sometimes both situations could be present

Two decades ago, most of these patients were considered unresectable. However, thanks to the new strategies, development of a R0-resection and acceptable OS could be achieved. All these cases require downstaging of the tumor as well as increasing the volume and quality of the less affected lobe. Oncosurgical strategies for these patients include the following:

- *Two-stage hepatectomy (TSH)* TSH was described in 2000 by Adam et al. [61] as a strategy for patients with a poor prognosis as a result of widespread liver and bilobar tumors. First, hepatectomy aims to treat all metastases of the less-invaded hepatic lobe by resection or local ablation. If the volume of the FLR is inadequate, a contralateral portal vein branch percutaneous embolization or surgical ligature must be associated. The aim of the second hepatectomy is to perform a R0 resection. Usually, this stage consists of major hepatectomy of the high-involved lobe. Disease progression or recurrence and poor performance status after the first hepatectomy are the two most frequent reasons for not performing the second resection. This takes places in 28.1% of the cases [62]. Patients in whom the second stage is not performed have worse survival than those in which the strategy is completed. The 3-year OS rate was 45% when TSH was completed and 30% when it was not. Likewise, the 5-year OS was 23% when the second stage could be performed and 0% when it could not.

  Oncological outcomes of patients who require TSH are poorer than those who undergo R0 resection with a single hepatectomy in terms of 3-year OS (43.7% vs 50.7%) and 5-year OS (21.4% vs 32.4%, $p = 0.002$) [63].
- *ALPPS procedure* Associating liver partition and portal vein ligation for stage hepatectomy (ALPPS) was described in 2012 as a new approach for patients with liver tumors initially deemed unresectable [64]. Since then, several authors have used this new strategy to increase the rate of resectable patients as an alternative

to conventional approaches (i.e., TSH). However, in a subset of patients, ALPPS was performed in patients who might not have been eligible for any other operative treatment or even as a salvage procedure after insufficient future liver remnant hypertrophy following PVE [65]. The criteria for indicating the ALPPS procedure are not uniform and vary between working groups.

Whether TSH and ALPPS procedures have comparable results is an issue that needs to be addressed. Moris et al. [66] performed a recent meta-analysis comparing the results of two surgical strategies in patients with CRClm. The likelihood of patients proceeding to the second surgery varied greatly in TSH (range 63.3–100%). However, all ALPPS patients underwent the second stage. No difference was noted with regard to the increase in FLR and postoperative FLR. However, the kinetic growth was faster for ALPPS (ALPPS vs TSH, mean difference: 19.07 ml/day, 95% CI 8.12–30.02, $p = 0.0006$). Therefore, the time to perform the second surgery was shorter for ALPPS than for TSH. In relation to postoperative results, ALPPS was associated with a higher incidence of major morbidity (relative risk 1.57, 95% confidence interval [CI]: 1.18–2.08, $p = 0.002$), overall morbidity (relative risk 1.39, 95% CI 1.07–1.8, $p = 0.01$) and mortality (relative risk 1.84, 95% CI 1.03–3.3, $p = 0.04$). However, due to the learning curve, mortality decreases in centers with high volume (4% in centers with $\geq 8$ procedures vs 13% in centers with $< 8$ procedures).

Long-term oncological results have been assessed only by a few authors. Most of them reported comparable OS. Only Adam et al. [67] described worse OS (median survival: 20 months for ALPPS vs 37 months for TSH, $p = 0.006$) but similar disease-free survival. In addition, recurrence-free survival was similar in studies that specifically reported this outcome [66]. Taking into account the reported increased mortality rate and similar oncologic outcomes, an adequate selection of patients is necessary to optimize the ALPPS results.

## Role of systemic treatment

In 2004, Adam et al. [68] published the rescue of 12.5% of patients with initially unresectable liver metastases (IULM) after treatment with chemotherapy, confirming previous data from Bismuth. Despite a high recurrence rate, the 5-year survival rate was 33%. Oxaliplatin-based chemotherapy was administered in 70% of cases [68]. The survival benefit obtained, which exceeds that of patients treated exclusively with chemotherapy, introduced the concept of conversion chemotherapy.

However, new questions arise, such as the definition of irresectability, the optimal time for re-evaluation and maximum response, the method of radiological evaluation, the optimal scheme of chemotherapy or the survival benefit of this strategy when faced with new targeted therapies.

Response to treatment should be closely monitored every 2 months to perform the resection as soon as the metastases become resectable, avoiding further progression or liver toxicity [69]. Since anti-angiogenic treatments have little influence on tumor size, criteria based on the morphological modifications of the lesions were described. These criteria were correlated with pathological response and OS [70].

Regarding the optimal treatment regimen, since resection rates are related to response rates (RRs) to treatment, we have to look for schemes with high RRs or with an important decrease in time to response. Folprecht et al. [55] showed a strong correlation between RRs and resection rates in patients with exclusively liver disease. This observation should be viewed with caution since the treatment schemes used in the analyzed studies were different.

Several studies showed R0-resection rates of 11–33% after doublets of chemotherapy with either irinotecan or oxaliplatin plus 5-fluorouracil. Subsequently, the combination of oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil (FOLFOXIRI) demonstrated benefits in RR, R0-resection rate, PFS and OS versus the combination of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) in a randomized study [71].

The current trend is to combine targeted therapies with chemotherapy to obtain the highest RR. Addition of antiEGFR to chemotherapy obtained a significant benefit in RRs and higher R0-resections rates in native RAS patients [72]. In the CELIM trial, the addition of cetuximab to FOLFOX-4 obtained a significant benefit in RRs and higher R0-resection rates in native KRAS patients [73]. Other studies show similar data [72]. The combination of cetuximab/panitumumab with a triplet of chemotherapy has also been studied. In the POCHE study, cetuximab + chrono-IFLO achieved a R0 resection rate of 60% in IULM patients [74]. In the PLANET trial, a randomized, open-label trial conducted in 77 untreated patients with (WT)-KRAS mCRC and multiple or unresectable liver-limited disease, patients received panitumumab–FOLFOX4 or panitumumab–FOLFIRI and the ORR was 74% with panitumumab–FOLFOX4 and 45% and 59% underwent surgical resection [75].

Regarding bevacizumab, a multicenter study showed a high RR in patients with IULM when combined with CAPOX, transforming 40% of cases into resectable [76]. In the TRIBE trial, FOLFOXIRI/bevacizumab had a benefit in PFS and RR compared to FOLFIRI/bevacizumab, without differences in R0-resection rates [77]. A subsequent analysis also showed survival benefit. In the OLIVIA study, bevacizumab/FOLFOXIRI was associated with a higher RR, resection rate and increase in PFS compared with bevacizumab/mFOLFOX6 (a dose modification of FOLFOX) [78].

Based on these findings, we can consider the combination of a doublet of chemotherapy combined with antibodies against EGFR in patients with RAS wild-type mCRC or the combination of FOLFOXIRI ± bevacizumab, the standard treatment options in this situation.

## Unresectable liver metastases

These patients could be defined as those with multiple and bilobar disease who avoid obtaining a R0 resection by maintaining an adequate FLR [20–25% of total liver volume as future liver remnant (FLR) with adequate inflow, outflow and biliary drainage]. Currently, there are no criteria that allow us to distinguish between those patients for whom purely palliative treatment and those for whom potentially curative treatment is appropriate. Due to the increasing efficacy of systemic drugs and agents, patients with CLM only must be considered definitively unresectable after receiving 2–4 months of optimal treatment, when the maximal tumor shrinkage is deemed to have occurred in most cases. Therefore, the opportunity for resection is not missed in patients who a priori have a low chance of further resection.

### Role of systemic therapy

These patients could be defined as those with multiple and bilobar disease, which prevents obtaining a R0 resection by maintaining adequate FLR. Due to the increasing efficacy of systemic therapy, patients with CRClm only must be considered definitively unresectable after receiving 2–4 months of optimal treatment.

The choice of a systemic treatment strategy is based on patient-related factors, the mutational profile of the tumor, and the differing toxicity profiles of the constituent drugs [14].

The chemotherapy options for the treatment of patients with metastatic CRC are typically a cytotoxic doublet such as FOLFOX, CAPOX or FOLFIRI or, in selected patients, the triplet FOLFOXIRI or fluoropyrimidine monotherapy in unfit patients.

All patients considered for systemic therapy should be stratified according to RAS and BRAF mutations [79].

*RAS wild-type* The combination of chemotherapy plus anti-EGFR therapy has shown benefit over exclusive chemotherapy. Bevacizumab is an anti-angiogenic drug with proven benefits in combination with chemotherapy [80, 81]. Two phase III studies have compared the combination of chemotherapy and anti-EGFR vs chemotherapy and bevacizumab with discordant results. The FIRE-3 trial compared FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in a first-line, KRAS exon 2 wild type [82]. This trial did not meet its primary endpoint of the investigator-read objective response rate. PFS was nearly identical between the arms, but a statistically significant improvement in OS was reported in the cetuximab arm (28.7 vs. 25.0 months). Updated analysis with all RAS mutations considered showed similar results. In the CALGB/SWOG 80,405 trial [83], comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, the primary endpoint of OS was equivalent between the arms (29.0 vs 29,9 months). Based on these data, the addition of anti-EGFR therapy or the addition of bevacizumab to chemotherapy are equivalent choices in the first-line, RAS wild-type, metastatic setting.

*RAS mutant* Bevacizumab has demonstrated its effectiveness independent of the state of RAS; therefore, the treatment of choice in these patients is the combination of chemotherapy plus bevacizumab in those who can tolerate an intensive treatment [84].

*BRAF mutant* Approximately 5–9% of colorectal cancers are characterized by a specific mutation in the BRAF gene (V600E). The evidence increasingly suggests that BRAF V600E mutation is associated with poor response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy [85]. Another option is the possibility of adding bevacizumab to FOLFOXIRI. The results of the phase III TRIBE trial showed that in the patients with BRAF mutation treated with FOLFOXIRI plus bevacizumab, the median OS was 19 months, the median PFS was 7.5 months, and the best response was 56%. Based on these data, FOLFOXIRI plus bevacizumab is recommended in patients with BRAF mutant [77].

*The role of primary tumor sidedness* The results of a retrospective pooled analysis of six trials (CRYSTAL, FIRE-3, CALGB 80,405, PRIME and PEAK in first line, and 20,050,181 in second line) on the prognostic and predictive value of primary tumor location (left- versus right-sided) for the treatment of patients with RAS wt mCRC with chemotherapy and EGFR antibody therapy have been published [86]. The individual trial data for the six trials showed that patients with left-sided tumors receiving chemotherapy plus EGFR antibody therapy had superior treatment outcomes in terms of overall survival, PFS and response rate compared to patients with right-sided tumors. A significant benefit ($p < 0.001$) of chemotherapy plus EGFR therapy was observed in patients with left-sided tumors for overall survival and PFS compared with no benefit in patients with right-sided tumors. Patients in the FIRE-3 and CALGB 80,405 first-line trials, with left-sided RAS wt, receiving chemotherapy plus EGFR antibody therapy, had significantly better treatment outcomes in terms of overall survival, PFS and response rate than those receiving chemotherapy plus Bev. Limited benefit was observed from EGFR antibody therapy in patients with right-sided tumors. Furthermore, individual patient data for patients with right-sided tumors from the FIRE-3 trial suggested that patients with

right-sided RAS wt tumors might benefit from chemotherapy plus bevacizumab compared with cetuximab in terms of overall survival but not ORR.

### Locoregional therapies

Locoregional treatment also plays a role in non-resectable patients [14, 36]. Recently, the CLOCC trial has marked a shift in the paradigm of percutaneous ablation in metastatic CRC. The goal is not necessarily to cure the patient. According to this study, radiofrequency or microwave ablation is not limited to patients with resectable tumors and may not be limited by the size of the metastatic nodule. After 7, 8 years of follow-up, in patients with advanced disease who obtained a reduction of the tumoral load by applying additional aggressive treatment consisting of local ablation plus systemic treatment, a beneficial effect was demonstrated clinically and was associated with a statistically significant improvement in overall survival [87]

Chemoembolization is also indicated in some non-resectable patients. Use of drug eluting beads, TACE with irinotecan (DEBIRI), is indicated as a third-line treatment when systemic chemotherapy has failed [88, 89]. Selective intra-arterial administration of irinotecan inside tumoral arteries, while the embolization limits drug washout, permits a higher and prolonged intratumoral dose of irinotecan and up to 70–75% lower plasma levels [90]. Current evidence for DEBIRI is mostly limited to the salvage setting. Two randomized controlled trials demonstrated an improved objective response rate (ORR) compared with FOLFOX and FOLFIRI [91, 92]. DEBIRI could provide an opportunity for some patients who need downstaging prior to surgery [93].

There is clinical evidence that the use of TARE is safe and well tolerated. TARE is indicated in third-line liver-dominant disease after chemotherapy or in combination with chemotherapy [94, 95]. The results obtained in different studies are homogenous with regards to ORR, which ranged between 24 and 41%, and OS, which ranged between 8 and 13 months [94–98]. The level of evidence of the clinical data obtained so far from more than 1,500 patients has led to the inclusion of 90Y microspheres in the 2016 ESMO Clinical Guidelines (recommendation 16) [14]. Regarding radioembolization within the therapeutic algorithm of metastatic CRC, it is not entirely clear. Kennedy et al. [97] evaluated the experience of 11 US centers and found median survival following radioembolization as a second-line, third-line, or fourth-plus line therapy of 13.0 (range, 10.5–14.6), 9.0 (range, 7.8–11.0), and 8.1 (range, 6.4–9.3) months, respectively. There are phase III trials, such as the TS-102 EPOCH, currently underway; in these studies, radioembolization associated with chemotherapy is included in the second line, which aims to clarify the ideal place for this therapy within the therapeutic algorithm.

Recent trials have been carried out to demonstrate the utility of TARE in first-line treatment associated with chemotherapy regimens. The results of phase III randomized controlled trials have recently been published. The combined study results represent the largest randomized analysis performed in the field of interventional oncology to address the question of whether improved local control of colorectal liver metastases impacts overall survival. Chemotherapy-naive patients were included and assigned to either oxaliplatin-based chemotherapy (FOLFOX: leucovorin, fluorouracil, and oxaliplatin) or FOLFOX plus single treatment TARE concurrent with cycle 1 or 2 of chemotherapy [95, 99].

Although PFS, as the primary endpoint, was not met, a prolonged liver PFS was demonstrated for the study arm (20.5 months for the FOLFOX/90Y arm vs 12,6 months for the chemotherapy only arm; hazard ratio 0,69; 95% CI, 0,55–0,90; $p = 0.002$). This difference was even greater in patients without extrahepatic disease (12.4 vs 21.1 months) [99, 100].

A post hoc analysis of data from these trials indicates that adding TARE to standard first-line mFOLFOX6 chemotherapy in patients with right-sided primary tumors led to a statistically significant and clinically meaningful 4.9-month median overall survival benefit (hazard ratio 0.64; 95% CI, 0.46–0.89; $p = 0.007$). This translates into a 36% reduction in the risk of death at any given time compared to patients who received chemotherapy alone [101]. To further define the role of TARE in metastatic colorectal cancer, careful patient selection, including the side of the primary tumor, and studies investigating the role of TARE as consolidation therapy after chemotherapy are needed.

In conclusion, locoregional therapies also play a role in unresectable CRClm. Ablation for the debulking of liver metastasis has demonstrated an increase in OS. TACE with irinotecan has demonstrated an RCT benefit in terms of OS, PFS and QoL. TARE is safe and well tolerated, and, according to 2016 ESMO Clinical Guidelines, is indicated as a third-line treatment for liver-dominant disease.

## Conclusions

Liver metastatic disease from colorectal cancer is a complex clinical situation that requires evaluation by a multidisciplinary team. The first step must be to clearly define if we are dealing with a resectable disease, if the tumor may be resectable after systemic treatment or if we are facing a non-resectable metastasis, and primary tumor management must be considered in cases of synchronous metastases. In addition to this evaluation, performance status of the patient must be assessed. Figures 1a and b show the proposed treatment algorithm.

The following aspects should be kept in mind:

- Surgical resection is the only curative treatment and the "gold standard" when resectable liver metastases are present in a fit patient
- In this setting, neoadjuvant chemotherapy might provide benefit in high-risk patients
- Neoadjuvant chemotherapy may initially turn unresectable liver metastases into resectable liver metastases with good long-term results. Percutaneous transhepatic portal vein embolization, two-stage hepatectomy and ALPPS are useful surgical techniques to achieve R0 resections.
- Systemic chemotherapy is the standard of care for patients with non-resectable disease. The choice of a systemic treatment strategy is based on patient-related factors, the mutational profile of the tumor, and the differing toxicity profiles of the constituent drugs.
- Ablative treatments (RF, MW ablation, cryoablation, and SBRT) are good alternatives for patients who have technically resectable disease, but the metastases are inoperable due to poor clinical conditions or comorbidities.
- TARE, TACE, and ablative treatments may play a role in the palliative setting for patients with CRClm.

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## Compliance with ethical standards

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