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REVIEW ARTICLE

Managing Synchronous Liver Metastases in Colorectal Cancer

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Abstract

The most common site of blood-borne metastases from colorectal cancers (CRC) is the liver. Resection of (liver) metastases is a part of standard treatment of metastatic colorectal cancer. Hepatic resection is the first-line treatment of liver metastases, with 5-year survival rates between 25 and 58%. The enhanced efficacy of systemic chemotherapeutic regimens has increased tumor response rates and improved the progression-free and overall survival of patients with these malignancies. In approximately 20% of patients with initially unresectable liver metastases, the metastases may become resectable after administration of neoadjuvant chemotherapy. Unresectable liver metastases can be managed with systemic therapy and/or a variety of liver-directed techniques such as radiofrequency ablation, hepatic artery infusion, or yttrium-90 radioembolization. Our examination of the literature led us to propose a new patient-oriented algorithm to guide clinicians' decisions on the best choice of upfront therapy for CRC and synchronous liver metastases. The need for multidisciplinary consensus has become especially important for metastatic CRC.

Keywords Colorectal cancer · Synchronous liver metastases · Surgery · Systemic therapy

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the USA and is the second leading cause of cancer-related mortality. The liver is the most common site of distant metastases. Gastrointestinal tract tumors metastasize to the liver via the portal vein and tumors elsewhere via the hepatic artery. Between the early 1990s and 2009, the median survival for patients with liver metastases increased from 10 months to 2 years. This increase is largely secondary to the use of newer chemotherapeutic regimens combined with biological therapies and aggressive surgery. When colorectal metastases are isolated in the liver, surgical resection affords an opportunity for cure, yielding 5-year survival rates from 20 to 50% [1]. Synchronous metastases were defined as metastases detected by pre-operative screening or during resection of the primary tumor [2–4], and occurring within 3 or 6 months [5–7] of the initial diagnosis of CRC. Approximately 20% of patients with CRC have metastatic disease at the time of diagnosis [8]. Metachronous lesions will develop in another 25%. Some authors have suggested that the presence of synchronous lesions predicts a worse outcome than for patients in whom metastases develop at a later date [9, 10]. In recent years, the eligibility criteria for liver resection have been expanded to include patients not previously deemed to be surgical candidates [11]. For patients with colorectal liver metastases, the treatment strategy necessitates attention to (1) the extent of the tumor and (2) the quality and volume of the anticipated remnant liver after negative margins are achieved (Table 1). LiverMetSurvey (http://www.livermetsurvey.org/) is an international database that prospectively collects clinical and pathological data of patients undergoing surgery for colorectal liver metastases [12–14]. This registry includes the results of surgical treated patients, duration and effects of preoperative treatment, location and treatment of recurrence, and the post-operative and long-term outcome. This review will focus on treatments unique to the treatment of isolated liver metastases. The interplay of surgical therapy, liver-directed therapy, and systemic therapy in patients with colorectal cancer will be emphasized.

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Table 1 Summary of the evolving indications for surgical resection of liver metastases

Characteristics	Current approach	Comments
Does the number of tumors matter?	Any	The number of liver metastases is less important than obtaining an R0 resection
Does tumor size matter?	Any	Large tumor size alone should not be considered a factor in the resectability of liver metastases
Does the surgical margin matter?	R0 or radiofrequency ablation for R1	
Is extrahepatic disease a contraindication to liver resection?	Treatable extrahepatic disease	Resectable extrahepatic disease is not an absolute contraindication to resection
Future liver remnant	Adequate remnant liver	R0 resection possible only with complex procedure (portal vein embolization (PVE) used to induce compensatory hypertrophy in the future liver remnant, two-stage hepatectomy, hepatectomy combined with radiofrequency ablation)
Lymph nodes	In absence of celiac axis metastases, hepatic pedicle lymph node metastases may be resected	
Venous involvement	Caval/hepatic vein resection with reconstruction can be performed	

Patient Scenario 1: Patients with Resectable Liver Metastases and Asymptomatic CRC

This patient represents the most favorable clinical scenario seen in the metastatic colorectal cancer today (Fig. 1). In the setting of resectable liver metastases, neoadjuvant chemotherapy can be administered as a means of identifying patients most likely to benefit from surgical resection. The routine use of neoadjuvant chemotherapy (administered prior to operative therapy) offers several theoretical advantages. The theoretical advantages include eliminating micrometastatic disease, in vivo cytoreduction to reduce the amount of hepatic parenchyma required for complete resection, the ability to individualize the chemotherapeutic efficacy, and most importantly, to select patients who may benefit from metastasectomy. The European Organization for Research and Treatment of Cancer (EORTC) 40,983 randomized trial comparing patients treated with surgical resection alone versus surgical resection with perioperative (i.e., three cycles preoperatively and three cycles postoperatively) FOLFOX (folinic acid, fluorouracil, and oxaliplatin) chemotherapy showed a significant improvement in progression-free survival (PFS) in patients with resectable hepatic CRC metastases. Postoperative complications were more frequent in the chemotherapy group, although they were reversible and there was no increase in mortality [15]. Five-year overall survival (OS) was not significantly better in the chemotherapy group (51 vs. 48%, HR for death 0.88, 95% CI 0.68–1.14).

Bevacizumab, a recombinant monoclonal antibody that blocks the activity of vascular endothelial growth factor A, has proved of benefit in extending survival in patients with metastatic disease [16] and is frequently added to the FOLFOX and FOLFIRI (infusional FU-based irinotecan) regimens. Nasti et al. reported the results of a single-center, phase II study designed to assess the feasibility and activity of bevacizumab plus FOLFIRI as neoadjuvant treatment of resectable liver-confined metastases from CRC. This study suggests that a neoadjuvant treatment with an irinotecan-based chemotherapy and bevacizumab is feasible and potentially active for patients with initially resectable liver metastases from CRC, but further clinical trials are needed to define whether such a treatment may be considered a reasonable

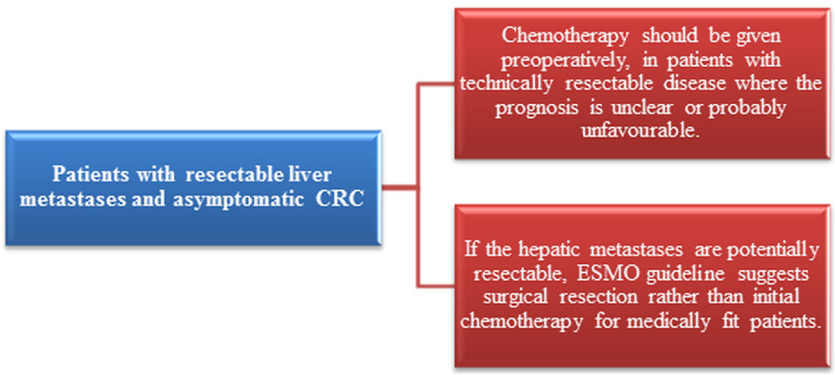

Fig. 1 Management of patients with resectable liver metastases and asymptomatic CRC

option in clinical practice [17]. The addition of bevacizumab to 5FU/LV or capecitabine, irinotecan and oxaliplatin (FOLFOXIRI) appeared to further improve the pathologic response and degree of necrosis compared to regimens that do not include bevacizumab. However, it still does not help us select the most suitable patient group for this aggressive approach [18]. Cetuximab is a chimeric IgG1 monoclonal antibody that recognizes and binds to the extracellular domain of the epidermal growth factor receptor (EGFR). Panitumumab is a fully human IgG2 monoclonal antibody that also targets the EGFR. Both cetuximab and panitumumab are only effective in the subset of patients whose tumors have wild-type (WT) and not mutated RAS (NRAS, KRAS) oncogenes (approximately 40% of all mCRCs). The British "New EPOC" trial randomly selected patients with liver metastases to receive perioperative chemotherapy with or without the EGFR-antibody cetuximab. PFS and OS were worse with the addition of cetuximab [19]. An analysis of a multi-centric cohort from the LiverMetSurvey International Registry, who had undergone curative resections for synchronous colorectal liver metastasis, was undertaken. Patients who received neo-adjuvant chemotherapy prior to liver surgery ($n = 693$) were compared with those treated by surgery alone ($n = 608$). The use of neo-adjuvant chemotherapy in resectable synchronous liver metastasis was demonstrated no survival advantage in this study [20].

Hepatoxicity is very problematic for patients who require major hepatic resections, because they will require significant hepatic regeneration. Chemotherapy-induced hepatotoxicity can be broadly categorized into two main types: steatohepatitis and sinusoidal injury. Steatohepatitis is seen in 30 to 47% of patients treated with fluorouracil and in 12 to 25% of patients treated with irinotecan. Sinusoidal injury occurs in 19 to 78% of patients treated with oxaliplatin [21]. The rare, but potentially lethal, side effects of bevacizumab include hypertension, increased risk of arterial thromboembolism, gastrointestinal bleeding, and perforation [22]. Its antiangiogenic effects and long circulating half-life (approximately 6 to 8 weeks) have been associated with delayed wound healing. Most physicians interrupt bevacizumab therapy at least 4 to 6 weeks before surgical metastasectomy [23].

Currently, no definitive evidence supports routine use of preoperative chemotherapy for resectable colorectal liver metastases. At the university of Texas M.D. Anderson Cancer Center patients with resectable colorectal cancer, liver metastases receive 2 to 3 months of chemotherapy before resection. So, it remains uncertain whether there is a benefit from neo-adjuvant chemotherapy treatment compared with initial resection for patients seen with potential resectable CRC liver metastases and the decision is often made on a case-by-case basis. NCCN guidelines suggest FOLFOX or FOLFIRI or XELOX with or without bevacizumab, or FOLFIRI with or without cetuximab or panitumumab, or FOLFOX with or without panitumumab or cetuximab (if RAS wild type). Updated consensus-based 2016 guidelines from the European Society for Medical Oncology (ESMO) suggest FOLFOX or XELOX in this setting [24] (Fig. 1).

Patient Scenario 2: Patients with Non-resectable Liver Metastases and Asymptomatic CRC

This scenario is commonly encountered in our daily practice (Fig. 2). The term "conversion therapy" has been proposed to designate the use of induction chemotherapy in patients with isolated but initially unresectable CRC liver metastases [25].

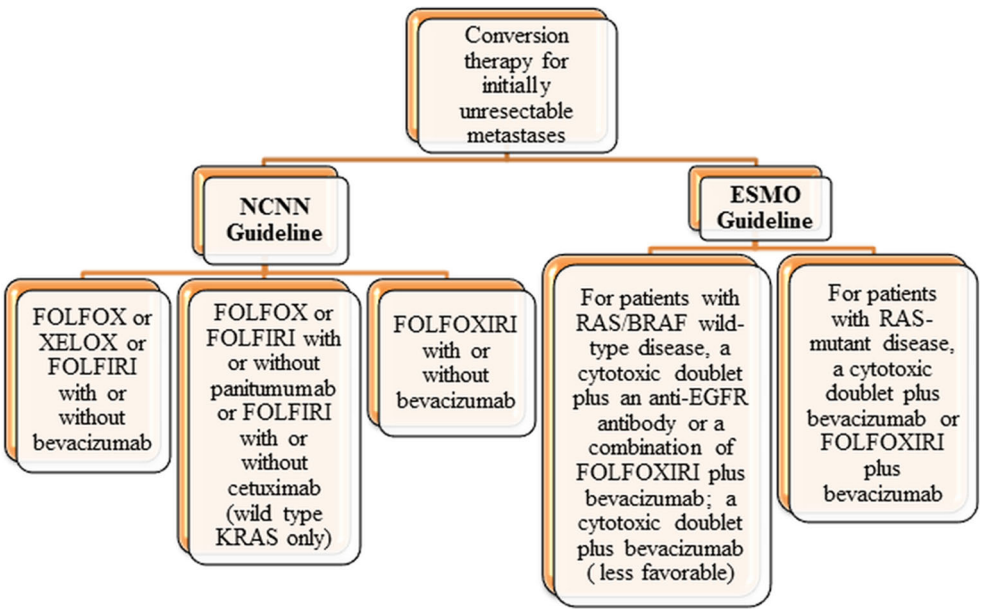

Fig. 2 Management of patients with non-resectable liver metastases and asymptomatic CRC

Conversion therapy does have the advantage of downstaging borderline resectable patients who achieve a partial response with therapy allowing them to undergo surgery with a higher likelihood of an R0 resection [26]. For patients with metastases isolated to the liver that initially are deemed anatomically unresectable, induction chemotherapy permits complete resection by shrinking tumors in 12.5 to 30% of patients [26–30]. In patients with initially unresectable colorectal liver metastases who then undergo resection, the survival rate at 5 years (30 to 35%) approaches the survival rate of patients who undergo upfront hepatic resection for initially resectable disease [29, 30]. The randomized phase II CELIM trial of cetuximab in combination with either an irinotecan or oxaliplatin-based regimen showed a high resectability rate of 34% in patients wild-type K-RAS tumors [27]. Two randomized trials, the CRYSTAL (cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer) and OPUS (oxaliplatin and cetuximab in first-line treatment of metastatic CRC) trials, showed modestly improved resection rates from 3.7 to 7%, and from 2.4 to 4.7%, respectively, with the addition of cetuximab to an irinotecan or oxaliplatin-based regimen [31, 32]. In Chinese trial in which 138 patients with KRAS exon 2 wild-type liver-limited disease were randomly assigned chemotherapy (FOLFIRI or mFOLFOX6) with or without cetuximab. The cetuximab combination yielded a high complete resectable rate (25.7%) compared with that in the chemotherapy-alone cohort (7.4%) [33].

A double-blinded randomized controlled trial of 1401 patients with metastatic colorectal cancer that evaluated the benefit of adding bevacizumab to the capecitabine plus oxaliplatin or FOLFOX regimen demonstrated no survival benefit to the addition of bevacizumab [34].

Three randomized studies comprising 2014 participants were included in the meta-analysis (Table 2) [35–38]. Meta-analysis of randomized clinical trials comparing first-line anti-EGFR therapy with anti-VEGF therapy in advanced colorectal cancer indicates better response rates and OS with anti-EGFR therapy but no difference in PFS [38]. Moreover, data from the FIRE-3 [35] and CALGB [37] studies show that a cytotoxic doublet plus cetuximab in RAS wild-type patients is associated with higher response rate compared with bevacizumab, although this did not translate into higher resection rates in either of these studies.

On the basis of the capacity to induce tumor shrinkage, the FOLFOXIRI (folinic acid, FU, oxaliplatin, and irinotecan) triplet regimen has been regarded as an active regimen that should be downsize initially unresectable metastases to resectable proportions. The smaller randomized phase II OLIVIA trial, which enrolled 80 patients with initially unresectable liver metastases from CRC, did note a significantly higher R0 resection rate with bevacizumab plus FOLFOXIRI compared with bevacizumab plus modified FOLFOX-6 (49 vs. 23%) [39]. In the phase III TRIBE trial, which compared bevacizumab plus either FOLFOXIRI or FOLFIRI in 508 patients with unresectable mCRC, the secondary resection rate was not significantly different between treatment arms (15 vs. 12%) [40]. On the other hand, in the GONO trial [41], the triplet chemotherapy regimen was associated with an increase in the radical resection rate and provided a substantial benefit in terms of relapse-free survival, which might have contributed to the OS benefit observed. French phase II, multicenter, prospective trial randomized patients between bi-chemotherapy (FOLFIRI [56 patients]; FOLFOX4 [70 patients]) versus tri-chemotherapy (FOLFIRINOX [130 patients]). The population was initially stratified by targeted therapy depending on KRAS status and then by RAS status (from 02 December 2013 due to the change in cetuximab's marketing authorization): Cetuximab for wt (K) RAS patients and bevacizumab for mutant RAS patients [42]. First-line FOLFIRINOX chemotherapy, in association with a targeted therapy, showed a higher rate of liver metastases R0/

Table 2 Summary of randomized phase II/III studies comparing first-line anti-EGFR versus anti-VEGF antibodies in combination with chemotherapy for the treatment of advanced colorectal cancer

	RAS-WT		
	n	OS	ORR
FIRE-3 (*n* = 592 [35]			
FOLFIRI-cetuximab	205	33.1 months	65%
FOLFIRI-bevacizumab	202	25.6 months	60%
P value		P = .011	P = 0.032
PEAK (*n* = 285) [36]			
FOLFOX-panitumumab	88	41.3 months	63.6%
FOLFOX-bevacizumab	82	28.9 months	60.5%
P value		P = .058	–
CALGB/SWOG 80405 (*n* = 526) [37]			
Cetuximab + FOLFIRI or FOLFOX-6	270	32.0 months	68.8%
Bevacizumab + FOLFIRI or FOLFOX-6	256	31.2 months	56%
P value		P = .40	P < .01

R1 resections than standard FOLFIRI or FOLFOX4 combined with the same targeted therapy. In a study, 5624 and 791 consecutive patients of a prospective international cohort received one and two preoperative chemotherapy lines before colorectal liver metastases resection (group 1 and 2, respectively). Colorectal liver resection following second-line preoperative chemotherapy, after oncosurgically favorable selection, could bring similar OS compared to what observed after first-line. This study propose liver surgery on the patients whose liver metastases are sufficiently downsized to envisage resection, not only after front-line but also after active salvage chemotherapy [43].

Is surgery really helpful in patients with advanced colorectal liver metastases who respond to chemotherapy? A recent analysis from the MD Andersen Cancer Center compared patients with extensive tumor burden who exhibited a radiographic response to systemic chemotherapy. After controlling for a number of relevant patients and tumor characteristics, patients who underwent hepatic metastasectomy had significantly improved survival compared with patients who underwent only chemotherapy for advanced colorectal liver metastasis (67 vs. 41% 3-year overall survival rate and 51 vs. 15% 5-year overall survival rate; $P = .005$) [44]. Studies investigating long-term outcomes in patients with colorectal cancer and initially unresectable liver metastases who underwent neoadjuvant chemotherapy demonstrate that 12.5 to 47% of patients proceeded to surgical resection with a 23 to 33% 10-year survival rate [45].

In practice, the decision to pursue surgical resection of an asymptomatic primary site is based upon the curability of metastatic disease. The decision as to whether to resect the primary tumor is more complex for asymptomatic patients who have unresectable metastatic disease; in such patients, the risk to benefit ratio of resecting the primary tumor must be carefully considered. The NSABP C-10 trial prospectively addressed this question, treating 90 patients with unresectable stage IV disease and intact, asymptomatic primary tumors with initial medical management with FOLFOX-6 plus bevacizumab. The cumulative incidence of major morbidity was 16.3%, and only 10 of the 86 enrolled patients (12%) required surgery (eight for obstruction, one for perforation, and one for pain). This study met its prespecified end points for acceptability of initial nonoperative management, and the investigators concluded that good performance status patients with asymptomatic primaries can be spared initial noncurative resection of their primaries [46]. Survival did not appear to be compromised by leaving the primary tumor intact (median OS 19.9 months). Our study utilizing chemotherapy with bevacizumab did not result in an increased rate of morbidity related to the unresected primary tumor. Survival is not compromised by leaving the primary colon tumor intact [47]. A pooled analysis of individual data from four randomized trials of first-line chemotherapy in patients with non-resectable stage IV CRC strongly suggests that a history of resection of the primary tumor is independently associated with an important OS benefit [48].

A recent study by Hu et al. showed that the relative survival rate of patients presenting with stage IV CRC improved over time, as the primary tumor resection rate decreased [49]. Those authors therefore suggested that primary tumor resection may be overused. Tarantino and co-authors [50] recently contributed to this discussion by reporting the largest observational study conducted to date. Overall, 37,793 stage IV colorectal cancer patients were identified. Of those, 23,004 (60.9%) underwent palliative primary tumor resection. On the basis of this population-based cohort of stage IV colorectal cancer patients, palliative primary tumor resection was associated with improved overall and cancer-specific survival.

The optimal timing for surgical resection in patients with synchronous colorectal liver metastases is poorly defined (Fig. 3). Some patients (the minority) are eligible for a combined resection, and others may be treated with the more traditional approach involving initial resection of the primary followed by a second operation directed at the liver**.** Major liver resection is generally defined as the removal of three or more contiguous liver segments. Extended resection is defined as resection of a hemiliver with extension to include one or more segments of the contralateral liver. Liver resections can also be stratified as anatomic (removing one or several liver segments) or atypical (wedge) resections. While

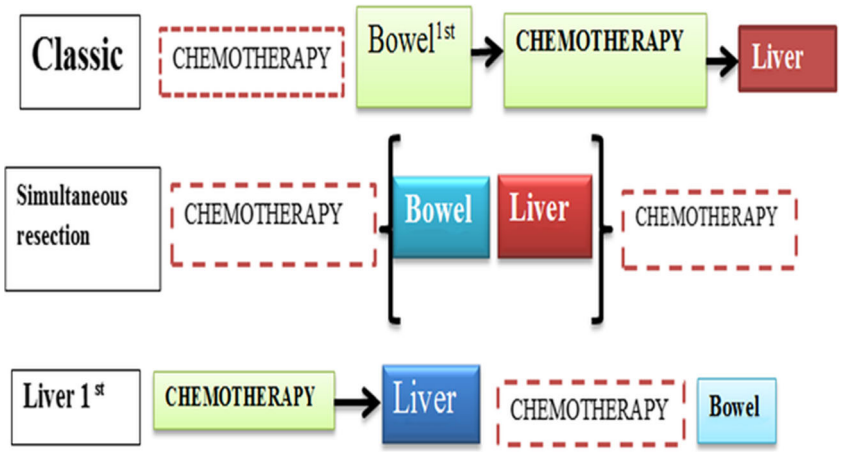

Fig. 3 Which procedure first? Liver first, bowel first, or simultaneous resection

small, superficial lesions, particularly metastatic tumors, may be resected with non-anatomical or wedge resections, larger and/or multiple lesions typically require major resections. Although simultaneous resection of the primary and liver metastases results is clearly more desirable from the patient's perspective, the increased morbidity and mortality associated with a simultaneous approach may outweigh the potential. In a series of 610 patients who underwent simultaneous ($n = 135$) or staged ($n = 475$) liver resection for colorectal liver metastases, Reddy et al. [51] reported that the extent of hepatic resection was an important factor for both severe morbidity and mortality. Mortality (1.0 vs. 0.5%) and severe morbidity (14.1 vs. 12.5%) were similar after simultaneous colorectal resection and minor hepatectomy compared with isolated minor hepatectomy (both $P > 0.05$). However, for patients requiring major hepatic resection, those with simultaneous resections had increased overall morbidity (44 vs. 27%), severe morbidity (36.1 vs. 15.1%), and mortality (8.3 vs.1.4%) [51]. Mentha et al. [52] designed a management strategy that involves chemotherapy first, resection of liver metastases second, and finally, removal of the primary tumor in those patients with advanced synchronous liver metastases from colorectal cancer.

This new strategy produced resectability and survival rates better than those expected from the published data on patients with disease of similar severity. The results of this preliminary experience now need to be confirmed in a larger cohort of patients. For patients who present with synchronous metastatic disease and a symptomatic primary tumor (obstruction, bleeding, perforation), resection of the primary tumor is warranted. Simultaneous resection of the primary and metastatic disease is a reasonable option for patients who present with low-volume (four or fewer, less than three segments involved, or all in the same lobe) resectable hepatic metastases.

Patient Scenario 3: Patients with Non-resectable Liver Metastases and Symptomatic CRC

CRC patients with synchronous metastases may present with a variable degree of symptoms of their primary tumor, and a palliative resection of the primary tumor prior to the initiation of systemic treatment might be required in some, if not all, circumstances [53–55]. In general, patients with a perforated tumor need surgery, while for those with bleeding or obstruction, decisions regarding surgery are dependent upon the clinical situation. However, surgical intervention can also be associated with high postoperative morbidity and mortality. Temple et al. [56] reviewed the linked SEER-Medicare databases and found that of 9011 elderly patients presenting with synchronous stage IV disease, that 72% had undergone resection of the primary, and that the 30-day mortality for these resections was 10%. In summary, recommendations are for resection of a primary tumor for bleeding, obstruction, and perforation, followed by chemotherapy and then surgery of liver metastases.

Patient Scenario 4: Management of Unresectable Liver Metastases

Unfortunately, most patients with metastatic CRC are not candidates for surgical resection. There are several nonsurgical treatment options for patients with liver-isolated CRC metastases who are not candidates for potentially curative resection. The approach to unresectable liver metastases includes systemic chemotherapy, hepatic-directed therapy, and local ablation techniques. For patients with locally treatable metastases, no head-to-head comparisons have been made between local and systemic therapy. Guidelines from the NCCN suggest that any of the following regimens are appropriate: (1) FOLFOX or XELOX or FOLFIRI with or without bevacizumab, (2) FOLFOX or FOLFIRI with or without panitumumab or FOLFIRI with or without cetuximab (wild-type KRAS only), (3) FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan) with or without bevacizumab, (4) infusional 5-FU/LV (5-fluorouracil/leucovorin), (5) capecitabine.

Radiofrequency ablation (RFA) can be performed intraoperatively during open or laparoscopic procedures, or percutaneously in a nonoperative setting. Response rates are higher when tumors are less than 5 cm in diameter and less than 3 in number. Although hepatic resection is currently the gold standard for resectable liver tumors, some retrospective studies suggest that RFA can confer similar disease-free survival in carefully selected patients who have small tumors. There are no randomized prospective trials in patients with potentially resectable liver metastases, comparing RFA with hepatic resection with or without postoperative chemotherapy treatment. Currently, the only randomized controlled trial assigned unresectable tumors to chemotherapy plus local ablation versus chemotherapy alone [57]. PFS rate at 3 years was 27.6% for combined treatment versus 10.6% for systemic treatment only ($P = 0.025$). Median PFS rate was 16.8 months (95% confidence interval [CI] 11.7 to 22.1) for combined treatment versus 9.9 months (95% CI 9.3 to 13.7) for systemic treatment only. However, in a later analysis of 10-year overall survival results presented at the 2015 annual American Society of Clinical Oncology (ASCO) meeting, patients randomly assigned to RFA in conjunction with chemotherapy had a significantly longer median OS (45.6 vs. 40.5 months), and 8-year overall survival (36 vs. 9%; HR 0.58, 95% CI 0.33–0.88) [57]. For the first time in the literature, randomized data show an improvement in overall survival with local therapy over systemic treatment alone for CRC liver metastases.

Hepatic metastases preferentially derive their perfusion from the hepatic arterial circulation. Hepatic artery infusion

(HAI) was developed to target chemotherapy directly to liver metastases via a port or pump placed directly into the hepatic artery at the time of surgical resection. Use of HAI has been associated with favorable response rates when used in patients who have been refractory to contemporary chemotherapy, suggesting that there is likely to be a role for this modality of treatment [58, 59]. Of the improvements in systemic therapy, which yields enhanced response rates and improved survival, the role of HAI in the management of CRC hepatic metastases remains unclear and has not been embraced by most medical oncologists. National guidelines from NCCN suggest that HAI with or without systemic therapy be considered in selected patients at institutions with extensive experience in HAI [60].

An alternative means of delivering focal radiation employ radioactive isotopes (e.g., 131-labeled-lipiodol or yttrium-90 [90Y]-tagged glass or resin microspheres) that are delivered selectively to the tumor via the hepatic artery. The 90Y microspheres deliver high doses of radiation to liver metastases while sparing normal liver parenchyma. A prospective randomized phase 3 trial of 44 patients with unresectable colorectal liver metastases who did not respond to chemotherapy underwent systemic administration of fluorouracil or systemic administration of fluorouracil plus 90Y radioembolization. Radioembolization was well tolerated in conjunction with infusional FU, and it significantly improved time to liver progression (5.5 vs. 2.1 months). Although there was no significant difference in objective response rate (10 vs. 0%), there was a significant difference in overall disease control rate (partial response plus stable disease, 86 vs. 35%) [61]. SIRFLOX was a randomized, multicenter trial designed to assess the efficacy and safety of adding radioembolization using yttrium-90 resin microspheres to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)-based chemotherapy in patients with previously untreated liver isolated or liver-dominant CRC liver metastases. Five hundred and thirty patients were randomly assigned to treatment (mFOLFOX6, $n = 263$; mFOLFOX6 plus radioembolization, $n = 267$). There was no significant improvement in the median overall progression-free survival with the addition of SIR-Spheres (10.7 vs. 10.2 months), but there was a significantly longer median duration of liver progression-free survival in a competing risk analysis (20.5 vs. 12.6 months, HR 0.69, 95% CI 0.55–0.90) [62]. Objective response rate (ORR) in the liver was improved with the addition of radioembolization (68.8 vs. 78.7% in control vs. SIRT; $P = .042$). There was no significant improvement in the rate of subsequent liver resection in the SIRFLOX group (14% in both groups). The true value of this approach should be clarified when the results of two additional studies (FOXFIRE and FOXFIRE Global) are reported [63, 64]. Today, radioembolization should not be considered a standard first-line therapy.

Patient Scenario 5: Synchronous Rectal Primary and Metastases

The use of pelvic radiotherapy in patients with synchronous presentation of primary and metastatic disease is controversial. No firm guidelines can be made in the management of

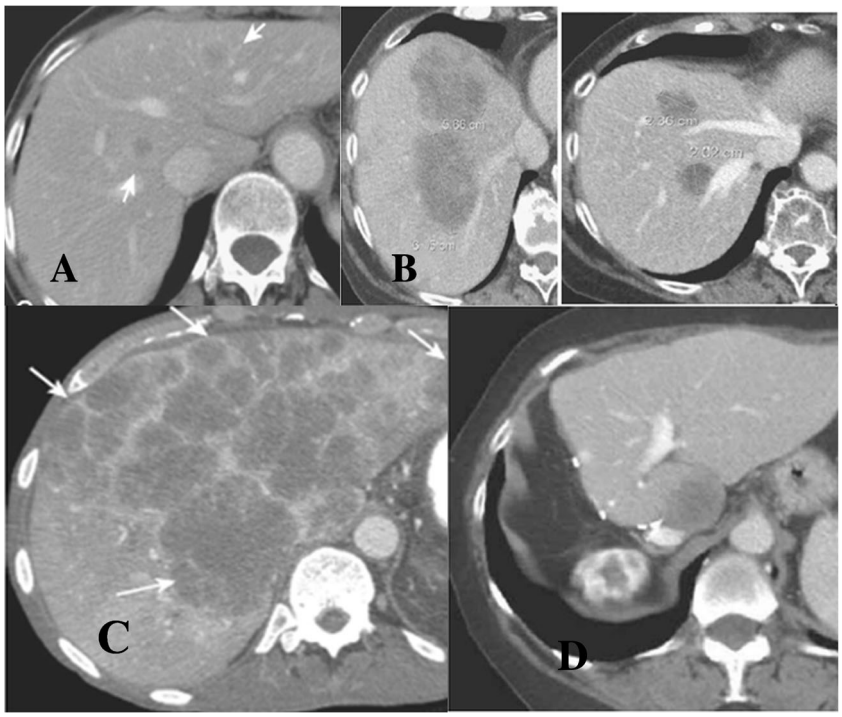

Fig. 4 **a** Liver metastasis from colon cancer. Contrast CT demonstrates two hypodense nodules (arrows). **b** Partial response-RECIST.CT-scan after chemotherapy and 3-month follow-up scan. **c** A 55-year-old man with colon cancer. Contrast-enhanced CT scan shows multiple solid lesions. **d** Patient had undergone a prior right hepatectomy for metastatic colon cancer 2 years ago

these complex patients, and treatment decisions must be made on an individual basis. Approaches to these patients have included adjuvant or neoadjuvant systemic chemotherapy alone combined with resection, preoperative chemotherapy followed by short-course RT and resection, or perioperative chemoradiotherapy conventional fractionation RT followed by resection of both the primary tumor and the metastases [65–69]. In "potentially resectable disease," treatment of the primary rectal tumor per se consists of surgery after a short course of radiotherapy or radiochemotherapy. However, complications in rectal surgery are not uncommon after chemoradiation, and it may take more than 6 months to start adequate metastatic therapy. Because the liver metastases define the prognosis of the patient, it seems reasonable to treat the hepatic metastases first.

For patients with a symptomatic rectal primary tumor and synchronous, unresectable metastatic disease, creation of a diverting stoma or palliative resection is often carried out before initiation of systemic chemotherapy. RT with modern combination systemic chemotherapy may allow selected patients to avoid surgery, even those with a nearly obstructing lesion. Forty patients with symptomatic primary rectal adenocarcinoma and synchronous distant metastases deemed to be unresectable received 5×5 Gy irradiation and then oxaliplatin-based chemotherapy. Only eight patients (20%) required surgery during the course of their disease [70].

Chemotherapy After Resection

Adjuvant chemotherapy has been shown to decrease the risk of recurrence and improve survival for patients with stage III colorectal adenocarcinoma. For this reason, it seems sensible to use systemic treatment after hepatic resection. EORTC assessed the combination of perioperative chemotherapy and surgery compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer. Three hundred and sixty-four patients with histologically proven colorectal cancer and up to four liver metastases were randomly assigned to either six cycles of FOLFOX4 before and six cycles after surgery or to surgery alone (182 in perioperative chemotherapy group vs. 182 in surgery group). When restricted to eligible patients who underwent surgical resection, the patients demonstrated improved 3-year PFS [15]. A multicenter study of 321 patients undergoing complete resection with liver isolated metastatic disease was randomly assigned to receive short-term infusional FU plus LV or FOLFIRI [71]. No difference was demonstrated in the median disease-free survival between patients treated with irinotecan and patients not treated with irinotecan (25 vs. 22 months, respectively). The benefit of cetuximab was addressed in a new EPOC study evaluating perioperative oxaliplatin plus a fluoropyrimidine chemotherapy with or without cetuximab in patients with initially resectable liver metastases. The addition of cetuximab was associated with significantly worse PFS (14.1 vs. 20.5 months) [19]. At present, the use of cetuximab in this setting cannot be recommended.

Treatment of Recurrent Disease

Recurrent metastases are isolated to the liver in 35 to 40% of patients. In patients with isolated recurrences in the liver, re-resection is often an option. Repeated hepatectomy for recurrent metastatic CRC can also achieve 5-year survival rates as high as 34% [72]. One third of patients with hepatic recurrences are often eligible for re-resection [73]. In several reported series, perioperative mortality rates were less than 5%.

Conclusions

Resection is the current standard of care for patients with limited metastatic disease from colorectal cancer, and combined treatment has resulted in improved survival rates (Fig. 4). The treatment of hepatic malignancies, particularly in patients with colorectal cancer liver metastases, requires a multidisciplinary approach that includes not only the surgeon but also the medical oncologist. Major advances in chemotherapeutics and surgical techniques have revolutionized the current approach to colorectal cancer liver metastases. As a result, many more patients are now eligible for curative-intent surgery.

Compliance with Ethical Standards

Conflict of Interest All authors have no conflict of interest.

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