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SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Current Status of Biologics in Perioperative Treatment for Resectable or Borderline Resectable Liver Metastases

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Abstract

Purpose of Review This review provides an overview of the current role of biologics, anti-vascular endothelial growth factor (VEGF) inhibitors and anti-epidermal growth factor receptor (EGFR) inhibitors, in the perioperative treatment of colorectal liver metastases as well as a discussion of their future trends.

Recent Findings Over the past decade, a number of clinical trials have suggested that the use of biologics with cytotoxic agents may increase median overall survival in certain subsets of patients with colorectal liver metastases. The benefit of these agents is limited to borderline resectable and unresectable hepatic metastases and is not seen in upfront resectable disease. In the RAS wild-type population, the difference in efficacy of VEGF and EGFR inhibitors in combination with chemotherapy is minimal. These agents perform differently depending on primary tumor location; bevacizumab has greater efficacy in right-sided tumors, whereas cetuximab has greater efficacy in left-sided tumors. While biologics benefit patients in the neoadjuvant setting, studies have not shown similar results in the adjuvant setting.

Summary Given the variability of patient presentations as well as the risk of treatment-related toxicity, the addition of biologics requires careful consideration of patient's medical fitness, surgical risk, and tumor profile.

Keywords Colorectal cancer · Liver metastases · Metastasectomy · Bevacizumab · Cetuximab

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and impacts 1.2 million patients each year. As many as 25–30% of patients with CRC eventually develop hepatic metastases [1]; some of these with liver-only metastases. Liver resection for colorectal liver metastases is widely accepted as the cornerstone of treatment for these patients, and it can potentially be curable; indeed, it drives much of the improved outcomes for patients with metastatic CRC that have been seen over the past decade. Liver resection can achieve promising 5-year survival rates of 40–60%, compared to only about 5% for patients who undergo palliative intent [2], and there may be a proportion of patients who are cured of their disease [3]. However, only about 25% of patients are initially amenable to hepatic resection [4]. Thus, much focus has been placed on innovative medical and regional approaches to increase the number of patients who could benefit from hepatic resection and improve the outcome of those patients. Here we review the selection of patients for liver resection, provide an overview of perioperative chemotherapy for patients undergoing liver metastasis resection, and focus on the role of biologic agents in the perioperative setting.

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Background

Evolving Definition of Resectability

Traditionally, liver resection was limited to a select group of patients; however, that paradigm has changed in the recent era. Based on data from the 1970–1980s, Ekberg et al. initially proposed that resection of colorectal liver metastases should

be limited to patients with less than four intrahepatic metastatic lesions, no extrahepatic metastatic disease, and the ability to achieve a resection margin of at least 10mm. Since then, what is considered resectable has expanded significantly as surgical techniques improved and systemic therapies have been incorporated [5]. Currently, there is no universally accepted definition of resectability in liver metastases. Classically recognized independent risk factors include tumor number, tumor size, bilobar involvement, and status of resection margin. While scoring systems have been developed, the hepato-pancreato-biliary expert consensus statement of 2012 suggests determining resectability based on appropriate medical fitness, oncologic factors, and technical aspects [6].

Comorbidities, age, and general health fitness should be taken into account when selecting patients for liver resection. For older patients, postoperative complications occur at about the same rate as compared to younger patients (19.7 vs. 23.3% respectively), but the overall 5-year survival rate of patients with advanced age is significantly lower [7]. The impact of comorbidities such as obesity have also been evaluated in patients undergoing hepatectomies. Overall morbidity has been found to be greater in obese patients [8]. Thus, all patients considering hepatic resection should undergo careful preoperative evaluation.

Oncologic factors determining aggressive tumor biology should be evaluated before deciding to embark on liver resection. Extrahepatic disease is often thought of as one marker of tumor biology. The presence of extrahepatic disease indicates a worse overall 5-year survival for patients undergoing hepatic resection compared to patients without extrahepatic disease (34 vs. 20%, p= 0.005) [9]. Progressive disease (pathologically or radiographically) in response to neoadjuvant chemotherapy likewise is another surrogate marker of aggressive tumor biology. Morphologic changes assessed according to the tumor-liver interface and attenuation on CT scans, in response to preoperative chemotherapy, were a strong predictor of 5-year survival rates after surgery. Similarly, the degree of pathologic response in response to preoperative chemotherapy appears to be a predictor of 5-year overall survival rates in patients receiving hepatic resections [10]. Lastly, studies have evaluated the prognostic relevance of molecular profiling in patients undergoing metastasectomy. Mutations in KRAS and BRAF are strongly associated with worse overall survival and recurrence free survival after resection of metastatic disease [11].

From a technical aspect, resectability is impacted by the resection status as well as the ability to preserve adequate remnant liver volume and function. Historically, negative margins (R0) were critical to resectability in liver metastases. But in the era of modern chemotherapy, close or microscopically positive (R1) resections may be acceptable. Determining the postsurgical or future remnant liver volume (FLR) is also important for determining resectability. FLRs <25% of total liver volume have been associated with an increased risk of postoperative hepatic dysfunction in patients with a normal liver [12]. Postoperative liver function may also be evaluated by the ability of the remnant liver to hypertrophy in response to portal vein embolization. It appears that a hypertrophy <5 % after portal vein embolization predicts postoperative hepatic dysfunction, as well as 90-day mortality rate [13].

Perioperative Chemotherapy

Upfront Resectable Patients

While resection of liver metastases has demonstrated long-term survival, the majority of patients eventually relapse [14]. These recurrences are thought to be a result of microscopic residual metastases. Theoretically, neoadjuvant chemotherapy could treat the micro-metastatic disease and decrease recurrence after resection. However, in patients with resectable hepatic metastases, the decision to offer preoperative chemotherapy rather than upfront resection remains controversial. In 2008, the EORTC-40983 Intergroup trial was able to show that upfront combination of perioperative FOLFOX4 and surgery increased progression-free survival but failed to result in long-term overall survival for patients with liver-only metastases who were deemed resectable on preoperative imaging [15]. Following this trial, many other meta-analyses also failed to show significant benefit to overall survival with the addition of neoadjuvant chemotherapy in this population of patients [16–18].

Borderline Resectable and Initially Unresectable Patients

When patients with liver metastases are not deemed amenable to upfront resection, they are clinically categorized as either “borderline resectable” or “initially unresectable.” These patients typically have bilaterally positioned metastases, aggressive tumor biology, or perceived low future liver remnant. Because patients with unresected disease consistently show poor long-term survival rates, there is an impetus to convert initially unresectable patients to resectable patients with the use of chemotherapy. Studies have suggested that the conversion rate from unresectable to resectable disease with chemotherapy can be expected in 26–47% of patients [19, 20]. An early study by Bismuth et al. looked at resections of unresectable liver metastases with neoadjuvant FOLFOX and showed a promising 5-year survival rate of 40% [21]. Since then, a phase III trial by GONO in 2007 showed that the triplet chemotherapy combination FOLFOXIRI was shown to be superior to doublet therapy in PFS and OS [22]. With these contemporary chemotherapy agents, the 5-year survival rates in patients whose disease was resected after

conversion therapy is not inferior to that of patients with initially resectable disease [23].

Chemotherapy Toxicities

However, perioperative chemotherapy is not without risks. Chemotherapy-induced hepatotoxicity is one of the most concerning side effects in patients receiving perioperative chemotherapy. In a pathologic review of patients who underwent chemotherapy (median range 16 weeks) with standard fluoropyrimidine, irinotecan, and oxaliplatin-based regimens, 8.4% of patients were found to have steatohepatitis, and 5.4% patients were found to have sinusoidal obstruction syndrome. Irinotecan-based therapy is closely linked to chemotherapy-associated steatohepatitis, which is found to increase 90-day mortality after surgery. The inferior outcomes are thought to be due to hepatic insufficiency and poor regeneration after surgery [24]. Sinusoidal obstruction syndrome has been reported in patients receiving resections following oxaliplatin therapy, and data has only shown that it increases morbidity after hepatic surgery [25]. Though there is not much data on the optimal duration and timing of giving chemotherapy, increased number of cycles is associated with higher rates of complications. Rates of surgical complications were also higher with shorter intervals between chemotherapy completion and surgery [26].

Biologics with Neoadjuvant Chemotherapy in Patients with Liver Metastases

Targeted therapies, including epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) antibody, have improved the overall survival of patients with metastatic colorectal cancer [27]. While these therapies have activity in the metastatic colorectal cancer setting, many results from clinical trials are inconsistent, and the populations that derive the most benefit are often not well defined.

VEGF Inhibitors

VEGF (vascular endothelial growth factor) is protein made by cells that induces the growth of blood vessels. In 2004, bevacizumab, a humanized monoclonal antibody directed against VEGF, was approved by the FDA for treatment of metastatic colorectal cancer after data from the landmark AVF 2107 trial showed a benefit to overall survival of adding bevacizumab to irinotecan, fluorouracil, and leucovorin [28]. Subsequently, there have been many randomized controlled trials that have assessed the efficacy of bevacizumab in combination with various backbone chemotherapy regimens and patient characteristics, and it is a well-accepted part of the treatment arsenal for metastatic colon cancer, regardless of mutational subtype (Table 1). However, it should be noted that bevacizumab does carry risk for increase in treatment-related toxicity, including arterial thrombotic events, bowel perforation, bleeding, hypertension, and stroke. These factors, as well as impaired wound healing and potentially decreased hepatic regeneration after metastasectomy, should be considered before using it in the perioperative setting.

Upfront Resectable

For patients with initially resectable liver metastases, the benefit to adding bevacizumab to chemotherapy has not been proven. There have been no prospective randomized trials looking at the role of bevacizumab in this population. A phase II single arm trial by Nasti et al. found that upfront FOLFIRI plus bevacizumab led to an 85% R0 rate but at the cost of 43% surgical complications [29]. Several prospective single armed studies have reported encouraging objective response rates but lower median progression-free survival compared to the EORTC 40983 trial [29, 43, 44]. ESMO guidelines do not recommend bevacizumab with neoadjuvant chemotherapy in patients with technically resectable liver metastases, mostly due to concerns over increased complications [45].

Initially Unresectable

Bevacizumab in combination with conventional doublet chemotherapy has been shown to promote conversion to resectability, however, at increased risk of adverse events. An initial trial showed that bevacizumab plus chemotherapy could convert approximately 20% of unresectable metastatic colon cancer patients to resectability (60% of these patients were liver-only metastases) [46]. In 2015, the phase II single armed TRICC0808 trial yielded a 44% R0 hepatectomy rate in patients with initially unresectable liver-only metastases with FOLFOX plus bevacizumab and showed improved overall survival for patients able to undergo hepatectomy (mOS 43 vs. 21 months) [30, 44].

However, we now have more definitive data in a subset of this population of patients with initially unresectable liver-limited metastases. In 2020, the BECOME trial demonstrated with statistical significance that bevacizumab added to FOLFOX improved the R0 resection rates in patients with RAS mutated liver-limited metastatic colon cancer to 22.7% compared to 6% with chemotherapy alone. The chemotherapy plus bevacizumab combination was also shown to improve median PFS (9.5 vs. 5.6 months), as well as the median overall survival (25.7 vs. 20.5 months) [31•]. This was at the expense of higher rates of hypertension and proteinuria but not bleeding or thrombosis risk. We are still awaiting the read out from the CLMO-001 (NCT01383707) trial, a single arm, phase II trial looking at response rate, R0 resection rate, disease-free

Table 1 Results of clinical trials with VEGF inhibitors and neoadjuvant chemotherapy [29–42]

Year	Trial/investigator	Study design	Intervention	Control	Primary endpoint	Median OS (m)	Median PFS (m)	ORR (%)	R0 (%)
2011	Wong	Phase II	Bevacizumab + CAPOX	N/A	ORR	N/A	N/A	78	40
2012	VELOUR (Van Cutsem)	Phase III	Aflibercept + FOLFIRI	FOLFIRI	OS	*13.5 v 12.06*	*6.9 v 4.67*	*19.8 v 11.1*	N/A
2013	Nasti	Phase II	Bevacizumab + irinotecan, leucovorin, 5-FU	N/A	PFS	38	14	66.7	84.6
2013	AVEX (Cunningham)	Phase III	Bevacizumab + Capecitabine	Capecitabine	PFS	20.7 v 16.8	*9.1 v 5.1*	*19 v 10*	N/A
2015	OLIVIA (Gruenberger)	Phase II	Bevacizumab + FOLFOXIRI	Bevacizumab + mFOLOFX6	RR	NR v 32.2	18.6 v 11.5	81 v 62	49 v 23
2019	TRICC0808 (Yasuno)	Phase II	mFOLFOX + bevacizumab	N/A	R0	33.6	5.9	N/A	44
2015	RAISE (Tabernero)	Phase III	Ramucirumab + FOLFIRI	FOLFIRI	OS	*13.3 v 11.7*	*5.7 v 4.5*	72 v 67	N/A
2015	Cao	Phase II	Bevacizumab + FOLFIRI	FOLFIRI	ORR	15.2 v 11.3	8.5 vs. 5.1	*47.7 v 28.5*	N/A
2015	TRIBE (Cremolini)	Phase III	Bevacizumab + FOLFOXIRI	Bevacizumab + FOLFIRI	PFS	*29.8 v 25.8*	*12.1 v 9.7*	*65 v 54*	15 v 12
2016	WJOG4407G (Yamazaki)	Phase III	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI	PFS	*30.1 v 31.4*	10.7 v 12.1	62 v 64	9 v 10
2018	QUATTRO (Oki)	Phase II	Bevacizumab + FOLFOXIRI	N/A	PFS	NR	13.3	72	24.6
2019	STEAM (Hurwitz)	Phase II	Bevacizumab + cFOLFOXIRI or sFOLFOXIRI	Bevacizumab+ FOLFOX	ORR, PFS	34/ 28.3 v 30.7	*11.9/ 11.4 v 9.5*	11.9 / 11.4 vs. 9.5	17.2 / 9.8 v 8.4
2019	MAVERICC (Parikh)	Phase II	mFOLFOX6 + bevacizumab	Bevacizumab + FOLFIRI	PFS	23.9 v 27.5	10.1 v 12.6	61 v 65.4	N/A
2020	BECOME (Tang)	Phase III	mFOLFOX6 + bevacizumab	mFOLFOX6	R0	*25.7 v 20.5*	*9.5 vs. 5.6*	*54.5 v 36.7*	*22 v 5.8*

OS overall survival, *PFS* progression-free survival, *ORR* overall response rate (complete + partial) by radiologic criteria (WHO, RECIST version 1.1), *RR* resection rate, *NR* not reached, *R0* microscopically margin-negative resection, *N/A* data not available

Values in italics, significant p value <0.05

Table 2 Results of clinical trials with EGFR inhibitors and neoadjuvant chemotherapy [53, 54, 55•, 56–63]

Year	Trial/investigator	Study design	Intervention	Control	Primary endpoint	Median OS (m)	Median PFS (m)	ORR (%)	R0 (%)
2009	CRYSTAL (Van Cutsem)	Phase III	Cetuximab + FOLFIRI	FOLFIRI	PFS	19.9 v 18.6	*8.9 v 8*	*46.9 v 38.7*	*4.8 v 1.7*
2009	OPUS (Bokemeyer)	Phase II	Cetuximab + FOLFOX4	FOLFOX4	ORR	N/A	*7.7 v 7.2*	*61 v 37*	4.7 v 2.4
2010	Peeters	Phase III	Panitumumab + FOLFIRI	FOLFIRI	PFS, OS	14.5 v 12.5	*5.9 v 3.9*	*35 v 10*	N/A
2010	PRIME (Douillard)	Phase III	Panitumumab + FOLFOX4	FOLFOX4	PFS	23.9 v 19.7	*9.6 v 8*	55 v 48	8.3 v 7
2010	POCHER (Garufi)	Phase II	Cetuximab+ Irinotecan 5-FU, FA, L-OHP	N/A	R0	37	14	79.1	60
2011	MRC COIN (Maughan)	Phase III	Cetuximab + Oxaliplatin/FU	Oxaliplatin/FU	OS	17 v 17.9	8.6 v 8.6	*64 v 57*	15 vs. 13
2011/2014	CELIM (Folprecht)	Phase II	Cetuximab + FOLFOX6	Cetuximab + FOLFIRI	ORR	35.8 v 29	11.2 v 10.5	68 v 57	20 v 16
2013	Ye	RCT	Cetuximab + mFOLFOX6	mFOLFOX6	RR	*30.9 v 21*	*10.2 v 5.8*	*57.1 v 29.4*	*25.7 v 7.4*
2013	Ji	Phase II	Cetuximab + FOLFOX6	N/A	R0	N/A	N/A	72.6	27
2019	VOLFI (Modest)	Phase II	Panitumumab + mFOLFOXIRI	FOLFOXIRI	ORR	35.7 v 29.8	9.7 v 9.7	*87.3 v 60.6*	*33.3 v 12.1*
2020	New EPOC (Bridgewater)	Phase III	Cetuximab + Chemotherapy	Chemotherapy	OS	*55.4 v 81*	15.5 v 22.2	72 v 61	79 v 82

OS overall survival, *PFS* progression-free survival, *ORR* overall response rate (complete + partial) by radiologic criteria (WHO, RECIST version 1.1), *RR* resection rate, *NR* not reached, *R0* microscopically margin-negative resection, *N/A* data not available

Values in italics, significant p value <0.05

interval, and overall survival in mCRC patients with borderline or non-resectable liver metastases after getting FOLFOX plus bevacizumab and then bevacizumab maintenance.

Several recent trials have focused on bevacizumab in conjunction with a triplet chemotherapy regimen with mixed results with regard to liver metastasis resection. The 2014 phase II OLIVIA trial found improvements in response rates, overall resection rates, and progression-free survival using FOLFOXIRI plus bevacizumab compared to FOLFOX plus bevacizumab in patients with initial unresectable liver metastases, suggesting that the addition of a third chemotherapy agent to a bevacizumab-containing regimen may be preferred [32•]. The first TRIBE trial, published in 2014 and updated in 2015, looked at first-line FOLFOXIRI plus bevacizumab vs. FOLFIRI plus bevacizumab in patients with unresectable mCRC. They found an overall survival benefit (mOS 29.8 vs. 25.8 months) for the triplet combination at the expense of increased grade 3 and 4 toxicities. While response rates were higher in the triplet combination group (65.1% vs. 53.1%), this did not translate to a significant benefit in R0 resection rate (15% vs. 12%).

VEGF Inhibitor Toxicities

While there is evidence that the chemotherapy agents oxaliplatin and irinotecan lead to increased postoperative complications as mentioned above, the effect of bevacizumab on perioperative complications remains under debate. The concerns regarding bevacizumab include increased bleeding, bowel perforation, stroke and arterial thrombosis, delayed wound healing, and diminished regeneration after resection. Clinical studies have not clearly shown an increase in perioperative complications of hepatic resection with the incorporation of bevacizumab to chemotherapy [47]. Instead, some studies even observed a benefit of bevacizumab in reducing the incidence of postoperative hepatic insufficiency. Currently many groups still recommend that liver surgery should be delayed 6 weeks after the last dose of bevacizumab given the long, 20-day half-life of the drug [48, 49]. However, studies have not clinically shown a significant impact of shorter or longer delays on the occurrence of postoperative complications [50].

EGFR Inhibitors

Mutation Status

Epidermal growth factor receptor (EGFR) inhibitors are antibodies that specifically target EGFR and inhibit pathways involved in cellular proliferation, angiogenesis, and metastases. The addition of EGFR inhibitors, such as cetuximab and panitumumab, to the standard oxaliplatin or irinotecan-based

chemotherapy regimens (FOLFOX and FOLFIRI) have been shown consistently to increase overall survival in patients with advanced disease harboring RAS wild-type tumors where the primary is left sided [51–53] (Table 2). While many of the original studies of cetuximab and panitumumab were not designed to evaluate the role of EGFR inhibitors in downsizing liver metastases and increasing curative resection rates, retrospective subgroup analyses have shown that the addition of EGFR inhibitors to chemotherapy also numerically improves the R0 resection rate in the subset of patients with RAS wild-type metastatic colorectal cancer [54, 64].

Upfront Resectable Liver Metastases

Use of anti-EGFR agents is controversial in this population. In early 2020, the phase III NEW EPOC trial was published, which looked at the effect of cetuximab with chemotherapy (FOLFOX, XELOX, or FOLFIRI) on patients with upfront resectable and borderline liver metastases [55•]. The long-term results surprisingly showed a median overall survival that was 26 months *shorter* for patients receiving cetuximab with chemotherapy compared to those only receiving chemotherapy (55.4 vs. 81 months), without any difference in response rate or resection rate. These results were more pronounced in the groups that received oxaliplatin.

Initially Unresectable Liver Metastases

Most of the initial data for initially unresectable disease comes from subset analyses of larger trials that were conducted in patients with and without RAS mutations. In the 2009 CRYSTAL trial, FOLFIRI plus cetuximab was found to improve resection rates over FOLFIRI alone (7% vs. 3.7%) while modestly prolonging overall survival [56]. The 2009 OPUS trial similarly showed an improvement in R0 rates with FOLFOX plus cetuximab compared to cetuximab alone (4.7 vs. 2.4%) [53]. CELIM, a phase II trial in patients with unresectable liver metastases, compared FOLFOX plus cetuximab vs. FOLFIRI plus cetuximab and found similar response rates (68% for FOLFOX combination and 57% for FOLFIRI combination) and resection rates (38 vs. 30%) with either chemotherapy backbone [54]. Similarly, the PRIME trial compared FOLFOX plus panitumumab versus FOLFOX alone in metastatic colorectal cancer patients. While there was an overall survival benefit to the addition of panitumumab (23.9 vs. 19.7 months), the improvement in R0 resection rates was modest at best (8.3 vs. 7%) [53]. Of note, there is one phase III trial (MRC-COIN) that found no improvement in overall survival with the addition of cetuximab to FOLFOX or XELOX in a mutation-unselected population (17 vs. 17.9 months) and no improvement in R0 resection rates (15 vs. 13%) [57]. The effect was more pronounced in the group receiving capecitabine, leading to speculation that there may be an interaction between capecitabine and cetuximab.

To try to directly answer the question if the addition of an EGFR inhibitor to chemotherapy in this population improves long-term outcomes, a small Chinese trial in 2013 randomized patients with initially unresectable liver metastases to chemotherapy (FOLFIRI or mFOLFOX6) plus cetuximab versus chemotherapy alone. The addition of cetuximab significantly increased 3-year overall survival (41 vs. 18%) and R0 resection rates for liver metastases (25% vs. 7.4%, $p<0.01$) [58•]. The FC-6 trial (NCT00803647) was a phase II trial with the primary endpoint of surgical conversion rate with preoperative FOLFOX plus cetuximab for patients with initially unresectable liver metastases. While the results have not been published, a 75% R0 resection rate with a 13.3-month recurrence-free survival time in those patients who had R0 resection has been reported on clinicaltrials.gov.

As with bevacizumab, there is emerging data that combining anti-EGFR agents with triplet chemotherapy may provide additional benefit. POCHER, a single armed phase II trial, showed that resection rates of 60% could be obtained after triplet chemotherapy plus cetuximab in patients with unresectable liver metastases [59]. VOLFI, a phase II randomized trial in RAS wild-type patients, found that FOLFOXIRI plus panitumumab improved response rate and resection rate of metastases (33 versus 13 percent) compared to FOLFOXIRI alone but again at the risk of higher rates of treatment-related toxicity [60]. Likewise, the phase II FOLCUM trial (NCT02063529) looked at rate of curative liver treatment (resection or ablation) in FOLFOXIRI plus cetuximab vs. FOLFOXIRI alone. The trial was completed in December 2019 with final results pending.

Comparisons

There has been considerable debate as to whether bevacizumab or cetuximab should be the preferred first-line therapy for patients with RAS WT metastatic colorectal cancer. The 2017 CALBG/SWOG 80405 study did not find a significant difference in overall survival between the additions of cetuximab vs. bevacizumab to chemotherapy among patients with untreated RAS WT metastatic colorectal cancer [65]. FIRE-3, published in 2014, was a randomized phase III trial patients that looked at FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab in first line therapy. There was no difference in objective response (62 vs. 58%) or resection rate (12 vs. 14%), but a significant improvement in overall survival with cetuximab and FOLFIRI was seen (28.7 vs. 25 months, $p=0.017$), with the difference being even more pronounced in RAS WT patients (33 vs. 25 months) [66]. Furthermore, the benefit of cetuximab was limited to patients with left-sided tumors (overall survival 38 vs. 28 months), while patients with right-sided tumors benefited more from

Table 3 Clinical trials comparing VEGF and EGFR inhibitors with neoadjuvant chemotherapy [52, 66, 67, 68•, 69]

Year	Trial/investigator	Study design	Intervention	Control	Primary endpoint	Median OS (m)	Median PFS (m)	ORR (%)	R0 (%)
EGFR-Chemotherapy v. VEGF-Chemotherapy									
2014	FIRE-3 (Heinemann)	Phase III	Cetuximab + FOLFIRI	Bevacizumab + FOLFIRI	ORR	*33.1 v 25.6*	10.4 v 10.2	65 v 60	N/A
2014	PEAK (Schwartzberg)	Phase II	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	PFS	*34.2 v 24.3*	10.9 v 10.1	57 v 53	10 v 8
2017	Venook	Phase III	Cetuximab + FOLFIRI/mFOLFOX6	Bevacizumab + FOLFIRI/mFOLFOX6	OS	30 v 29	10.5 vs. 10.6	59.6 v 55.2	N/A
2019	ATOM (Oki)	Phase II	Cetuximab + mFOLFOX6	Bevacizumab + mFOLFOX6	PFS	NR v 30.4	14.8 v 11.5	*84.7 v 68.4*	37.3 v 43.9
EGFR-VEGF- Chemotherapy									
2015	Liu	Phase II	Panitumumab + Bevacizumab + FOLFIRI	FOLFIRI	ORR, OS, PFS	*15.2 v 11*	*5.7 v 3.8*	*47 v 26*	N/A

OS overall survival, PFS progression-free survival, ORR overall response rate (complete + partial) by radiologic criteria (WHO, RECIST version 1.1), RR resection rate, NR not reached, R0 microscopically margin-negative resection, N/A data not available

Values in italics, significant p value <0.05

bevacizumab (overall survival 23 vs. 18 months). Multiple hypotheses have been posited to explain these differences and shed light to the complex interplay between chemotherapy, first-line therapy, and the tumor microenvironment. One theory is that irinotecan synergizes with cetuximab in all tumor molecular subtypes, while oxaliplatin has variable effects depending on the molecular subtype. It is not known if panitumumab has similarly variable interactions with oxaliplatin.

There have been limited trials directly looking at choice of biologic therapy for liver-only metastatic colorectal cancer (Table 3). The 2014 PEAK trial compared FOLFOX plus bevacizumab vs. FOLFOX plus panitumumab in previously untreated RAS WT metastatic colon cancer patients [67]. PFS was similar between the two groups, but there was a significant difference in overall survival (34.2 vs. 24.3 months, p = 0.009) favoring the panitumumab arm. There was no difference in R0 resection rates (10% with panitumumab vs. 12% with bevacizumab).

The Japanese ATOM trial, published in 2019, evaluated the effect of cetuximab vs. bevacizumab with FOLFOX in 122 patients with RAS WT, unresectable liver-limited metastases with resection rate as the primary endpoint. At the 2-year follow-up, there was no difference between the groups in PFS (14.8 vs. 11.5 months, p=0.33). Response rate was improved for the cetuximab group (84.7 vs. 68.4%), but this did not translate into a difference in R0 resection rates (37 vs. 44%). Median overall survival was not reached for the cetuximab group and 30.4 months in the bevacizumab group. Of note, a significant benefit in overall survival with cetuximab plus mFOLFOX6 was seen in a subgroup analysis among patients with fewer, larger metastases. Despite the minimal differences, both VEGF and EGFR inhibitors in combination with chemotherapy appear to be viable options in patients with suboptimal resectability [68•].

Role of Biologics in Adjuvant Therapy

The role of adjuvant therapy following metastasectomy is controversial. As there is limited data looking at adjuvant therapy for stage IV disease, much of the information we have is extrapolated from trials in stage III disease. While fluoropyrimidine plus oxaliplatin chemotherapy has shown to provide a survival benefit (NSABP C-01, MOSAIC trials), combinations with irinotecan provide no benefit of fluoropyrimidine alone [70–72]. Likewise, multiple studies combining bevacizumab with FOLFOX or capecitabine and studies of cetuximab plus FOLFOX showed no benefit to the combination with the biologic agents in resected stage II or stage III colon cancer patients over chemotherapy alone [73–77]. Therefore, extrapolating from this data, standard of

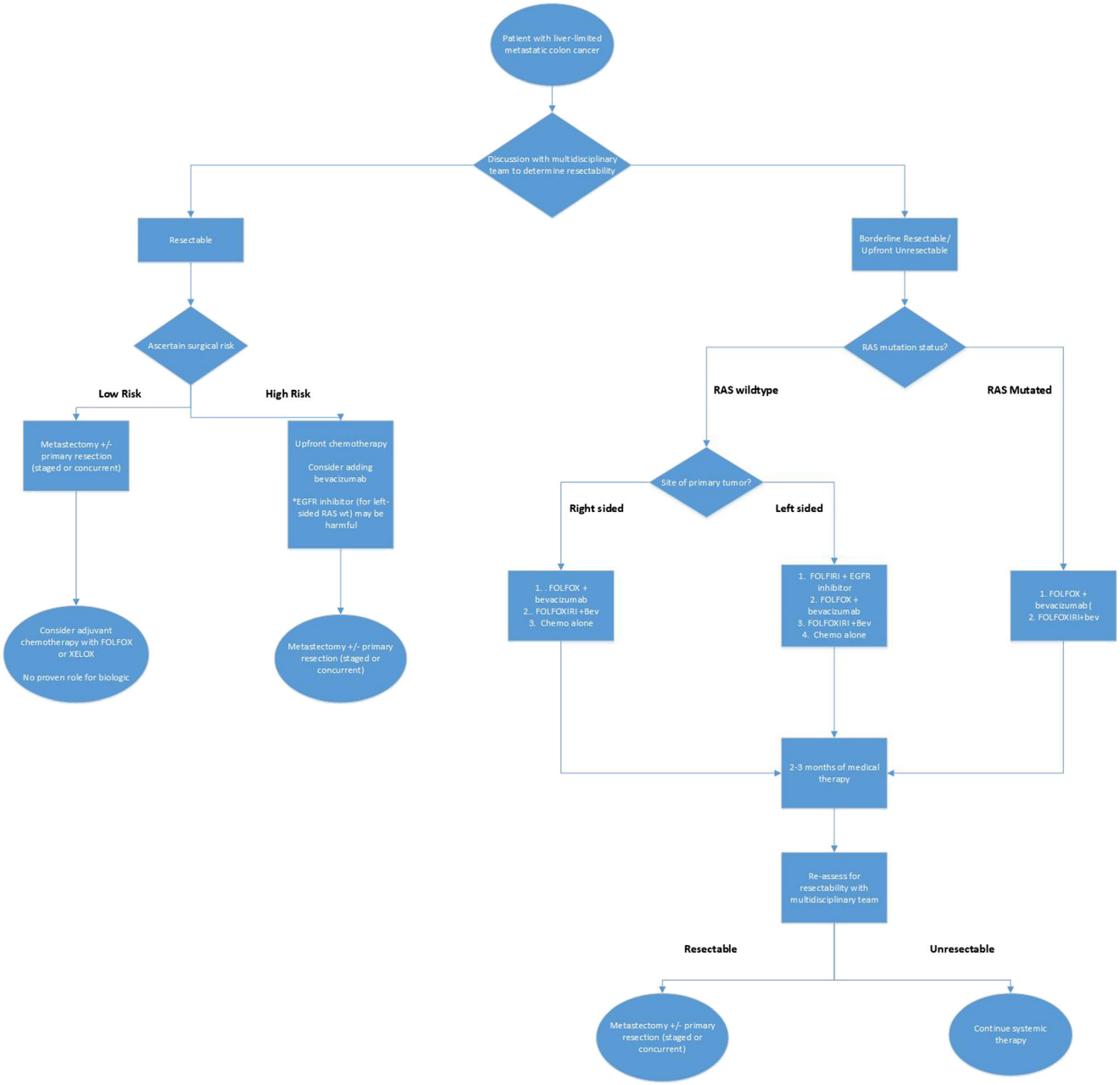

Fig. 1 Algorithm for perioperative management of liver-limited metastatic colon cancer

care is not to use bevacizumab or cetuximab after resection of liver metastases.

Future Directions

As we are now fully in the era of personalized medicine, the future of perioperative use of biologics will be more and more driven by genetic and molecular profiling of colorectal tumors. As mentioned above, there are differences in outcomes in patients who have resection of liver metastases between RAS-mutated and RAS-wildtype tumors, with RAS-mutated cancers having poorer DFS and OS after resection [78].

We have emerging data on the use of checkpoint inhibitors in the upfront treatment of metastatic MSI high colorectal cancer (ASCO 2020 plenary session), with adjuvant trials in resected stage III colon cancer underway. If there is proven efficacy in these trials, adjuvant checkpoint inhibitors may become part of the standard of care for patients with MSI-high metastatic disease limited to the liver, much like they are in resected stage IV melanoma.

Several phase II clinical trials (CONVERSION; NCT03401294) are looking at the rate of conversion from unresectable to resectable liver metastases in patients getting FOLFOXIRI and bevacizumab. With previous trials showing

survival benefit to triplet regimens, these combinations potentially hold promise for patients with liver-only metastases.

Another novel approach is combining traditional chemotherapy regimens with hepatic arterial infusion (with FUDR) in additional to biologic agents. Currently enrolling trials include NCT01312857 (phase II trial looking at HAI plus FOLFIRI with or without panitumumab) and NCT02885753 (5FU + cetuximab or bevacizumab + systemic oxaliplatin or intraarterial oxaliplatin; primary outcome hepatic progression-free survival).

Guidelines and Recommendations

Use of biologics in addition to chemotherapy in the perioperative setting for colorectal cancer patients with liver-only metastases should be undertaken with a personalized approach to the patient's comorbidities, tumor biology, and surgical feasibility (Fig. 1). All patients should undergo discussion in a multidisciplinary setting to determine resectability status and fitness for medical and surgical treatment. If patients are deemed to have resectable disease, we recommend upfront resection of liver metastases for patients who fall into low-risk categories (few comorbidities, metachronous disease, limited number of liver metastases), followed by adjuvant FOLFOX or XELOX. This is supported by the current NCCN recommendations [79]. For patients with higher risk resectable disease, upfront chemotherapy is generally recommended per ESMO and NCCN guidelines. The NCCN recommends FOLFOX or XELOX potentially with bevacizumab, with FOLFOX or FOLFIRI with an EGFR inhibitor also options for RAS WT patients, though it should be noted that this recommendation has not been updated since the new EPOC trial survival data have been published. ESMO recommends chemotherapy without biologics in this setting [45]. We would recommend using chemotherapy, potentially plus bevacizumab after conversation with the surgical team, but would avoid EGFR inhibitors in this setting.

For patients with initially borderline resectable or unresectable disease, a limited course of neoadjuvant therapy should be given if medically feasible in most cases. For those patients in whom it is deemed safe, bevacizumab may be used in combination with FOLFOX or FOLFOXIRI, with the acknowledgement that the triplet regimen comes with a higher risk of toxicity. Patients with RAS-mutated disease should not receive EGFR inhibitors. Patients with left-sided RAS-wildtype disease may receive neoadjuvant chemotherapy with EGFR inhibitors. While FOLFOX or FOLFIRI may be used in this setting, the overall survival data is stronger for FOLFIRI, and thus that is the recommended chemotherapy backbone to be used with EGFR inhibitors. Regardless of regimen, neoadjuvant treatment ideally should not exceed approximately 3 months due to risk of liver and other toxicities, and frequent re-assessment with imaging should be performed. Resection should be undertaken as soon as patient is deemed resectable by multidisciplinary team, with surgery happening approximately 4 weeks after the last treatment (6 weeks if bevacizumab was a part of the regimen).

Conclusion

While perioperative use of chemotherapy for metastatic colorectal cancer with liver-limited metastases has been shown to modestly improve survival, the data supporting the use of biologic agents is more nuanced. While we have a growing body of evidence that biologics added to chemotherapy may improve response rate and resection rates, we do not yet have strong evidence that they impact overall survival, and therefore an individualized approach should be taken in each patient, taking into account previous therapies, comorbidities, surgical goals, mutational status, and sidedness of the primary tumor.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare that they have no conflict of interest.

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