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Review

REVIEW

Use of perioperative chemotherapy in colorectal cancer metastatic to the liver

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Abstract

A curative-intent approach may improve survival in carefully selected patients with oligometastatic colorectal cancer. Aggressive treatments are most frequently administered to patients with isolated liver metastasis, though they may be judiciously considered for other sites of metastasis. To be considered for curative intent with surgery, patients must have disease that can be definitively treated while leaving a sufficient functional liver remnant. Neoadjuvant chemotherapy may be used for upfront resectable disease as a test of tumor biology and/or for upfront unresectable disease to increase the likelihood of resectability (so-called 'conversion' chemotherapy). While conversion chemotherapy in this setting aims to improve survival, the choice of a regimen remains a complex and highly individualized decision. In this review, we discuss the role of *RAS* status, primary site, sidedness, and other clinical features that affect chemotherapy treatment selection as well as key factors of patients that guide individualized patient-treatment recommendations for colorectal-cancer patients being considered for definitive treatment with metastasectomy.

Key words: metastatic colorectal cancer; perioperative chemotherapy; conversion chemotherapy; liver resection; KRAS; steatohepatitis

Introduction

While historically the mainstay of metastatic colorectal-cancer therapy has been palliative chemotherapy, now, in selected patients with metastasis, resection can offer a possibility of cure [1, 2]. Compared to the 5-year overall survival (OS) rate of 13.8% [3], survival outcomes may be much better in patients undergoing a more aggressive treatment approach [4, 5]. Resection of liver metastases is by the far the most common and most well studied, but must be considered on a case-by-case basis.

Unfortunately, only 10%–20% of patients presenting with isolated hepatic metastasis have resectable disease [2, 6, 7]. The remaining 80% are typically considered unresectable either due to extra-hepatic disease, involvement of too large a liver volume, or location(s) involving crucial structures [8]. There is now substantial evidence to support the use of neoadjuvant chemotherapy in selected patients to downsize tumors and therefore facilitate a curative approach with resection [9–14]. With the use of neoadjuvant chemotherapy, early studies showed that the proportion of patients eligible for resection could increase by over 10%, which has further improved with more modern regimens [10, 15, 16]. Acknowledging the highly selective nature of these retrospective studies, resection in this population has continually been shown to improve survival: numerous studies show 5-year OS rates ranging from 25% to 58%—similar to those who presented with initially resectable liver metastases [17–27]. One study demonstrated a 10-year OS rate of 27% [13, 28], which is a substantial improvement over the current 5-year OS rate of 13.8% expected with chemotherapy alone [3].

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Here, we discuss which patients with metastatic colorectal cancer are most likely to benefit from an aggressive approach to definitively address all sites of disease in the so-called 'curative-intent' approach and review the use of perioperative chemotherapy to achieve the maximum benefit from this strategy.

Patient selection: optimally selecting who may benefit from an aggressive 'curative-intent' approach

Patient selection is crucial when deciding which patients with metastatic disease would benefit from curative-intent treatment. The survival benefit is restricted to patients in whom all sites can be reasonably definitively treated. This requires early and frequent multidisciplinary review to decide which patients are appropriate candidates. As the goal of curative intent is to remove all viable disease, the decision to aggressively treat metastatic disease is largely driven by factors influencing resectability. While there are no set criteria to determine resectability, factors associated with improved outcomes include the number of metastases, the sites of metastatic disease (favoring unilateral and/or unifocal disease), limited primary-tumor stage, and long disease-free interval (if metastases are metachronous) [23, 25, 29]. The best outcomes have historically been seen in patients with no major pre-existing medical comorbidities, fewer than three metastases, no extra-hepatic disease, and predicted clear surgical margins [30].

Metastasis-site considerations

Curative-intent therapy is most often pursued and has been best studied in patients with liver metastases. For patients with isolated liver metastasis, possible management strategies for liver-directed therapy include surgery, ablation, Yttrium-90 (Y-90) radioembolization, chemoembolization, and external beam radiation. However, hepatic resection remains the only proven 'cure' for liver metastasis [28, 31]. Decisions regarding isolated extra-hepatic disease are more complicated, with the best 5-year OS seen in patients with isolated lung metastases or periportal lymphadenopathy [32]. In patients with a few isolated or long-term stable lung metastases, it may still be reasonable to pursue curative-intent treatment—a localized therapy technique (e.g. surgery, ablation, irradiation). Patients with limited-volume peritoneal disease have intermediate 5-year survival and aggressive treatment strategies remain very controversial [33]. In highly selected patients, cytoreduction and intraperitoneal chemotherapy are occasionally considered, but the benefit remains unproven [34]. Patients with aortocaval adenopathy or multiple sites of disease have the worst survival and data do not exist to support aggressive treatment strategies in this population [33]. Needless to say, it is imperative that patients receive appropriate high-quality imaging (typically a contrasted computed tomography scan of the chest, abdomen, and pelvis) to accurately assess the extent of their metastatic disease [35].

Resectability

For patients to be considered for treatment with curative intent, all viable disease must be either resectable or have the possibility to convert to resectable disease with down-staging by chemotherapy. Though various definitions of resectability exist, key factors include the estimated volume of functional liver remnant that will remain following resection and whether there is involvement of non-resectable structures such as major vessels [23, 25, 29]. Following resection, there should be a predicted sufficient remaining liver-remnant volume (typically >30%), adequate perfusion and biliary drainage, and adequate function [35, 36]. There is also often a subjective component including surgeon opinions about technical operability and attitudes about the risk of resection [35, 37]. While an R0 resection (negative margins) is ideal, given increasing surgical indications, R1 resections (resections with microscopically positive margins) may be justified for certain patients, but do connote a higher local recurrence risk [38].

Conclusions

i. Patients may be appropriate for treatment with curative intent if all sites of disease can be reasonably definitively treated. Appropriate patient selection is crucial and should involve multidisciplinary review.
ii. Curative-intent treatment is most often recommended for patients with isolated liver metastasis, though it may be reasonable to consider this more aggressive strategy for highly selected patients with lung metastases or periportal adenopathy. Localized treatment of peritoneal disease remains controversial.
iii. Resectability should include an assessment of predicted remaining liver volume, liver function, and disease involvement of crucial structures (such as major blood vessels).

Choice of neoadjuvant treatment

The goal of neoadjuvant chemotherapy in metastatic colorectal cancer is ultimately to improve OS by improving complete surgical resection, but the role of chemotherapy is different, depending on whether the disease is resectable or not at diagnosis.

For upfront *resectable* metastases, chemotherapy primarily acts as a 'test' of tumor biology, helping to identify aggressive cancers that are likely to recur quickly after surgery. Studies have shown that the pathologic response to pre-operative chemotherapy is strongly predictive of prognosis after a resection [39]. Additionally, development of any new lesions during chemotherapy is one of the strongest predictors of poor post-hepatectomy outcomes [40]. The response rate can be assessed by standardized methods such as the Response Evaluation Criteria In Solid Tumors (RECIST). This method has proved to be a reasonable method for evaluating chemotherapy response [41]. However, in addition to tumor size [41, 42], there are other important considerations, including morphologic changes [43, 44] and metabolic activity [45, 46]. Morphologic features are increasingly important, as studies suggest that tumor size alone is an imperfect predictor of pathologic response and survival, particularly for biological agents such as bevacizumab [43, 44, 47].

For initially *unresectable* disease, chemotherapy also provides information about tumor biology, but it is done primarily to increase the likelihood and/or allow R0 resection of metastases and, presumably, improve OS. Folprecht *et al.* [48] demonstrated that there was a strong correlation between response rates and resection rates in studies of patients with isolated liver metastases ($r = 0.96$, $P = 0.002$). It is therefore critical to select a regimen with high response rates for patients with metastases that could become resectable [48]. While high response rates are desirable, the goal is NOT to achieve a maximum or complete

response, as over-treating increases toxicity and can make the surgery technically difficult, in turn causing loss of the window of resectability.

While many treatment combinations have been studied for neoadjuvant treatment in metastatic colorectal cancer, there is currently no standard of care and guidelines allow several combinations [49, 50].

Upfront resectable metastatic disease

Perioperative chemotherapy for resectable disease is frequently done in clinical practice to evaluate tumor biology, but has limited randomized data [51–54]. The landmark EORTC 40983 trial by Nordlinger *et al.* [55, 56] examined the use of perioperative FOLFOX (folinic acid, fluorouracil, and oxaliplatin) before and after surgery vs surgery alone in patients with upfront resectable liver metastases from colorectal cancer. In this trial, resectability was judged by a multidisciplinary team. They demonstrated a statistically significant improvement in progression-free survival (PFS) (20.9 months vs 12.5 months, $P = 0.035$) in the chemotherapy group. However, there was no difference in OS with the addition of perioperative chemotherapy vs surgery alone (61.3 months vs 54.3 months, $P = 0.34$), making the application of this approach controversial.

Even more limited data are available for the use of targeted therapies, including cetuximab in the perioperative setting for upfront resectable liver metastasis in colorectal cancer. The New EPOC trial examined perioperative chemotherapy either with or without cetuximab for resectable liver-only metastasis [57]. Surprisingly, they observed a detrimental effect in patients who received FOLFOX with cetuximab compared with those receiving FOLFOX alone (PFS 14.1 months vs 20.5 months, hazard ratio (HR) 1.48, $P = 0.03$). This detrimental effect was more pronounced in patients with a better prognosis and those who responded to treatment. Possible explanations for this finding include differences in baseline characteristics, differences in definitive management (the FOLFOX-alone arm had more resections while the FOLFOX-with-cetuximab arm had more ablations and fewer resections), and more positive margins in the cetuximab arm. Interestingly, this outcome was not thought to be due to overlapping toxicities, which have been previously described [58]. Additionally, outcome data were missing in 11% of patients, which may have skewed the conclusions. Regardless, these data argue against the utility of chemotherapy with anti-EGFR (epidermal growth factor receptor) therapy in patients with upfront resectable liver metastases. Randomized data for chemotherapy with bevacizumab in upfront resectable disease are lacking.

Safety and toxicity

The balance between efficacy and toxicity remains of paramount importance. Toxicity associated with perioperative chemotherapy may additionally impact surgical outcomes. Oxaliplatin has been associated with an increased sinusoidal injury, but does not increase perioperative morbidity or mortality [59]. However, irinotecan has been associated with an increased risk of steatohepatitis, which is associated with increased postoperative mortality due to death from liver failure (14.7% vs 1.6%, $P = 0.001$) [59]. Bevacizumab may cause issues with postoperative bleeding and wound healing so it should ideally be discontinued 4–6 weeks prior to surgery to reduce the risk of post-operative complications [60, 61]. Karoui *et al.* [62] also observed an effect based on chemotherapy duration. Notably, they found that prolonged pre-operative chemotherapy increased the risks of post-operative complications (complication rate, 54% for patients undergoing more than six cycles of neoadjuvant chemotherapy vs 19% for those receiving fewer than six cycles, $P = 0.047$) primarily due to transient post-operative liver insufficiency. However, even with prolonged chemotherapy, there was no major impact on mortality in the setting of hepatic resection. Therefore, the duration, timing, and type of chemotherapy should be carefully considered to minimize toxicity and post-operative complications. This also reinforces the goal of using neoadjuvant chemotherapy with the aim of converting to resectable disease, not treating to maximum chemotherapy effect.

Upfront unresectable metastatic disease

Perioperative chemotherapy for patients with initially unresectable liver metastases has been well studied. Upfront aggressive systemic chemotherapy in this setting can allow a patient with unresectable disease to be 'converted' to resectable and is therefore referred to as 'conversion' therapy. Conversion chemotherapy has shown a clear survival benefit, with 5-year OS rates ranging from 25% to 58% (vs 5%–10% with chemotherapy alone) [17–27]. Most initial studies of conversion chemotherapy were performed using oxaliplatin- and fluorouracil-based regimens [15, 19, 57, 63]. FOLFOX and FOLFIRI (fluorouracil, folinic acid, and irinotecan) are both commonly used doublet regimens that have been widely accepted as conversion treatment strategies based on their utility in stage IV colorectal cancer in general [64]. In a randomized trial comparing FOLFIRI and FOLFOX, the two regimens had identical response rates (55%) and similar levels of R0 resections [65]. In two prospective phase II trials, FOLFOX [37] and FOLFIRI [66] also showed similar response rates of ~50% with similar rates of liver metastases resection (33% and 40%, respectively). While both have demonstrated similar efficacy, it is reasonable to choose an oxaliplatin-based regimen due to the perioperative toxicity concerns discussed above.

Triplet regimens including FOLFOXIRI/FOLFIRINOX (folinic acid, fluorouracil, oxaliplatin, and irinotecan) have also been studied. Falcone *et al.* [67] showed that, compared to FOLFIRI, FOLFOXIRI improves response rates, PFS, OS, and increases resection rates (15% in the FOLFOXIRI arm vs 6% FOLFIRI arm, $P = 0.033$) for patients with metastatic colorectal cancer. In the study's multivariate analysis, only FOLFOXIRI treatment was an independent predictive factor for achieving an R0 resection (HR, 3.1; 95% confidence interval (CI), 1.2 to 7.9; $P = 0.018$). However, there was increased toxicity with FOLFOXIRI. The METHEP trial by Ychou *et al.* [68] studied doublet regimens (FOLFOX or FOLFIRI) vs 'intensified' chemotherapy (high-dose FOLFIRI, FOLFOX7, or FOLFIRINOX) in patients with potentially resectable or unresectable liver-only metastases. They also found that FOLFIRINOX had high response rates and resulted in secondary resection in 52% of patients overall, but only 40% of patients received a chemotherapy doublet vs 67% of patients who received the FOLFIRINOX chemotherapy triplet.

Use of targeted therapies

Anti-EGFR targeted treatments

Anti-EGFR targeted therapies including cetuximab and panitumumab have been studied as potential adjuncts for conversion chemotherapy for colorectal cancer with liver metastasis.

Van Cutsem *et al.* [69] studied the use of cetuximab with FOLFIRI as first-line treatment for metastatic colorectal cancer. They found, compared to FOLFIRI alone, FOLFIRI + cetuximab reduced the risk of progression in patients with *KRAS* wild-type tumors, improved surgical resection rates (7.0% vs 3.7%), and improved R0 resection rates with curative intent (4.8% vs 1.7%, $P = 0.002$). Bokemeyer *et al.* [70] showed a similar effect with FOLFOX + cetuximab. In this trial, they showed increased OS and response rate (61% vs 37%, $P = 0.011$) and reduced disease progression (HR 0.57, $P = 0.163$) in patients with *KRAS* wild-type tumors receiving FOLFOX + cetuximab as first-line treatment of metastatic colorectal cancer. The CELIM trial directly compared cetuximab with either FOLFOX or FOLFIRI in patients with unresectable colorectal cancer with metastasis isolated to the liver. Both groups demonstrated high response rates (68% in the FOLFOX group and 57% in the FOLFIRI group) and increased resectability rates (32% at baseline to 60% after chemotherapy, $P < 0.001$) [71]. Conversely, the MRC COIN trial evaluating the addition of cetuximab to an oxaliplatin-based regimen for first-line treatment of advanced colorectal cancer demonstrated increased response rates but no survival benefit or increase in the number of potentially curative liver resections even in patients selected by additional mutational analysis [72]. However, given the numerous other trials that have shown a substantial benefit in terms of both response rates and resection, cetuximab has been widely used in first-line therapies in patients known to have wild-type *KRAS*, *NRAS*, and *BRAF* colorectal cancer [69–71, 73].

Panitumumab has also been studied in combination with common first-line chemotherapy regimens for metastatic colorectal cancer. The PRIME trial by Douillard *et al.* [74] explored panitumumab plus FOLFOX and reported improved PFS (9.3–11.4 months vs 7.5–9.5 months, $P = 0.01$), improved OS in patients with *KRAS* wild-type tumors, and improved response. However, there was no significant difference in resection rates. Peeters *et al.* [75] studied panitumumab plus FOLFIRI vs FOLFIRI alone as second-line treatment in metastatic colorectal cancer and observed an improvement in PFS (5.9 months vs 3.9 months, $P = 0.04$). Most recently, the VOLFI trial studied FOLFOXIRI with panitumumab vs FOLFOXFIRI alone in colorectal cancer with liver metastasis. The combination of FOLFOXIRI and panitumumab showed significantly higher response rates in patients without *RAS* wild-type tumors (85.7% vs 54.5%, respectively, $P = 0.0013$) and high rates of secondary resection (60% vs 36.4%), though OS and PFS were similar between the two groups [76]. However, treatment-related toxicity was also significantly increased in the FOLFOXIRI-with-panitumumab group (32.8% vs 12.1% with FOLFOXIRI alone, $P = 0.0297$).

Anti-VEGF targeted treatment

Anti-VEGF (vascular endothelial growth factor) therapy has also demonstrated a role in the conversion-chemotherapy setting. Wong *et al.* [77] showed that XELOX (capecitabine and oxaliplatin) plus bevacizumab resulted in high response rates for colorectal-cancer patients with liver metastasis with poor risk features who were initially unresectable. Additionally, 40% of patients became resectable with this combined regimen regardless of *KRAS* mutational status [77]. The OLIVIA trial studied bevacizumab plus FOLFOX or FOLFOXIRI in patients with initially unresectable liver metastases. This study showed that FOLFOXIRI with bevacizumab was associated with improved PFS (18.8 months vs 11.5 months), response rates (81% vs 62%), resection rates (61% vs 49%), and R0 resection rates (49% vs 23%) [78]. As expected, toxicity was increased in the triplet regimen. The TRIBE study assessed bevacizumab plus FOLFOXIRI or FOLFIRI as first-line treatment of metastatic colorectal cancer. This trial also demonstrated FOLFOXIRI plus bevacizumab improved PFS (12.3 months vs 9.7 months, $P = 0.006$) as well as OS (29.8 months vs 25.8 months, $P = 0.03$) [79]. However, in contrast to the OLIVIA trial, for bevacizumab plus FOLFOXIRI or FOLFIRI, there was no significant difference in resection rates.

Comparison of targeted therapies

The use of anti-EGFR and anti-VEGF targeted therapies has also been compared in trials. The FIRE-3 trial studied FOLFIRI plus cetuximab vs FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer. While PFS was similar, OS was significantly longer in the group receiving FOLFIRI plus cetuximab than in the control group (28.7 months vs 25.0 months, $P = 0.017$) and this was even more pronounced for patients with *RAS* wild-type tumors [52]. The percentage of patients who went on to secondary resection was similar between the two groups (36% for the cetuximab group vs 40% for the bevacizumab group). In the PEAK trial, Schwartzberg *et al.* [80] compared FOLFOX plus panitumumab vs FOLFOX plus bevacizumab. Similarly to the FIRE-3 trial, PFS was similar between the two groups, but OS was improved in the group receiving anti-EGFR treatment with panitumumab (34.2 months vs 24.3 months, $P = 0.009$). Again, patients with *RAS* wild-type tumors gained the most benefit from anti-EGFR therapy. In contrast, Venook *et al.* [81] studied cetuximab vs bevacizumab added to either FOLFOX or FOLFIRI in patients with *KRAS* wild-type advanced or metastatic colorectal cancer. They found no significant difference in OS (30.0 months in the cetuximab group vs 29.0 months in the bevacizumab group, $P = 0.08$) or PFS (10.5 months in the cetuximab group vs 10.6 months in the bevacizumab group, $P = 0.45$). Sidedness of the primary tumor, which will be discussed below, also plays a role in suggesting which patients would most benefit from anti-EGFR vs anti-VEGF therapy.

Sidedness

Colorectal cancer is increasingly recognized as a heterogeneous disease and the side (right vs left) where the primary tumor arises may have both prognostic and predictive implications in clinical practice [82–85]. This should be considered when choosing a chemotherapy regimen. Arnold *et al.* [86] reviewed six randomized trials (CRYSTAL [69], FIRE-3 [52], CALGB 80405 [81], PRIME [74, 87], PEAK [80] and 20050181 [75, 88]) to evaluate the prognostic and predictive value of tumor sidedness in colorectal cancer. They found that, in *RAS* wild-type tumors, patients with right-sided tumors had a worse overall prognosis in terms of OS, PFS, and overall response rates. Additionally, they showed the effect of chemotherapy combined with an anti-EGFR agent was greater in patients with left-sided tumors than in those with right-sided tumors. Patients with left-sided primaries who received chemotherapy and anti-EGFR therapy had improved OS and PFS (HRs: 0.75 and 0.78, respectively) and a trend toward a greater response rate compared with right-sided primaries. There was no survival benefit observed in patients with right-sided primaries who received anti-EGFR therapy. In fact, in the CALGB 80405 by Venook *et al.* [89], there was an observed detrimental effect for patients with right-sided tumors who received cetuximab with both decreased PFS and OS. The benefit of anti-EGFR therapy therefore seems to be primarily in those with left-sided primaries. Patients with right-sided primaries may, on the other hand, benefit more from initial treatment with bevacizumab in combination with chemotherapy [90]. Given the more aggressive nature of right-sided primaries,

these patients may benefit more from triplet therapy combined with bevacizumab to facilitate optimal downsizing.

Conclusions

i. Neoadjuvant therapy should be used with the goal of resection.
ii. There is a strong correlation between the neoadjuvant response rate and post-metastasectomy prognosis and outcomes; therefore, predicted high response rates are desirable to increase the likelihood of surgical resection in patients with upfront unresectable disease.
iii. Patients should not be over-treated, as this may result in loss of the resectability window and/or therapy-limiting toxicity from the chemotherapy.
iv. When assessing response to chemotherapy, change in tumor size as well as morphologic changes should be considered.
v. For patients with upfront unresectable disease, conversion chemotherapy is often utilized in clinical practice with the goal of increasing rates of resection, which presumably improves survival.
vi. While numerous trials have shown improved efficacy with triplet therapy combined with a targeted agent, toxicity should be taken into account when considering these regimens [51, 67, 76, 78, 79, 91].
vii. The benefit of anti-EGFR therapies is most marked in patients with left-sided primaries and *RAS* wild-type tumors.
viii. Patients with right-sided primaries may need a triplet regimen (alone or with bevacizumab) for optimal downsizing.
ix. Irinotecan is associated with steatohepatitis, which increases 90-day mortality so should be avoided in the neoadjuvant setting except in the context of a triplet regimen.
x. There is increased perioperative morbidity associated with greater duration of chemotherapy exposure (>6 weeks).

Adjuvant therapy following metastasectomy

The goal of adjuvant chemotherapy following metastasectomy is to eliminate micrometastasis. Much of the data are extrapolated from stage III disease, which supports the use of FOLFOX, but not irinotecan, bevacizumab, or cetuximab in the adjuvant setting [92–94]. Ychou *et al.* [95] studied combinations for adjuvant chemotherapy after complete resection of liver metastases from colorectal cancer. In this study, there was no demonstrated survival benefit seen with the addition of irinotecan (disease-free survival was 21.6 months for flurouracil + folinic acid vs 24.7 months for FOLFIRI, HR 0.89, $P = 0.47$). Therefore, FOLFOX alone is recommended for adjuvant treatment following resection of metastatic disease in colorectal cancer. In older patients (>70 years) or patients with residual neuropathy, it is also reasonable to consider a gentler regimen like 5-FU/capecitabine alone. It is also acceptable to consider close monitoring given the lack of robust data proving the efficacy of adjuvant therapy in this setting.

Similarly to stage III disease, there are no data to support the use of targeted therapies following resection; however, if a regimen is effective in the neoadjuvant setting, some clinicians elect to use the same regimen post-operatively.

Conclusions

i. FOLFOX alone is recommended as adjuvant therapy.
ii. There are limited/no data to support the use of irinotecan, bevacizumab, or cetuximab in the adjuvant setting.

Strategizing for an individual patient

Perioperative chemotherapy for metastatic colorectal cancer remains a nuanced decision. Figure 1 outlines a proposed treatment algorithm based on review of the current literature, which is summarized in Table 1. Multidisciplinary review early and

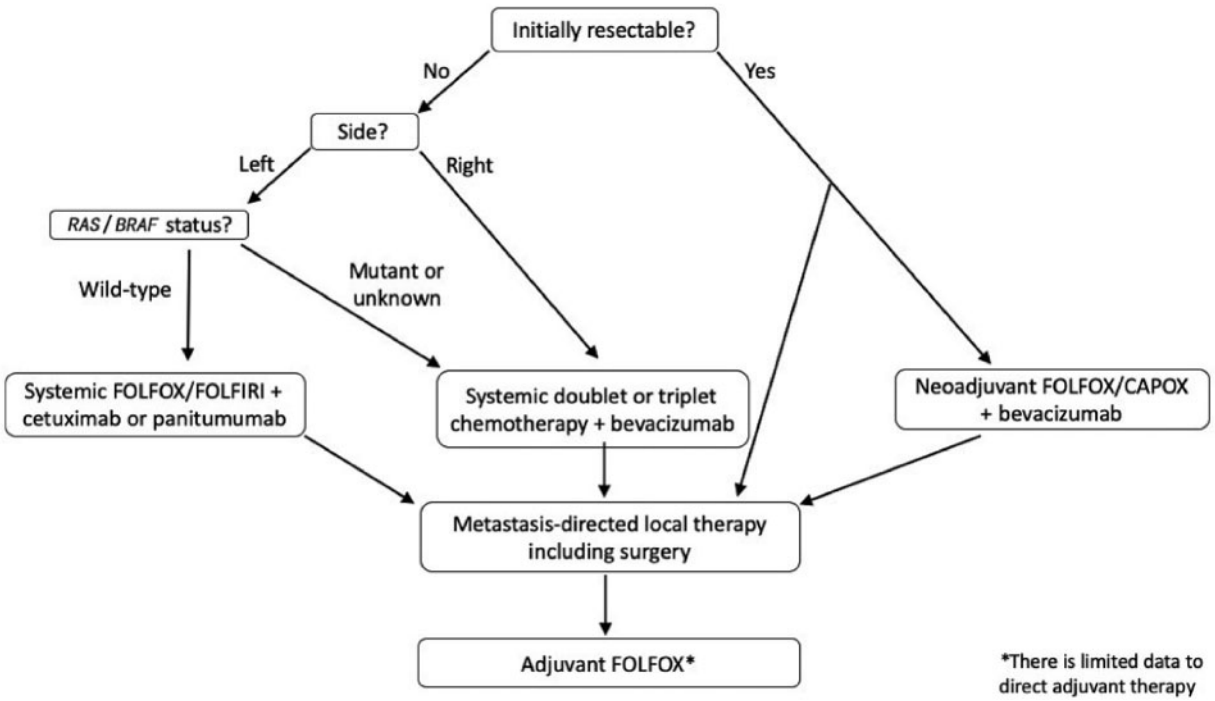

Figure 1. Proposed algorithm for perioperative chemotherapy for patients with metastatic colorectal cancer

Table 1. Selected key studies guiding recommendations

Recommendation	Trial/study	Regimen	Inclusion criteria	Unresectable definition	PFS (months)	OS (months)	Resection rate (%)	Other
Neoadjuvant FOLFOX should be considered for upfront resectable disease	EORTC 40983 [56]	Perioperative FOLFOX vs surgery alone	CRC with 1–4 resectable liver metastases and no detectable extra-hepatic tumors	Judged by multidisciplinary team	20.9 FOLFOX 12.5 surgery alone $P = 0.035$	61.3 FOLFOX 54.3 surgery alone $P = 0.34$	83.0% perioperative FOLFOX 83.5% surgery alone	N/A
	New EPOC [57]	Perioperative chemotherapy +/– cetuximab	CRC (KRAS wild-type) patients with resectable or sub-optimally resectable liver metastasis (no limit) and no detectable extra-hepatic tumors who had not previously received systemic therapy for metastatic disease	Judged by multidisciplinary team	14.1 cetuximab 20.5 FOLFOX-alone group $P = 0.03$	39.1 cetuximab Not reached in chemotherapy alone group	93% chemotherapy alone 85% cetuximab	N/A
Pre-operative irinotecan should be minimized (outside of triplet)	Vauthey *et al.* [59]	No chemotherapy vs FOLFOX vs FOLFIRI vs other	CRC patients who had previously undergone hepatic surgery with curative intent	N/A	N/A	N/A	N/A	Irinotecan was associated with steatohepatitis compared to no chemotherapy (20.2% vs 4.4%, $P = 0.001$). Patients with steatohepatitis had an increased 90-day mortality (14.7% vs 1.6%, $P = 0.001$)
Triplet therapy improves resection rates, but increases toxicity	Falcone *et al.* [67]	FOLFOXIRI vs FOLFIRI	Unresectable metastatic CRC who had not received prior chemotherapy for advanced disease	N/A	6.9 FOLFIRI 9.8 FOLFOXIRI $P = 0.0006$	16.7 FOLFIRI 22.6 FOLFOXIRI $P = 0.032$	15% FOLFOXIRI 6% FOLFIRI $P = 0.033$	There was an increase of grade 2 to 3 peripheral neurotoxicity (0% vs 19%, $P = 0.001$), and grade 3 to 4 neutropenia (28% vs 50%, $P = 0.001$) in the FOLFOXIRI arm
	METHEP [68]	Standard vs Intensified neoadjuvant chemotherapy	Patients with CRC with potentially resectable or unresectable liver metastases	Potentially resectable = complex hepatectomy and/or risky procedure, close contact with major vascular structures Unresectable = having a future liver remnant predicted to be less than 25%–30% of total liver volume.	9.2 standard 11.9 intensified $P = 0.115$	17.7 standard 33.4 intensified $P = 0.297$	43.3% FOLFOX-7 59.4% FOLFIRI-HD 66.7% FOLFIRINOX	N/A

(continued)

Table 1. Continued

Recommendation	Trial/study	Regimen	Inclusion criteria	Unresectable definition	PFS (months)	OS (months)	Resection rate (%)	Other
Pre-operative cetuximab should be used in patients with RAS wild-type primaries	CELIM [71, 96]	Cetuximab + FOLFOX-6 or FOLFIRI	Patients with unresectable, histologically confirmed CRC with liver metastasis and no extra-hepatic metastases	5 or more liver metastases, metastases viewed as technically non-resectable on the basis of inadequate future liver remnant Involvement of major vessels	N/A	N/A	38% FOLFOX 30% FOLFIRI	A partial or complete response was observed in 70% of patients with KRAS wild-type tumors vs 41% of patients with KRAS-mutated (exon 2) tumors, $P = 0.0080$
	Van Cutsem *et al.* [69]	FOLFIRI +/– cetuximab	Histologically confirmed CRC patients with first occurrence of metastatic disease that could not be resected for curative purposes with EGFR expression	Not defined	8.9 cetuximab 8.0 FOLFIRI alone $P = 0.048$	19.9 cetuximab 18.6 FOLFIRI alone $P = 0.31$	4.8% cetuximab 1.7% FOLFIRI alone $P = 0.002$	KRAS mutation status was a significant predictor of tumor response
	Bokemeyer *et al.* [70]	FOLFOX-4 +/– cetuximab	Patients with histologically confirmed, first occurrence of a non-resectable, EGFR-expressing metastatic CRC with at least one radiologically measurable lesion	Not defined	7.2 cetuximab 7.2 FOLFOX-4 alone $P = 0.617$	N/A	4.7% cetuximab 2.4% FOLFOX-4 alone	For KRAS wild-type tumors, cetuximab + FOLFOX significantly increased response (ORR 61% vs 37%, $P = 0.011$) and improved PFS (7.7 vs 7.2 months, $P = 0.0163$) compared with FOLFOX-4 alone
Right-sided primaries may need a triplet + bevacizumab for optimal downsizing	OLIVIA [78]	FOLFOXIRI + bevacizumab vs FOLFOX-6 + bevacizumab	Previously untreated patients with upfront unresectable CRC and exclusively hepatic metastases	No possibility of upfront R0/R1 resection of all lesions <30% residual liver volume after resection Metastases in contact with major vessels	18.6 FOLFOXIRI 11.5 FOLFOX-6	Not reached with FOLFOXIRI 32.2 FOLFOX-6	61 FOLFOXIRI 49 FOLFOX-6	There was increased toxicity in the FOLFOXIRI group
	TRIBE [79]	Cetuximab + modified FOLFOXIRI with Maintenance cetuximab or bevacizumab	Patients with histologically confirmed CRC (RAS and BRAF wild-type) with unresectable and measurable metastatic disease by RECIST	Determined by multidisciplinary team using OncoSurge criteria	10.1 Maintenance cetuximab 9.3 Maintenance bevacizumab HR, 0.83; 95% CI, 0.57—1.21)	33.2 Maintenance cetuximab 32.2 Maintenance bevacizumab HR, 0.92; 95% CI, 0.57—1.47	24.1 Maintenance cetuximab 14.7 Maintenance bevacizumab	N/A

CI: confidence interval; CRC: colorectal cancer; EGFR: epidermal growth factor receptor; 5-FU: 5-fluorouracil; FOLFOX: 5-FU, oxaliplatin; FOLFIRI: 5-FU, irinotecan; FOLFOXIRI/FOLFIRINOX: 5-FU, oxaliplatin, irinotecan; HD: high-dose; HR: hazard ratio; N/A: not applicable.

often throughout treatment planning is key to selecting the appropriate patients for treatment with a curative-intent strategy. For patients with upfront resectable disease, neoadjuvant chemotherapy is primarily used as a test of tumor biology to help guide those who will benefit most from curative intent. FOLFOX alone is recommended in this population. For patients with upfront unresectable disease, neoadjuvant therapy should be used with the goal of converting a patient's disease to be resectable. The response rate is highly predictive of which patients go on to resection, but the goal should not be maximum response. When deciding on a regimen, *RAS* status and primary location (sidedness) should be considered: patients with extended *RAS* wild-type tumors derive the most benefit from cetuximab while patients with right-sided and/or *RAS*-mutant tumors may require a triplet regimen alone or with bevacizumab to convert resectability. Pre-operative irinotecan (outside of a triplet) should be minimized due to steatohepatitis-associated mortality. In the adjuvant setting, FOLFOX alone should be used regardless of initial resectability. Overall, the choice of chemotherapy should be tailored for the individual patient and ongoing research is still needed to identify optimal treatment strategies that improve survival.

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Conflicts of interest

None declared.

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