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Integrating Chemotherapy into the Management of Oligometastatic Colorectal Cancer: Evidence based Approach Using Clinical Trial Findings

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Abstract

Purpose—With the use of case presentations, we present a review of the role of systemic chemotherapy in oligometastatic colorectal cancer and suggest ways to integrate clinical research findings into the interdisciplinary management of this potentially curable subset of patients.

Methods—This educational review discusses the role of chemotherapy in the management of oligometastatic metastatic colorectal cancer.

Results—In initially resectable oligometastatic colorectal cancer, the goal of chemotherapy is to eradicate micrometastatic disease. Perioperative 5-fluorouracil and oxaliplatin along with surgical resection can result in 5-year survival rates as high as 57%. With the development of increasingly successful chemotherapy regimens, attention is being paid to the use of chemotherapy to convert patients with initially unresectable metastasis into patients with a chance of surgical cure. The choice of chemotherapy regimen requires consideration of the goals of therapy and assessment of both tumor and patient-specific factors.

Discussion—Herein we discuss the choice and timing of chemotherapy in patients with initially resectable and borderline resectable metastatic colorectal cancer. Coordinated multidisciplinary care of such patients can optimize survival outcomes and result in the cure of patients with this otherwise lethal disease.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer for both men and women in the United States and the third leading cause of cancer death. According to the American Cancer

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Society, 136,830 CRC cases will be diagnosed and 50,310 deaths are expected in 2014.[1] Given the prevalence of this disease and the associated mortality, optimizing therapy for patients with metastatic disease is critical.

In the era before effective systemic therapy, patients with metastatic CRC achieved a median survival of roughly 6 months.[2] Subsequent advances in systemic therapy increased the median overall survival of these patients to longer than 24 months.[3] In a similar time frame, advances in surgery led to the identification of a subset of metastatic CRC patients whose outcomes are markedly improved with surgical intervention. This distinct clinical state where macroscopic disease is confined to a limited and potentially resectable anatomic distribution is referred to as oligometastatic CRC.[4] However, because of a high likelihood of occult micrometastatic disease, integrating chemotherapy along with surgical extirpation of macroscopic disease is crucial. In patients who undergo such therapy, median overall survival rates in the range of 5 years and a distinct chance for cure can be expected.[5,6] Herein, with the use of case presentations, we highlight clinical trials that have advanced our understanding of the role of systemic chemotherapy in oligometastatic CRC and suggest ways to integrate these clinical trial findings into the interdisciplinary management of patients with oligometastatic CRC.

CASE 1

> A 46 year old male presents with several weeks of low abdominal pain and hematochezia. Colonoscopy demonstrates a mass near the splenic flexure, biopsy confirms moderately differentiated adenocarcinoma. Staging studies demonstrate a solitary 5 cm mass in segment 6 of the liver (Figure 1). CEA is 39.8 ng/mL. How should this patient be approached?

About 10–20% of patients with liver metastases from CRC are considered resectable with curative intent.[7,8] Five-year survival rates in large series of patients with complete resection alone range from 28–47%.[5,9–11] The number of metastases is no longer a deciding factor, but rather whether negative surgical margins can be obtained with ≥ 30% of remaining healthy liver mass.[12,13] One option would be initial surgical resection consisting of extended left colectomy and synchronous liver resection. The extent of the liver resection would depend on the relationship of the metastases to the hepatic vein and portal pedicle. If a right hepatectomy is required to achieve negative margins then it is important for the surgeon to determine whether the residual liver volume is adequate. Excellent resources have been developed to calculate liver volumetry either manually or using 3D modeling software. Normally 25% residual liver volume is adequate but in patients who undergo extensive systemic chemotherapy often 40% is deemed appropriate. If residual liver volume is deemed to be inadequate, then portal vein embolization is one option and the other is to consider preoperative systemic chemotherapy to decrease the size of the liver metastases. In this case presentation, the primary tumor and liver metastases are amenable to complete resection without involved margins (R0 resection) leaving an adequate volume of residual liver. However, with synchronous CRC liver metastasis, there is a significant risk of undetected micrometastatic disease. Thus, the first question to be addressed is whether to proceed

immediately to surgical resection or to first undertake a period of neoadjuvant chemotherapy.

There are multiple theoretical advantages to neoadjuvant systemic therapy versus primary surgical resection of oligometastatic CRC. One potential advantage is that it allows for early administration of agents with the ability to eradicate micrometastatic disease when the likelihood of such occult disease is high. Other potential advantages include the ability to reduce the volume of macroscopic disease that requires resection and the ability to assess response as an *in vivo* test of chemotherapeutic sensitivity to inform future treatment decision-making.[14,15] Potential disadvantages to neoadjuvant therapy include toxicity that hampers the outcome from subsequent surgical resection and the possibility that tumor progression on treatment precludes future surgery.[16–18] Nonetheless, the presence of primary chemotherapy refractory disease is uncommon and is a stronger predictor of poor outcome than the sequence of therapy itself.[19] Here, we will address perioperative chemotherapy and adjuvant chemotherapy approaches sequentially.

Perioperative Chemotherapy

The landmark European Intergroup EORTC 40983/EPOC trial originally published in 2008 is perhaps the most robust clinical trial dataset in the resectable oligometastatic setting.[20] Three-hundred and sixty-four patients with colorectal cancer and up to 4 liver metastases were assigned to surgery alone or to 6 cycles of the FOLFOX4 regimen consisting of oxaliplatin, leucovorin, bolus and short-term infusional 5-fluorouracil (5-FU) both before and after surgery. The study was powered to detect a 40% increase in progression-free survival (PFS).

In the primary analysis of all randomly assigned patients there was a trend towards increased PFS amongst patients assigned to perioperative chemotherapy with a hazard ratio (HR) of 0.79 (95% CI 0.62–1.02; p=0.058). Median PFS increased from 11.7 months to 18.7 months. In sensitivity analyses of those patients deemed eligible for surgery and those who proceeded to surgical resection, there was a significant increase in PFS with HRs of 0.77 (95% CI 0.6–1.00; p=0.041) and 0.73 (95% CI 0.55–0.97; p=0.025) respectively. Only 12 of the 171 patients receiving pre-operative chemotherapy progressed (7%) and of those only 8 did not undergo surgical resection. The overall operative mortality was less than 1% in both treatment groups. An updated survival analysis did not detect a statistically significant difference in overall survival (OS) between the groups (HR 0.88, p=0.34); however, the study was not designed nor powered to detect a difference in overall survival.[21] Nonetheless, *a posteriori* calculations suggested that a 33% or greater improvement survival with perioperative chemotherapy could have been detected with 80% power.[21]

Several limitations of EORTC 40983 warrant attention. The control group did not get adjuvant chemotherapy; therefore, the results do not provide direct evidence that the perioperative strategy is superior to an adjuvant approach. Only 63% of patients in the perioperative group started the post-surgical period of chemotherapy. Despite being the largest controlled study in this setting, it was not adequately powered to detect clinically meaningful overall survival differences between the arms. A further limitation is that patients with more than 4 liver metastases were not included. Notwithstanding these

limitations, this study provides the strongest evidence to date that a perioperative chemotherapy approach is safe and can improve outcomes in patients with oligometastatic CRC. To date, no regimen has proven superior to FOLFOX in initially resectable patients, although the addition of bevacizumab to capecitabine and oxaliplatin (XELOX) demonstrated safety in a phase II study.[22] Moreover, a cautionary signal was raised by the initial results of the New EPOC study, comparing FOLFOX with or without cetuximab in resectable oligometastatic CRC.[23] While response with FOLFOX plus cetuximab was superior (70% vs. 62%), PFS was statistically significantly *inferior* to FOLFOX alone (14.8 versus 20.5 months, p<0.030).

Adjuvant Chemotherapy

In the 5-FU era, the FFCD ACHBTH AURC 9002[24] and the EORTC/NCIC/GIVIO [ENG][25] randomized phase III trials were designed to address the issue of adjuvant chemotherapy after resection of limited liver and/or lung metastases. Unfortunately each trial failed to meet its accrual goal and was closed early. As both trials were of similar design and used similar bolus 5-FU and leucovorin regimens, a pooled analysis was performed.[26] A total of 278 patients were included, of which 138 patients were assigned to adjuvant chemotherapy and 140 patients were assigned to surgery alone. Inclusion criteria included resection of the primary tumor and four or fewer metastases located in a single location (liver in the FFCD trial and liver or lung in the ENG trial). In the pooled analysis, median disease-free survival (DFS) was 18.8 months in those assigned to surgery alone and 27.9 months in those assigned to adjuvant chemotherapy (HR = 1.32; 95% CI 1.00–1.76; p=0.058). Corresponding median OS was 47.3 months compared to 62.2 months (HR=1.32; 95% CI 0.95 to 1.82, p=0.095). In multivariate analysis, the risk of recurrence (HR: 1.39, p=0.02) and death (HR: 1.39, p=0.046) were significantly increased among patients assigned to surgery alone compared to those assigned to chemotherapy. Despite the inherent limitations of an underpowered, pooled analysis, these data suggest a benefit for adjuvant 5-FU-based chemotherapy.

In the oxaliplatin era, there have been no completed phase III trials evaluating the benefit of adjuvant oxaliplatin based chemotherapy versus surgery alone in the oligometastatic setting. A retrospective analysis of 60 patients suggested an improvement in DFS and OS compared to historical controls.[27] A strong argument can be made to extrapolate data from the stage III adjuvant CRC experience to the oligometastatic setting since the goal of eradicating micrometastatic disease is identical. Phase III data supporting adjuvant chemotherapy with either 5-FU or 5-FU in combination with oxaliplatin in stage III CRC is robust.[28,29]

The additional utility of irinotecan added to 5-FU was prospectively studied in the oligometastatic setting. The CPT-GMA-301 trial randomized 306 patients following R0 resection of oligometastatic hepatic metastasis to adjuvant bolus and short term infusional 5-FU and leucovorin (LV5FU2) or the same regimen with irinotecan (FOLFIRI).[30] Median DFS in patients receiving LV5FU2 was 21.6 versus 24.7 months in the FOLFIRI arm [HR: 0.89, P=0.44]. No overall survival advantage was observed with the addition of irinotecan to LV5FU2 therapy. Interestingly, the lack of benefit of irinotecan in the oligometastatic setting mirrors the results of trials in stage III CRC, where multiple studies have failed to

demonstrate a benefit from adjuvant irinotecan.[31–33] Similarly, no prospective data supports the addition of bevacizumab, cetuximab or panitumumab to adjuvant chemotherapy in resected CRC.

Given the theoretical benefits of early eradication of micrometastatic disease, the ability to assess chemotherapy sensitivity *in vivo* and the absence of data to suggest inferior surgical outcomes with neoadjuvant chemotherapy, we generally recommend perioperative chemotherapy with FOLFOX in cases such as the one described here. Progression during preoperative chemotherapy is uncommon, reflects a poor disease biology, and necessities consideration of alternative treatment options to offer a chance of prolonged remission.[19] However, there is support for the use of adjuvant therapy in resected oligometastatic CRC in patients with good functional status and prolonged life expectancy. An adjuvant approach may be preferred in selected patients where less may be gained from early systemic therapy, such as those with very small solitary tumors or with an isolated metachronous recurrence.[34] Close cooperation between the treating medical oncologist and surgeon is essential to optimize the timing of therapy.

CASE 2

> A 67 year male was referred from a regional community hospital with a large right liver metastases with a prior history of a right hemicolectomy for stage II cecal adenocarcinoma. CT scan of the liver demonstrated that the large right lobe metastases extended to the caudate lobe in close proximity to the inferior vena cava (Figure 1). It was judged that the lesion could not be resected with a high probability of negative margins. How should such a case be approached?

A subset of metastatic CRC patients present with disease that is not initially resectable with high probability of negative margins, but in whom a good response to therapy can render all sites of disease resectable. “Conversion therapy” is defined as treatment intended to convert initially unresectable disease to resectable. The potential benefit was illustrated in a prospective study where a cure was obtained in 16% of patients with initially unresectable colorectal liver metastases with survival rates at 5 and 10 years of 33% and 27% respectively.[35] Even in the absence of cure, conversion to resection defines a subgroup of patients with superior survival to those who do not undergo resection where 5-year survival with chemotherapy alone is only on the order of 10%.[36] Despite published guidelines,[37,38] the specific definition of unresectable metastatic colorectal cancer amenable to conversion therapy is evolving. Nonetheless, the goals of conversion chemotherapy are uniform: to reduce tumor volume (overall response rate) while simultaneously avoiding end organ (particularly liver) toxicity that results in increased surgical morbidity and mortality.[36]

Conversion Therapy

Reported response rates with modern chemotherapy regimens vary (Table). Standard doublet regimens (FOLFOX and FOLFIRI) have front-line response rates ranging from 34–56% and are considered equivalent.[39–44] The response rate induced by the triplet regimen FOLFOXIRI that includes leucovorin, fluorouracil, oxaliplatin, and irinotecan is superior to

that of FOLFIRI (66% vs 41%, $p < 0.0001$),[41] and the regimen is associated with conversion to resectability in 19% of patients.[45]

The addition of biologic agents to a cytotoxic chemotherapy backbone in advanced CRC is the subject of active research. The ability of bevacizumab, a VEGF inhibitor, to increase PFS and OS with modern chemotherapy in the metastatic setting is established. However, its ability to increase response rate is the subject of debate. In the frontline setting, bevacizumab improved response when combined with a bolus 5-FU, leucovorin, and irinotecan regimen (IFL) (Table).[39,46] However, no such improvement in response was observed in the large N016966 trial of FOLFOX/XELOX with or without bevacizumab.[47] These results raise questions about the utility of this agent in the conversion setting where response is the primary goal.[47]

The response data for the use of monoclonal anti-EGFR antibodies (cetuximab or panitumumab) is more uniform. The addition of cetuximab or panitumumab to common frontline chemotherapy regimens consistently increases response rate, specifically in KRAS codon 12 and 13 wild type tumors (Table).[43,48–50] Potential benefit in the conversion setting has also been demonstrated in a phase II study, where R0 resections were achieved in 34% of initially unresectable patients treated with neoadjuvant FOLFOX or FOLFIRI and cetuximab.[51] In the CRYSTAL trial, which compared FOLFIRI with and without cetuximab, the R0 resection rate of tumors that were KRAS wild-type was higher in the cetuximab arm (5.1% vs. 2.0%, $p=0.027$).[52] Recently, the observation that anti-EGFR antibody therapy is ineffective in KRAS codon 12 and 13 mutated tumors has been extended to mutations in KRAS codons 59, 61, 117, and 146 as well as similar locations in NRAS.[53–55] Currently, in patients with mutation at any of these sites, the use of an alternative regimen such as FOLFOXIRI is indicated. However, predictive biomarker development for selection of EGFR-targeted therapy is an area of active investigation with resultant dynamic changes in our understanding of the utility of these markers. Therefore, future refinements to this selection strategy are expected.

There have been several attempts to enhance delivery of chemotherapy to the liver using hepatic arterial infusion (HAI). Indeed, several single institution studies have demonstrated the potential for efficacy of this approach.[56,57] However, due to the potential for serious liver toxicity and the expertise required for successful administration, HAI chemotherapy cannot currently be recommended outside of select experienced centers.

While a secondary goal of systemic therapy in the conversion setting is to avoid end organ toxicity, all active cytotoxic agents in colorectal cancer are associated with some hepatotoxicity. Prolonged 5-FU administration is associated with hepatic steatosis and increased surgical morbidity.[58,59] Oxaliplatin can also increase surgical morbidity and is associated with hepatic sinusoidal obstruction syndrome.[59–62] Irinotecan toxicity is perhaps the most worrisome due to the potential for increased surgical morbidity and mortality from reduced hepatic reserve and non-alcoholic steatohepatitis.[18,59,62–64] As the complication rate associated with hepatectomy is related to the number of cycles of chemotherapy administered,[65] the number of pre-surgical cycles of therapy should be carefully considered.

Overall, in the patient with initially unresectable oligometastatic CRC amenable to conversion therapy, the best chemotherapy or chemotherapy-biologic combination is not established. Furthermore, the optimal duration of pre-operative or total systemic therapy is also unclear. Given the high response rate and reasonable tolerability, we currently favor the FOLFOXIRI regimen in patients with a good functional status regardless of RAS tumor status. A regimen containing an EGFR inhibitor may be a reasonable alternative in pan-RAS wild-type tumors; however, the New EPOC results suggest caution and imply that the chemotherapy backbone should not contain oxaliplatin.[23] To limit chemotherapy-induced hepatotoxicity and surgical morbidity and mortality, we favor the fewest cycles of pre-operative chemotherapy to attain an adequate response, particularly when utilizing irinotecan. Our algorithm for approaching patients with oligometastatic CRC is given in Figure 2.

CONCLUSION

It is an exciting time to be treating colorectal cancer as outcomes have improved dramatically in the last several decades. An interdisciplinary approach to oligometastatic colorectal metastases, as described in this review, can improve outcomes in this potentially curable subgroup.

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SYNOPSIS

This educational review summarizes the rationale and clinical trial data supporting the integration of chemotherapy in the management of patients with oligometastatic colorectal cancer.

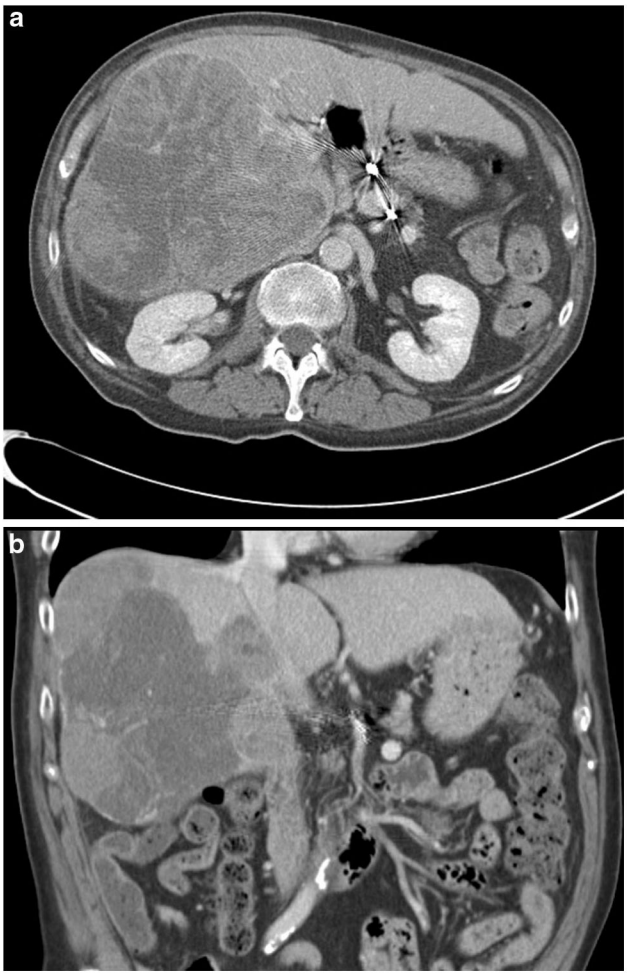

Figure 1.
(A and B) Case 2. Large colorectal liver metastases.

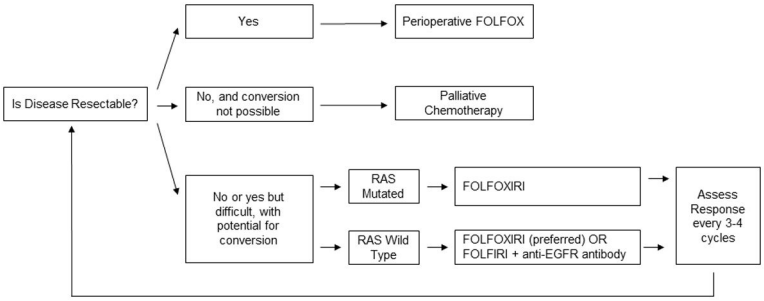

Figure 2.
Suggested treatment algorithm for patient with oligometastatic colorectal cancer.

Table 1

Overall response rates of selected combination chemotherapy regimens in front-line advanced colorectal cancer.

Author	Phase	Year	Regimen	N	Response Rate (%)	P-Value
Cytotoxics alone						
Goldberg et al.[39]	III	2004	IFL FOLFOX	264 267	31 45	0.002
Tournigand et al.[42]	III	2004	FOLFIRI FOLFOX	113 113	56 54	NS
Falcone et al.[41]	III	2007	FOLFIRI FOLFOXIRI	122 122	41 66	<0.001
Cytotoxics +/− bevacizumab						
Hurwitz et al.[46]	III	2004	IFL IFL + bevacizumab	411 402	35 45	0.004
Saltz et al.[47]	III	2008	XELOX/FOLFOX XELOX/FOLFOX + bevacizumab	701 699	38 38	NS
Falcone et al.[66]	III	2013	FOLFIRI + bevacizumab FOLFOXIRI + bevacizumab	254 250	53 65	0.006
Cytotoxics +/− EGFR antibody (KRAS exon 2 wild type)						
Van Cutsem et al.[43,52]	III	2009	FOLFIRI FOLFIRI + cetuximab	350 316	40 57	<0.001
Bokenmeyer et al.[48]	II	2009	FOLFOX FOLFOX + cetuximab	97 82	34 57	0.003
Douillard et al.[49]	III	2010	FOLFOX FOLFOX + panitumumab	331 325	48 55	0.068
Maughan et al.[50]	III	2011	FOLFOX/XELOX FOLFOX/XELOX + cetuximab	367 362	57 64	0.049

NS, not significant