Neoadjuvant Treatment for Surgically Resectable Metastatic Colorectal Cancer

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Here, we review the studies that have explored different treatment regimens, therapeutic sequencing, and biologic inclusions for the treatment of these patients, with neoadjuvant intent. We also describe how we have established our own treatment paradigm for the management of potentially curable metastatic colorectal cancer.

Overview

In the United States, colorectal cancer was predicted to have the fourth highest rate of incidence of new diagnoses among all cancers in 2015, with over 130,000 new cases expected.[1,2] Twenty percent of patients with newly diagnosed colorectal cancers present with metastatic disease. The average 5-year survival for metastatic colorectal cancer is 12.9%. Surgical resection is the only potentially curative option for patients with this disease. However, there are limitations to its use, since less than 15% of patients with metastatic colorectal cancer have disease that is considered resectable at diagnosis,[3] and the failure rate remains high.[4] Thus, a number of studies have evaluated the role of preoperative medical therapy to improve metastasectomy outcomes, both as neoadjuvant therapy for resectable metastatic disease and as a method for converting unresectable metastatic disease into resectable disease.[5] These preoperative medical approaches could also have implications for patients who have localized disease, since up to 20% of these patients will go on to develop metastatic recurrent disease within 5 years of their initial diagnosis.[2,6]

The most common site for distant metastases from colorectal cancer is the liver.[7] Among all patients with hepatic metastases, potential resection is limited to about 15% to 20% upon presentation. To improve outcomes in patients with unresectable liver metastases, systemic treatment has been evaluated as a method for converting unresectable to resectable disease.[5] Certain clinicopathologic features have been identified to suggest which patients could benefit from hepatic metastasectomy. In the past, the contraindications for hepatic metastasectomy were the presence of four or more metastases within the liver, the presence of extrahepatic metastases, the presence of large hepatic metastases, or the inability to obtain more than 1-cm negative margins at hepatic metastasectomy.[8] However, because of the inconsistent and conflicting prognostic value of these clinicopathologic features, the paradigm of resectability has changed. The new paradigm considers the ability to achieve an R0 resection upon metastasectomy as the most relevant indication for offering this intervention. The limitations to this approach are preserving adequate functional tissue after surgery, biliary drainage, and vascular inflow and outflow structure, as well as the need to spare at least two adjacent segments or 20% or more of the liver tissue.[8] Of all patients with metastatic colorectal cancer, up to 2.3% have lung metastases at presentation, and up to 22.4% have lung metastases with disease recurrence.[7] There are no defined criteria for resectability of lung metastases. Certain prognostic factors should be addressed carefully before surgery because they suggest an association with higher rates of recurrence. These factors include bilateral lung metastases or more than six lung lesions. Patients who have involvement of other organ sites are generally considered to be at high risk for recurrence as well.[8] However, surgery could be attempted if, after multidisciplinary discussion, R0 resection is deemed possible with acceptable morbidity and mortality.

Preoperative Treatment Approach

Potential advantages of preoperative therapy for liver or other metastases from colorectal cancer are the earlier treatment of micrometastases, assessment of tumor response to chemotherapy, avoidance of surgery in patients who have early disease progression, and conversion of unresectable
to resectable tumors. The drawback to a preoperative approach is potential toxicity from chemotherapy; for example, liver steatohepatitis has been reported at a rate of 4% to 11% and sinusoidal liver injury at a rate of 26% to 42%. A further disadvantage is interval disease worsening that could exclude surgery as an option. The ultimate goal of this preoperative treatment is of course cure, and different factors have been evaluated as surrogate measures of outcome to determine the benefit of such treatment in achieving a cure. John et al showed that 5-year survival in patients with R0 resection was 46.7%, compared with 14.6% in patients with R1 resection \(P < .001\). Similarly, Tan et al reported that 10-year disease-specific survival was 68% for liver metastasis resection in colorectal cancer patients. Therefore, if a different treatment approach, such as neoadjuvant therapy, can increase rates of R0 resection, it may in turn lead to higher rates of cure.

Multiple chemotherapy agents and antibody therapies have demonstrated effectiveness in the management of patients with metastatic colorectal cancer. Meanwhile, a limited number of agents (fluoropyrimidine with or without oxaliplatin) have demonstrated effectiveness in the adjuvant setting. Many of these regimens have been explored for their preoperative impact in the treatment of patients with both resectable and unresectable disease. The studies discussed here are summarized and categorized by these two different intentions in Tables 1 and 2.

**FOLFOX and CAPEOX**

Doublet chemotherapy regimens using a fluoropyrimidine paired with oxaliplatin have an established curative role for the adjuvant management of patients with stage III colorectal cancers, and thus serve as a natural choice of therapy for exploration in the preoperative management of potentially curable metastatic disease. In a phase II trial, Alberts et al reported outcomes of the use of folinic acid, fluorouracil (5-FU), and oxaliplatin (FOLFOX) as a conversion therapy in 42 patients with liver-only metastases that were deemed unresectable due to major liver vasculature involvement or more diffuse liver metastases.

The median number of treatment cycles was 10; the overall response rate (ORR) was 60% (95% confidence interval [CI], 46%–75%). Of the 17 patients who underwent surgery, 14 (33% of the total enrollment) had complete resection (R0). The overall median time to disease recurrence for all surgical patients who had a relapse was 19 months, and the median 3-year overall survival (OS) was 71%. Adam et al retrospectively evaluated conversion chemotherapy using 5-FU and oxaliplatin to treat 701 patients with metastatic colorectal cancer deemed to have unresectable disease; chemotherapy dose schedule was modified and optimized during the study period (1988–1996), in keeping with then-current standards. Patients received neoadjuvant therapy for a mean of 10.6 months. The conversion rate to resection was 13.6%, and 5-year OS after resection was 34%. Six patients had a pathologic complete response; of these patients, the 5-year OS was 83%, and 50% had no evidence of disease at 5-year follow-up. Coskun et al retrospectively reviewed capecitabine and oxaliplatin (CAPEOX) as a conversion therapy in 35 patients with unresectable liver metastases. The median number of treatment cycles was 4 (range, 2–9). The ORR was 37.2%; however, 20% of the patients were converted to surgically resectable disease based on imaging results. Of the five patients who had surgery, four (11.4%) had an R0 resection.

Neoadjuvant therapy using a fluoropyrimidine/oxaliplatin doublet has also been explored in patients with metastatic disease that is deemed resectable upon presentation. These investigations have only been early-phase studies; direct comparisons with upfront surgery have not been carried out. Wein et al used FOLFOX in the neoadjuvant setting for metastatic colorectal cancer patients who were considered to have resectable liver metastases upon presentation. Twenty patients were enrolled in this phase II trial, and all underwent resection, with 80% achieving an R0 resection outcome. Pathologic complete response was observed in 18.7% of patients. The 2-year disease-free survival (DFS) among patients who achieved an R0 resection was 52% (95% CI, 23%–81%), and the median OS was 4.8 years (95% CI, 3.303–6.362). Lorenz et al reported the outcome of neoadjuvant FOLFOX in 42 patients with resectable liver metastases. The phase II part of the study had two arms, in which patients were assigned to 3 or 6 cycles of FOLFOX. The ORR was 48%, and 36 of the patients (86%) underwent surgical resection. R0 resection was achieved in 31 patients (74%).

**FOLFIRI**

In several smaller studies, irinotecan chemotherapy doublets have been explored as preoperative systemic therapy in potentially curable metastatic colorectal cancer, as an alternative to oxaliplatin. In a phase II study of 35 patients with hepatic metastases considered resectable upon presentation,
Bathe et al evaluated the benefits of neoadjuvant folinic acid, 5-FU, and irinotecan (FOLFIRI). The ORR was 40%. All 30 patients who proceeded to surgery achieved an R0 resection. The median DFS for all resected patients was 23 months from the time of liver tumor resection, and the 2-year OS was 93%.[19]

In a study of 40 patients who presented with liver metastases deemed unresectable, Pozzo et al assessed FOLFIRI as a conversion therapy. They reported an ORR of 47.5%. All 13 patients (32.5%) who went to surgery had an R0 resection.[20] The median DFS in resected patients was 52.5 months, and the 5-year survival was 62%.[21] Ho et al reported similar results in 40 patients given a median of 12 cycles of FOLFIRI as conversion therapy. The ORR was 55% (95% CI, 39.5%–70.4%), but only 10% of the patients were able to undergo surgical resection.[22]

**FOLFOXIRI**

As a natural extension of the doublet therapies using oxaliplatin or irinotecan with fluoropyrimidines, Falcone et al explored the combination of all three drugs for conversion therapy. This phase III study demonstrated the efficacy of folinic acid, 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) vs FOLFIRI in unresectable liver metastases. The median number of cycles was 11 for FOLFOXIRI and 10 for FOLFIRI. The ORR was 60% vs 34%, favoring FOLFOXIRI ($P < .0001$), and the rate of R0 resection also favored FOLFOXIRI (15% vs 6%; $P = .033$).[23] Masi et al reported the follow-up results of three different trials for patients who underwent treatment with FOLFOXIRI for unresectable liver metastasis. The total number of patients was 196, and the median number of chemotherapy cycles was 11. The ORR was 70%, and R0 resection was achieved in 37 patients (19%). The 5-year survival in the R0 resection group was 42%.[24]

**Antibody therapy**

Beyond chemotherapy, preoperative antibody therapies have also been explored. Gruenberger et al assessed neoadjuvant CAPEOX combined with bevacizumab in 56 patients with metastatic colorectal cancer and resectable hepatic metastases. In this phase II trial, the median number of treatment cycles was 6. The ORR was 73.2%, and the R0 resection rate was 93%.[25] Wong et al assessed preoperative CAPEOX combined with bevacizumab in 46 patients with metastatic disease with both resectable and unresectable liver metastases. The phase II trial had an ORR of 78% (95% CI, 63%–89%). The rate of R0 resection was 20%, and 40% of unresectable metastases were converted to resectable.[26] Uetake et al reported that after 6 cycles of the combination of FOLFOX and bevacizumab, 19 patients with resectable disease had an ORR of 68.4% and 16 of these patients (84.2%) had an R0 resection. In the same study, 26 patients with unresectable disease had an ORR of 46.2% and 4 patients (15.4%) had R0 resections.[27] In a study by Bertolini et al, 21 patients with unresectable liver metastasis were given 6 cycles of FOLFOX combined with bevacizumab. The ORR was 57.1%. Thirteen patients (61.9%) achieved R0 resections. The progression-free survival (PFS) and the OS in the surgical group were 12.9 months and 22.5 months, respectively.[28] Recently, Gruenberger et al assessed the effect of combining bevacizumab with either FOLFOXIRI or FOLFOX in 80 patients with unresectable liver metastasis. The ORR was 81% vs 62%, favoring the FOLFOXIRI arm. For patients who underwent surgery, R0 resection was achieved in 20 (49%) and 9 (23%) patients, respectively, again favoring the FOLFOXIRI arm. The PFS was 18.6 months (95% CI, 12.9–22.3 months) and 11.5 months (95% CI, 9.6–13.6 months), favoring the FOLFOXIRI arm.[29] Masi et al evaluated the effect of combining preoperative FOLFOXIRI with bevacizumab in 57 patients with unresectable liver metastasis. The median number of cycles was 12. The ORR was 77%; 18 patients (32%) had surgery, and 15 (26%) achieved an R0 resection.[30]
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What Have Prior Efforts to Improve Outcomes for Patients With Resectable Metastatic Colorectal Cancer Achieved?

As noted in this review, a portion of patients with metastatic disease, principally in the liver or lungs, may achieve long-term survival following resection of their metastatic colorectal cancer. While a prior intense focus on refining surgical approaches, the use and timing of chemotherapy, and selection of patients increased the number of patients benefiting from this approach, the field has made few advances in the last decade. A sizable percentage of patients with limited organ involvement continue to die of their metastatic disease despite the use of multimodality therapy.

What Is Needed to Move Forward From Here?

It appears that we are reaching the limits of what surgery or ablative techniques may achieve, and we continue to be limited by the small number of systemic agents available to treat colorectal cancer. Thus, there is a strong and continued need to rethink our approach to patients in this setting, utilizing both the tools we have available and the growing body of molecular knowledge to develop new and innovative approaches. Identifying novel therapies that can control and ultimately eradicate micrometastatic disease appears to be one of the fundamental missing links in our ability to achieve meaningful advances. For now, however, it remains critical that patients with limited metastatic disease undergo multidisciplinary review prior to initiation of therapy. A small but meaningful number of patients do truly benefit from this approach.

The use of anti-epidermal growth factor receptor antibody therapy has also been explored. Primrose et al assessed the benefit of adding cetuximab to chemotherapy vs chemotherapy alone for resectable liver metastases in tumors that were KRAS wild-type at exon 2. The chemotherapy regimens were FOLFOX, FOLFIRI, and CAPEOX; cetuximab was the antibody used in those arms where included. Complete or partial tumor responses occurred in 73 of 117 patients (62%) receiving chemotherapy alone and in 83 of 119 patients (70%) receiving chemotherapy plus cetuximab. The ORR was 62% for patients receiving chemotherapy alone and 70% for patients receiving chemotherapy plus cetuximab ($P = .59$). The rate of R0 resection was 15% in both groups.[31] In a smaller study, Hatano et al assessed the addition of cetuximab to FOLFOX in 35 patients with unresectable liver metastases. The ORR was 77.3%, and the R0 resection rate was 50%.[32] Seven cycles of FOLFIRI combined with cetuximab in 23 patients with unresectable liver metastases resulted in an ORR of 39.1%. Although the rate of R0 resection was not reported, 7 patients (30.4%) had curative surgery.[33] Van Cutsem et al reported on the use of preoperative FOLFIRI with or without cetuximab in patients with unresectable liver metastasis and both KRAS-mutant and wild-type tumors. The ORRs were 57.3% and 39.7%, favoring the cetuximab arm for KRAS wild-type tumors. The rates of R0 resection were 7.9% and 4.6%, again favoring the cetuximab arm in KRAS wild-type tumors.[34,35] Saridaki et al demonstrated the effect of the preoperative combination of FOLFOXIRI and cetuximab in 30 patients with KRAS wild-type colon cancer and unresectable liver metastases; 24 patients (80%) had previous adjuvant therapy. The planned duration of preoperative therapy was 6 months. The ORR was 70%, and 11 patients (37%) achieved R0 resection.[36] Cetuximab given with either FOLFOX or FOLFIRI has also been evaluated in patients with metastatic colorectal cancer and unresectable liver metastases. Folprecht et al retrospectively identified 64 patients whose tumors were KRAS and BRAF wild-type and showed an ORR of 72%. The rates of R0
resection were not reported for KRAS and BRAF wild-type subsets.[37,38] Ye et al assessed the addition of cetuximab to either FOLFOX or FOLFIRI as a conversion therapy for unresectable liver metastases in KRAS wild-type colorectal cancers. The ORR was 57.1% vs 29.4%, favoring the addition of cetuximab (P < .01). The rates of R0 resection were 25.7% vs 7.4%, also favoring the cetuximab arm (P < .01).[39,40] In a phase II trial, the efficacy of adding cetuximab to FOLFOX was assessed in patients with unresectable liver metastases and KRAS wild-type tumors.[41] Of the 73 patients enrolled, 46 completed 12 weeks of therapy. The ORR was 73%, and the rate of R0 resection was 27%. The median time to progression for those who had R0 resection was 14.1 months (95% CI, 1.3–30.8 months).[41] In a retrospective review of 151 patients with unresectable liver metastases who received cetuximab combined with irinotecan, oxaliplatin, or both, the ORR was 15.2% and the R0 resection rate was 9%.[42] Adding panitumumab to CAPEOX in 49 patients with unresectable liver metastases produced an ORR of 65%. Surgery was performed in 21 of the patients (43%), and 14 (67%) had R0 resections.[43]

**Discussion**

In patients with stage IV colorectal cancer and a limited extent of metastatic disease, an upfront multidisciplinary discussion to consider the feasibility of resecting all metastases is required. This process and its timing are critical, since, based on the evidence we have summarized, the sequences of surgery and medical therapy should be quite different. No therapy or surgery should be undertaken until both medical and surgical providers have jointly discussed and agreed upon the plan of care.

The studies of preoperative medical therapy for the management of patients with metastatic disease that is deemed completely resectable at time of presentation, and thus curable, consistently suggest that there is no benefit to the use of upfront medical therapy in these patients. This remains so despite a number of different regimens used, including both chemo- and biologic therapies (again, as summarized in Table 1). Most of these studies were phase II studies and lacked a comparator arm in which the patients received upfront surgery. The single phase III study that compared neoadjuvant chemotherapy with upfront surgery did not demonstrate superiority with neoadjuvant chemotherapy.[37] Thus, our preferred treatment paradigm for these patients is to proceed directly to surgery, as would be the case with any lower stage of colon cancer. Medical therapy for the management of residual microscopic metastatic disease in these patients should be reserved for the postoperative setting, administered in a conventional adjuvant manner.

Conversely, for those patients who have a metastatic tumor burden deemed unresectable but potentially convertible to resectable if the burden were adequately reduced, the evidence does support the use of upfront medical therapy to achieve this conversion (as summarized in Table 2). Several regimens have been explored for conversion, and none has been shown to be clearly superior. However, in two phase III studies,[23,44] triplet chemotherapy with FOLFOXIRI achieved a better ORR, more frequent R0 margins of resection, and more surgical candidates than did treatment with a doublet of FOLFIRI. Therefore, for those patients whose performance status suggests that they would tolerate FOLFOXIRI, this is our preferred approach. While no studies have compared FOLFOXIRI/antibody therapy with FOLFOXIRI alone, Gruenberger, Masi, and their colleagues have demonstrated that the addition of bevacizumab is a feasible approach with good outcomes, and Saridaki and colleagues have demonstrated the same with cetuximab.[29,30,36] Barring a contraindication to the antibody, the addition of either bevacizumab or cetuximab to FOLFOXIRI is appropriate.

The administration of FOLFOXIRI is not universally feasible, given its highly toxic nature (adverse effects include marrow suppression, fatigue, and emetogenicity). While not all toxicity can be anticipated, the oncologist should consider whether the patient is likely to tolerate this regimen well enough to remain on the recommended dosage schedule. If not, an alternative chemotherapy doublet should be recommended. Since different studies have suggested better outcomes with either FOLFOX or FOLFIRI, we have no preference between the two as a standard paradigm and we select agents based on individual patient preference. This might include, for example, using FOLFOX in patients who prefer to avoid alopecia or who have baseline diarrheal symptoms, or using FOLFIRI in patients who have a baseline peripheral neuropathy. Even for those patients who cannot tolerate FOLFOXIRI, the addition of a biologic agent to the selected chemotherapy doublet is appropriate for incorporation in the conversion therapy.[26-28,30,32,33,35,37-39,41,43]

As with chemotherapy doublets, no clearly superior outcome has been described for an antibody class. Therefore, whether chemotherapy consists of FOLFOXIRI, FOLFOX, or FOLFIRI, we select an
antibody again based on individual patient preference and anticipated tolerance. However, the lower cost and absence of skin toxicity often tend to favor bevacizumab over cetuximab or panitumumab. Regardless of the regimen administered with intent of conversion to resectable disease, close monitoring of tumor response is essential in order to optimize timing of any surgery. As summarized in Table 2, there was a wide range in total number of cycles of therapy across the various trials. It is not appropriate to predetermine the number of cycles that should be used preoperatively. Rather, close monitoring of disease response should be undertaken, with repeat radiographic assessment and multidisciplinary consideration every 2 to 3 months. When it is agreed that maximal response has been achieved, based on this close interval monitoring, the multidisciplinary team should then consider whether surgery is feasible. Should the tumor response be inadequate for surgical attempt, there are no data to suggest that an alternative, second chemotherapeutic regimen is likely to achieve this outcome. If surgical resection is achieved, there is no strong evidence for an alternative adjuvant strategy beyond standard FOLFOX. Our usual approach is to recommend the standard 12 cycles of adjuvant FOLFOX therapy, with any chemotherapy that was administered neoadjuvantly omitted. While clinicians may elect to pursue another strategy (eg, use of other agents based on neoadjuvant tumor response, extended maintenance therapy with fluoropyrimidine monotherapy), it is imperative that the patient understand that there is not a strong level of evidence for such approaches and that the oncologist present the risks and benefits to the patient with an emphasis on the large extent of the unknown.

Future studies could conceivably establish a single best medical approach for the conversion of metastatic colorectal cancer to a resectable degree of disease, and moreover, that such an approach could offer benefit to patients in the neoadjuvant setting. However, given our increasing understanding of the diversity of colorectal cancer from patient to patient, it is much more likely that a variety of approaches will continue to be validated, with therapeutic recommendations relying on individual tumor characteristics and individual patient preferences and comorbid conditions. This variety again highlights how critical it is for a multidisciplinary team to synthesize treatment recommendations before commencing therapy or proceeding to surgery.

Financial Disclosure: Dr. Smaglo has financial arrangements with Taiho. Dr. Marshall has financial arrangements with Amgen, Bayer, Celgene, and Genentech. Dr. Al-Hajeili has no relevant disclosures.


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