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The Role of Peri-operative Chemotherapy for Resectable Colorectal Liver Metastasis: What Does the Evidence Support?

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Introduction

With improved patient selection, better surgical techniques, and more effective cytotoxic chemotherapy agents, 5-year survival following curative intent surgery of colorectal metastasis now approaches 45–60%.^{1–4} While there have been significant advances in prolonging overall survival of patients with colorectal liver metastasis, many patients still develop recurrent disease. De Jong et al.⁵ reported a contemporary experience in which the 5-year disease-free survival was only 30% following curative intent surgery for colorectal liver metastasis, with 60% of patients developing extrahepatic disease at 5 years. Tomlinson et al.⁶ noted that approximately one third of actual 5-year survivors succumb to cancer-related death. Noting that the chance of “cure” after hepatectomy was roughly a one-in-six chance, the authors estimated a “maximal cure” rate of only about 25% for patients undergoing surgical resection of colorectal liver metastasis. Given the persistent high recurrence rates and the overall poor “true” long-term survival following surgical resection of colorectal liver metastasis, there has been great interest in the use of adjuvant chemotherapy for patients with resectable colorectal liver metastasis.

The role of adjuvant chemotherapy after resection of colorectal cancer liver metastasis has recently been reviewed by Power and Kemeny.⁷ For both pedagogical and practical purposes, “peri-operative” chemotherapy for colorectal liver metastasis can be divided into three different treatment “strategies;” neoadjuvant, peri-operative, and adjuvant. We herein review each one of these peri-operative chemotherapy treatment strategies for resectable colorectal liver metastasis.

Adjuvant Chemotherapy

The use of adjuvant chemotherapy for colorectal cancer has been well studied in stage III disease. Specifically, multiple randomized clinical trials have noted a survival benefit associated with the use of adjuvant chemotherapy for patients with colorectal cancer and lymph node metastasis.^{8–11} Sargent et al.⁸ reported that surgery plus adjuvant 5-fluorouracil (5-FU) versus surgery alone was associated with an overall survival benefit (8-year overall survival— surgery+5-FU-based chemotherapy, 53% versus surgery alone, 43%; $P<0.0001$).

In the phase III NSABP C-07 trial that examined adjuvant FULV (5-fluorouracil plus leucovorin)+oxaliplatin, the FLOX regimen, in stage II or III colorectal cancer patients, there was noted to be a trend toward improved survival with the addition of oxaliplatin.¹⁰ In the MOSAIC trial, the addition of oxaliplatin (FOL-FOX4) was shown to provide an additional benefit over 5-FU monotherapy (LV5FU2) among patients with stage III disease (6-year overall survival—FOLFOX4, 73% versus LV5FU2, 69%; $P=0.023$).¹¹ Collectively, data from these studies have firmly established the beneficial role of adjuvant chemotherapy in the management of stage III colorectal cancer.

Multiple phase I and II studies have similarly shown improved efficacy of modern-era chemotherapy in the treatment of unresectable stage IV colorectal liver metastasis. While monotherapy with 5-FU previously resulted in response rates only in the range of 20–25%,¹² current regimens that include oxaliplatin or irinotecan have response rates in the range of 45–55%.^{13–17} More effective cytotoxic chemotherapy has translated into a significant increase in the median survival of patients with unresectable colorectal liver metastasis from 6 months with best-supportive care to 12–15 months with monotherapy 5-FU to now 20–24 months with oxaliplatin- or irinotecan-based therapies. Additional advances have been associated with the addition of biologic agents, such as bevacizumab or cetuximab, to cytotoxic chemotherapy, as outlined in the BEAT¹⁸ and CRYSTAL studies.¹⁹

Given the robust data on the role of systemic chemotherapy for both resected stage III and unresectable stage IV colorectal cancer, there has been interest in the potential use of adjuvant chemotherapy in the setting of resected stage IV colorectal liver metastasis. Unfortunately, data on the role of adjuvant chemotherapy for resected colorectal liver metastasis are scant.^{20–23} Of the four randomized trials published to date, two were published only in abstract form and each had fewer than 52 patients analyzed.^{20,22} Of the two other randomized trials,^{21,23} both suffered from poor accrual and had fewer than 175 patients analyzed. In the Langer et al.²¹ study, only 107 patients were analyzed and there was no noted difference in overall survival when daily bolus 5-FU was compared with observation alone following resection of colorectal liver metastasis. In the Portier et al.²³ trial, 173 patients were randomized to surgery alone versus surgery+5-FU. In this study, two patients were lost to follow-up, leaving 85 patients randomized to the surgery alone arm versus 86 patients to the surgery+5-FU arm. Among the patients randomized to adjuvant 5-FU, 94% of assigned patients received post-operative chemotherapy. No difference in overall survival was noted between the study arms (5-year overall survival—surgery alone, 42% versus surgery+5-FU, 51%; $P=0.13$). The authors did note, however, that adjuvant 5-FU conferred a disease-free survival benefit (5-year disease-free survival—surgery alone, 27% versus surgery+5-FU, 34%; $P=0.028$). Cox multivariate analysis confirmed a statistically significant beneficial effect of chemotherapy on disease-free survival (HR=0.66, 95% CI, 0.46–0.96).²³ While this study did show an improvement in disease-free survival, it failed to show an overall survival benefit with adjuvant therapy. The reasons for this lack of effect were undoubtedly multi-factorial and included the relatively small study sample size and lack of statistical power. In an attempt to increase the overall number of patients available for analysis, Mitry et al.²⁴ performed a pooled analysis of the Langer et al.²¹ and Portier et al.²³ studies. In this pooled analysis, a total of 278 patients were analyzed, 140 of whom had been randomized to surgery alone and 138 of whom had been randomized to surgery+5-FU. Among those patients randomized to adjuvant chemotherapy, 95% of assigned patients received chemotherapy. In this study, the authors again noted no difference in overall survival and a trend toward improved disease-free survival associated with adjuvant therapy. On multivariate analysis, after controlling for other competing risk factors, a marginal statistically significant associated benefit of adjuvant 5-FU chemotherapy was noted ($P=0.046$).

There have been several large retrospective, non-randomized studies that have also examined the issue of adjuvant chemotherapy for resectable colorectal liver metastasis.^{25–27} Each of these studies have reported a survival benefit for adjuvant 5-FU versus surgery alone for patients with resectable colorectal liver metastasis. In general, these studies have noted a relative 25–60% decreased risk of disease-specific death associated with receipt of adjuvant 5-FU. Obviously, these retrospective studies have serious threats to validity including selection bias and treatment bias, not to mention issues with possible confounding. As such, any causal inferences drawn from such data need to be carefully considered.

There has been one study that has examined the use of “modern” era chemotherapy in the adjuvant setting for resected colorectal liver metastasis. Ychou et al.²⁸ reported a randomized phase III study comparing adjuvant 5-FU versus FOLFIRI among patients having undergone complete resection of liver metastases from colorectal cancer. In this study, 321 patients were randomized to receive either 5-FU alone or FOLFIRI. Of those patients assigned to FOLFIRI, 95% received the assigned post-operative chemotherapy. The authors noted no benefit for FOLFIRI compared with 5-FU with regards to either disease-free or overall survival. In fact, survival curves for the 5-FU versus FOLFIRI arms of the study were nearly super-imposable with a reported overall 5-year survival of 63% and 65%, respectively, and a disease-free survival of 37.5% in both groups. The lack of benefit for FOLFIRI compared with 5-FU as adjuvant therapy for stage IV disease was perhaps not surprising given the findings of the ACCORD 02²⁹ and CALGB 89803³⁰ trials, which had previously shown no difference in disease-free survival with the addition of irinotecan to 5-FU in the setting of resected stage III colorectal cancer.

Peri-operative Chemotherapy

By administering chemotherapy prior to surgery, peri-operative chemotherapy has the theoretical benefit of earlier delivery of systemic treatment for stage IV disease. Peri-operative chemotherapy has been shown to have efficacy in the treatment of other solid gastrointestinal malignancies such as gastric cancer.³¹ The use of peri-operative chemotherapy in the treatment of colorectal liver metastasis has recently been reported in a large multi-institutional trial.³² The EORTC Intergroup trial 40983 randomized 364 patients to either surgery alone versus peri-operative chemotherapy with the FOLFOX4 regimen. Peri-operative chemotherapy consisted of six cycles (3 months) of FOLFOX4 followed by surgery and then an additional six cycles of FOLFOX4. Only patients with one to four liver metastases and no extrahepatic disease were eligible for the study. Of the 182 patients randomized to the surgery alone arm, 91.8% patients were taken to surgery and 81.9% underwent resection, for a non-therapeutic laparotomy incidence of about 10%. In contrast, of the 182 patients randomized to peri-operative chemotherapy, 86.8% were taken to surgery and 83.0% underwent resection, for a lower non-therapeutic rate of about 4%. Overall mortality was low in each study arm (surgery $n=2$ versus peri-operative chemotherapy $n=1$). While the overall complication rate was higher in the peri-operative chemotherapy group (25%) versus the surgery alone group (16%), most complications were minor. Regarding outcome, when all randomized patients were analyzed on an intention-to-treat analysis, the benefit of peri-operative chemotherapy was associated with a trend toward improved progression-free survival (HR 0.79, 95% CI 0.62–1.02; $P=0.058$). When only the eligible patients were considered in the analysis, peri-operative chemotherapy was associated with an overall 8% absolute improvement in progression-free survival at 3 years (surgery alone, 28.1% versus peri-operative FOLFOX, 36.2%) (HR 0.72, 95% CI 0.60–1.00; $P=0.041$). When only patients who underwent resection were considered, FOLFOX4 peri-operative chemotherapy was associated with an absolute increase in 3-year progression-free survival of 9.2%. The authors concluded that peri-operative chemotherapy with FOLFOX4 was compatible with major liver surgery and prolonged progression-free survival in eligible and

resected patients. The results of the EORTC 40983 trial have, however, been somewhat difficult to interpret. Specifically, it is not clear why the observed benefit of chemotherapy in the setting of stage IV disease was less than that reported in adjuvant trials for stage III patients, although the disease biology is likely different in these groups. In addition, whereas the EORTC 40983 trial assessed peri-operative versus no chemotherapy for patients with resectable colorectal liver metastasis, most patients in the USA are routinely offered chemotherapy in conjunction with resection. As such, the EORTC 40983 trial did not address the specific issue that may be of most interest in the USA: how best to sequence peri-operative chemotherapy. Specifically, given that the overwhelming majority of patients with resectable metastasis receive some type of systemic chemotherapy, the question remains: is it better to give the entire systemic chemotherapy course in the adjuvant setting or should part of the systemic chemotherapy regimen be given in the neoadjuvant setting?

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is the administration of chemotherapy in the pre-operative setting in patients with resectable disease. Neoadjuvant chemotherapy should be distinguished from conversion chemotherapy, which is also administered in the pre-operative setting but is administered to patients with initially unresectable disease, with the intention of downsizing the tumor burden, and, ultimately, considering resection. The administration of neoadjuvant chemotherapy to patients with initially resectable disease has a number of potential benefits and risks.

While already resectable, lesions treated with neoadjuvant chemotherapy may benefit from further downsizing to facilitate increased rates of margin negative as well as parenchymal sparing resections. The data on margin status and neoadjuvant chemotherapy, however, are conflicted and biased by the retrospective nature of most reports as well as the inclusion of some initially unresectable patients in these studies.^{33–35} Another theoretical benefit of neoadjuvant chemotherapy is that administration of chemotherapy in the pre-operative setting will allow the biology of the disease to declare itself. Data from the EORTC 40983 trial would suggest that this is an infrequent occurrence.³² Specifically, in the EORTC 40983 trial, only 14 patients (7.7%) experienced progressive disease while on peri-operative FOLFOX prior to surgery. Among these 14 patients, only seven patients (4%) were “saved” an operation due to progressive disease. As such, the routine administration of neoadjuvant chemotherapy as a means to define tumor biology appears to have a low yield. The administration of neoadjuvant chemotherapy does, however, provide an in vivo gauge of tumor response to a particular regimen, which may help tailor adjuvant therapy. In addition, response to neoadjuvant chemotherapy can be used as a powerful prognostic tool. Specifically, Adam et al.³⁶ reported that disease progression while on preoperative chemotherapy is an ominous prognostic factor. In fact, Adam et al.³⁶ noted that among patients with four or more liver metastases who had progressive disease while on neoadjuvant chemotherapy the 5-year survival following complete surgical resection was only 8%. In a separate study, Blazer et al.³⁷ reported that pathologic response to pre-operative chemotherapy was a potent predictor of long-term survival. Patients who had a complete or major pathologic response had a significantly better long-term outcome compared with patients who had a minor response.

There has been some concern, however, that neoadjuvant chemotherapy may result in liver-associated injury. Injury to the liver from chemotherapy has been shown to be drug specific as well as related to the duration of chemotherapy.^{38,39} Specifically, patients treated with irinotecan appear more likely to incur liver injury characterized by steatosis, while oxaliplatin is more typically associated with sinusoidal injury. The incidence of chemotherapy-associated steatohepatitis remains ill defined, with some centers³⁸ reporting

an incidence of 8% while other institutions have reported a much lower rate of only 2%.³⁹ The impact of chemotherapy on outcome has also been somewhat controversial. In one study, the use of pre-operative chemotherapy was associated with an increased risk of peri-operative mortality,³⁸ while others have reported no increased risk of peri-operative mortality with its use.³⁹ It is important to note that in the study by Vauthey et al.³⁸ pre-operative chemotherapy was only associated with an increased risk of mortality among those patients with underlying steatohepatitis (steatosis with associated inflammation) who had undergone a major hepatic resection (extended hepatectomy or hemihepatectomy with contra-lateral ablation). Data from the EORTC 40983 trial, as well as retrospective reports,^{40,41} strongly suggest that short-course pre-operative chemotherapy appears to be safe. One does, however, need to be mindful of the risk of chemotherapy-associated liver injury among those patients with high BMI and/or diabetes in whom a major hepatectomy is planned, as these patients are at a higher baseline risk of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

While the use of neoadjuvant chemotherapy may have some theoretical appeal, its routine use cannot currently be supported by any level 1 data. The NSABP C-11 trial will hopefully provide data to determine if neoadjuvant versus adjuvant chemotherapy for resectable colorectal metastasis is associated with a disease-free or overall survival benefit. The NSABP C-11 trial will evaluate the role of peri-operative/ neoadjuvant chemotherapy in patients with potentially resectable hepatic colorectal metastasis. Patients with potentially resectable hepatic colorectal cancer metastasis will be randomized to liver resection followed by adjuvant chemotherapy versus neoadjuvant chemotherapy followed by liver resection and then consolidation adjuvant chemotherapy. The chemotherapy regimen will include either oxaliplatin or irinotecan and will be determined by the patient's previous exposure to oxaliplatin, and both adjuvant and neoadjuvant treatment arms will receive bevacizumab. Of note, kras mutational status will not be assessed, nor stratified for in this study, as no EGFR-directed antibody therapy has been included in the chemotherapy regimens. Eligibility is not restricted by the number of liver metastases, as patients with four or more lesions can be enrolled in the trial. The primary endpoint is recurrence-free survival, with overall survival, R0/R1 resection rate, peri-operative complication rates, and chemotherapy toxicity as secondary endpoints.

Conclusion

Liver resection is the ultimate treatment strategy for colorectal liver metastasis; however, recurrence is common. There is a sound rationale for the use of adjuvant chemotherapy based on robust level 1 data demonstrating its benefit among patients with resected stage III colorectal cancer. Unfortunately, level 1 randomized controlled data on the use of peri-operative systemic chemotherapy for resected colorectal liver metastasis are limited. Only a handful of randomized trials have been reported and each has suffered from poor accrual and being underpowered. The largest adjuvant trial examining adjuvant 5-FU did demonstrate a disease-free survival benefit. Similarly, the EORTC 40983 trial reported a disease-free benefit among eligible patients treated with peri-operative chemotherapy. The predominance of evidence suggests that peri-operative chemotherapy has a role in the treatment of patients with resectable colorectal liver metastasis. As such, it is not feasible to perform clinical trials of chemotherapy versus surgery alone for patients with resectable colorectal liver metastasis in the USA. However, the sequence of chemotherapy for resected colorectal liver metastasis remains ill defined. Short-course neoadjuvant chemotherapy appears to be safe with limited hepatotoxicity. While neoadjuvant chemotherapy has the theoretical benefit of being able to deliver treatment earlier for both measureable and microscopic stage IV disease, the true benefit of neoadjuvant therapy is not established. Hopefully, the upcoming NSABP C-11 trial will help characterize the relative benefit of

neoadjuvant/peri-operative versus adjuvant chemotherapy in patients with resectable colorectal liver metastasis. Ultimately, rather than treating all patients with colorectal liver metastasis as a monolithic group, both the timing and type of chemotherapy will potentially need to be tailored in the future based on as yet unidentified factors and molecular markers.

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