Editorial

Perioperative chemotherapy for resectable colorectal hepatic metastases—What does the EORTC 40983 trial update mean?

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Abstract: The liver is the most common site of colorectal cancer metastasis. Although successful resection leads to durable overall survival (OS), local and distant recurrence is common. As a result, multidisciplinary strategies have been developed to decrease recurrence rates as well as increase the number of candidates for resection. A recent update to the European Organisation for Research and Treatment of Cancer (EORTC) Intergroup trial 40983 has been published comparing perioperative chemotherapy to surgery alone. This randomized trial initially demonstrated a benefit in progression free survival (PFS) with the administration of perioperative FOLFOX chemotherapy, albeit with an increased rate of complications. Although this led many investigators and clinicians to adopt the perioperative approach, the recent update failed to report any advantage in OS and therefore results in further controversy as to the role of perioperative systemic chemotherapy in the treatment of resectable colorectal hepatic metastases.

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Colorectal cancer (CRC) is the third most common cancer in the world with 1.4 million new cases in 2012 (1). Nearly 50% of patients present with or develop hepatic metastases during their lifetime. If complete surgical resection of these metastases can be performed, 5-year overall survival (OS) rates can be as high as 50%—an impressive achievement for a metastatic gastrointestinal malignancy (2,3). Unfortunately, only 15-20% of patients are initial candidates for resection and even after resection, recurrence rates are significant, both in the remaining liver as well as elsewhere (4).

This prompted interest in the use of adjuvant systemic chemotherapy to reduce these recurrence rates (similar to that used in stage 3 disease). In the 1990s, two prospective randomized trials attempted to address the role of adjuvant chemotherapy in the treatment of resected hepatic metastasis from CRC. In both studies, resected patients were randomized to 5-fluororacil/Leucovorin (5-FU/LV) for 6 months *vs*. observation. Unfortunately, both studies were plagued by poor accrual and were therefore closed. Subsequent pooled results from these studies demonstrated a small but statistically significant benefit to adjuvant 5-FU/LV after resection in regards to progression free survival (PFS) (HR: 1.39, 95% CI: 1.04-1.85, P=0.026) and OS (HR: 1.39, 95% CI: 1.00-1.93, P=0.046) (5). Since these results were pooled and failed to study more modern systemic agents such as oxaliplatin, irinotecan, and targeted therapies, the role of adjuvant chemotherapy after successful hepatic resection of metastatic CRC remained unclear.

In the early 2000s, Ychou *et al*. compared adjuvant 5-FU/LV to FOLFIRI (5-FU/LV and irinotecan) after complete resection of liver metastases from CRC. Patients in this study were randomized to receive 12 cycles of either regimen and there was no significant difference in disease free or overall survival (6). In addition, toxicity with the FOLFIRI regimen was significantly higher and therefore it has not been used in the adjuvant setting. Since this trial did not include a surgery-only arm, the specific question of whether there is role for adjuvant chemotherapy after resection of hepatic metastases from CRC was not addressed.

In the mid to late 2000s, interest in neoadjuvant strategies for potentially resectable hepatic metastases from CRC also emerged. The goals for neoadjuvant (and perioperative) systemic therapy included: (I) to convert patients from unresectable to resectable disease (7,8); and (II) to identify the best candidates for a curative treatment (9). In a recent issue of *Lancet Oncology*, the European Organisation for Research and Treatment of Cancer (EORTC) published their long-term results of the prospective randomized intergroup 40983 trial (EPOC) investigating the use of perioperative FOLFOX4 (folinic acid, fluorouracil, oxaliplatin) in patients with resectable colorectal hepatic metastases. This trial enrolled 364 patients with resectable hepatic metastases and primary tumor, if not already removed, who were randomized to 6 cycles of FOLFOX4 every 14 days before and after liver resection *vs*. liver resection alone. Importantly, the trial's primary endpoint was PFS; the trial was designed to detect a 40% increase in median PFS in all patients randomly assigned to perioperative chemotherapy with 80% power at a two-sided 5% significance level, requiring 278 events (10). After 6.5 years, only 235 events had occurred, but due to pressure from the medical community, an interim analysis was reported in 2008.

Of the patients who were deemed eligible to undergo resection, 3-year PFS was significantly better with the use of perioperative FOLFOX compared to surgery alone [36.2% *vs*. 28.1%, (HR: 0.77, 95% CI: 0.60-1.00, P=0.041)]. Of the patients who actually underwent resection, 3-year PFS was also significantly better in the chemotherapy group compared to surgery alone [42.4% *vs*. 33.2%, (HR: 0.73, 95% CI: 0.55-0.97, P=0.025)]. A total of 79% patients in the chemotherapy group completed all 6 preoperative cycles but less than half of those who received preoperative therapy received all 6 planned postoperative cycles. Interestingly, 87% patients in the chemotherapy group went onto operation and complete resection was achieved in 83% patients. Four percent (4%) patients were deemed unresectable at the time of surgery secondary to more advanced disease (seven patients) and liver injury (one patient). In the surgery alone group, 93% of patients underwent attempted resection and complete resection was achieved in 84% patients. Ten percent (10%) patients were deemed unresectable at the time of surgery and all were due to advanced disease.

Despite a significant improvement in PFS, there was an increased incidence of post-operative complications in those who received perioperative chemotherapy (25% *vs*. 16%), although mortality was similar in both groups at 1%. Notably, OS was not reported in the interim analysis.

Results of this trial as well as data regarding conversion of patients with initially unresectable disease to resectable disease resulted in some of the medical and surgical oncology community to utilize neoadjuvant therapy in patients with potentially resectable colorectal liver metastases (11). Nevertheless, this strategy has gained more acceptance in patients with initially unresectable disease rather than upfront resectable, perhaps due to the concern for increased complications with the use of preoperative chemotherapy as well as lack of OS benefit.

In the recently published article, the authors report their long-term secondary outcome results of OS. With a median follow up of 8.5 years, 107 (59%) patients in the perioperative chemotherapy group had died *vs*. 114 (63%) patients in the surgery group (HR: 0.88, 95% CI: 0.68-1.14, P=0.34). In all randomized patients, median OS in the perioperative chemotherapy group was 61.3 *vs*. 54.3 months in the surgery alone group (P=0.34). In patients eligible to undergo resection, median OS was 63.7 months in the perioperative chemotherapy group *vs*. 55.0 months in the surgery alone group (P=0.30). In patients that underwent resection, median OS was 77.5 *vs*. 73.3 months (P=0.35) (12). The authors also reported long term PFS results. In all randomly assigned patients, median PFS was 20.0 months in the perioperative chemotherapy group *vs*. 12.5 months in the surgery alone group (P=0.068). In patients eligible for resection, median PFS was 20.9 months in the perioperative chemotherapy group *vs*. 12.5 months in the surgery alone group (P=0.035).

There are several important findings to note from this recent update. Although it may be somewhat surprising that perioperative chemotherapy did not show an OS benefit, there are several potential explanations for this. First and perhaps most importantly, as the authors discuss, the original study was not designed nor powered to detect differences in OS. In addition, the OS in the surgery alone group was 54 months and an impressive 73 months in those that underwent resection. Although perioperative chemotherapy resulted in an absolute difference in survival of 4-8 months depending on the comparison group (equal or better than other randomized adjuvant trials) this trial was not nearly large enough to detect that difference from a statistical standpoint. Second, as the authors also discuss, more patients in the surgery group with disease progression received chemotherapy as treatment when compared to the patients in the perioperative chemotherapy group

who progressed. This confounding variable could clearly affect OS (but not PFS) making it difficult to demonstrate a benefit to perioperative chemotherapy. Also, any further therapies after the initial treatment were not recorded and therefore not reported in this study—yet another confounding variable. Third, since OS would include all causes of death, any increased number of non cancer-related deaths in the perioperative chemotherapy group likely diminished any OS benefit in that group. Finally, Nordlinger *et al*. cite the higher than expected PFS in the surgery group as a potential confounder as it made the "demonstration of treatment benefit for perioperative chemotherapy… more difficult" (12).

Several other important points are also worth mentioning. In the EORTC trial, less than half of the patients in the perioperative chemotherapy group actually completed their adjuvant doses of chemotherapy. Presumably some of this may have been due to complications after surgery and general deconditioning of patients after resection. It is possible that the lack of OS benefit was due to inadequate duration of therapy. To that end, it is also unclear what role the neoadjuvant portion *vs*. the adjuvant portion plays in the benefit of prolonged PFS. Certainly for colon cancers, adjuvant therapy for stage 3 and high risk stage 2 provides a survival benefit (13) while in rectal cancer, neoadjuvant therapy has shown a benefit in PFS (14). Since the current trial did not include an adjuvant only arm, this question still remains. Furthermore, although fewer patients may be able to receive adjuvant therapy following hepatic resection, the increase in complication rates and presumed hepatic toxicity may be avoided if resection was to be performed first. What role these factors play, if any, would only be answered in a randomized trial comparing perioperative therapy to adjuvant therapy.

In conclusion the EORTC Intergroup trial 40983 is the first prospective randomized trial comparing perioperative chemotherapy to surgery alone for the treatment of resectable hepatic metastases from colon cancer. While it demonstrates a significant improvement in PFS, this most recent update did not demonstrate any significant benefit in OS. Systemic chemotherapy, with or without targeted therapy, be it before and or after hepatic resection most likely provides a benefit in patients with resected colorectal hepatic metastases. Unfortunately, several questions remain unanswered and therefore widespread use of this strategy may still be hindered. These include what specific agents to use as well as how and when to administer it.

Moving forward, randomized trials that can definitely show a benefit for the use of adjuvant systemic therapy using modern chemotherapy and targeted therapy combinations should be undertaken. Assuming there is a benefit compared to resection alone, additional studies comparing the role of neoadjuvant or perioperative therapy *vs*. adjuvant only should be undertaken in hopes of defining the best strategy for patients with colorectal hepatic metastases. Special attention must be given to properly define "resectable" disease and to exclude and/or stratify those that are not upfront resectable when studying neoadjuvant strategies. In addition, defining the proper endpoint will be crucial. As is the case with the current study, it is very difficult to draw conclusions from analyses of secondary endpoints since the trials are not often designed or powered to detect a difference. Although both PFS and OS are acceptable primary endpoints (15), both have their advantages and disadvantages that must be kept in mind when these future trials are designed.

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