Chemotherapy and resection for colorectal metastases

The past two decades have seen the outlook for patients with hepatic colorectal metastases improve substantially, from near-certain death within 1 year to more than 40% of patients being cured.\(^1\) Chemotherapy plays a major part in this improvement in outcome; 15–20% of patients with unresectable disease at diagnosis were reported to have resectable disease after receiving neoadjuvant chemotherapy, with resultant favourable long-term survival.\(^2\) Chemotherapy is also used in the adjuvant setting to improve outcomes in patients with advanced, resected metastatic colorectal cancer.\(^3\) Nevertheless, routine use of neoadjuvant chemotherapy remains controversial,\(^4\) as does the choice of chemotherapy to give after hepatectomy.

The European Organisation for Research and Treatment of Cancer (EORTC) Intergroup 40984 phase 3 study, which randomly assigned 364 patients with resectable liver metastases to surgery alone or neoadjuvant and adjuvant FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin), is a landmark study that partly addresses these questions. The initial results from this trial, published in 2008,\(^5\) showed that perioperative FOLFOX4 significantly improved progression-free survival compared with surgery alone, and guided clinical practice. The long-term overall survival results, reported by Bernard Nordlinger and colleagues\(^6\) in The Lancet Oncology, have been greatly anticipated. The major finding of this follow-up study was that overall survival was not significantly greater in patients who received perioperative FOLFOX4 than in those who received surgery only. At a median follow-up of 8.5 years, 107 (59%) of 182 patients in the perioperative chemotherapy group had died versus 114 (63%) of 182 patients in the surgery-only group (hazard ratio 0.88, 95% CI 0.68–1.14; p=0.34). This result is surprising and should be interpreted carefully.

Most importantly, adjuvant chemotherapy should not be disregarded in the treatment of metastatic colorectal cancer. Third-party payers and national regulatory agencies that control access to health-care resources should not deny access to adjuvant chemotherapy solely on the basis of the outcome of this study. As discussed well by Nordlinger and colleagues,\(^6\) their follow-up study was underpowered to prove the significance of the 5% between-group difference in 5-year overall survival. Furthermore, only 115 (63%) patients in the perioperative chemotherapy group received postoperative chemotherapy. Thus, the inability to show a significant difference in overall survival might be a result of inadequate duration of chemotherapy, especially since adjuvant chemotherapy has previously been shown to be important in the treatment of resected, advanced stage colorectal cancer.\(^3\)

Additionally, Nordlinger and colleagues\(^6\) report that second-line treatment with chemotherapy for disease progression was given more frequently to patients in the surgery-only group than in the perioperative chemotherapy group. An interesting question, therefore, is whether the findings mean that administration of chemotherapy at minimal recurrence of disease is just as beneficial as administering it as an adjuvant to surgery. This question should be assessed in a formal trial, especially because, if found to be true, 20–25% of patients cured by surgery alone\(^7\) could be spared the toxicity and cost of chemotherapy altogether.

I hope that physicians do not react to the inability of the trial to show a survival benefit by adding more agents to the adjuvant chemotherapy regimen, particularly those that have not been tested or proven in this setting. Several studies into metastatic colorectal cancer have shown more complex chemotherapy regimens to be inferior to simpler regimens.\(^8\)–\(^10\)

Finally, the data presented suggest that the routine use of preoperative neoadjuvant chemotherapy has no proven role for use in conjunction with resection for colorectal hepatic metastases. In the EORTC 40984 study,\(^5\) only 3.8% of patients developed extrahepatic disease while they were receiving neoadjuvant chemotherapy, preventing resection of liver disease. Thus, the idea that the time spent receiving neoadjuvant chemotherapy could help patient selection by allowing appearance of distant unresectable disease is not a strategy supported by data. Also, this follow-up study does not show neoadjuvant therapy to have a survival advantage.\(^6\)

Many studies are in progress or are being discussed that might provide evidence for definitive adjuvant care for this population, but I believe two questions in particular need to be addressed. First, in patients who are chemotherapy naive after liver resection, FOLFOX4...
needs to be compared with FOLFOX4 plus bevacizumab or cetuximab to establish whether the addition of molecularly targeted agents improves outcome. Second, in patients who have previously received chemotherapy, second-line chemotherapy as an adjuvant treatment should be compared with close observation only (no adjuvant therapy) and immediate systemic treatment at recurrence.

Yuman Fong
Memorial Sloan-Kettering Cancer Center, New York, NY 10022, USA
fongy@mskcc.org

I declare that I have no conflicts of interest.