Editorial

Perioperative chemotherapy and hepatic resection for resectable colorectal liver metastases

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Abstract: The role of perioperative chemotherapy in the management of initially resectable colorectal liver metastases (CRLM) is still unclear. The EPOC trial [the European Organization for Research and Treatment of Cancer (EORTC) 40983] is an important study that declares perioperative chemotherapy as the standard of care for patients with resectable CRLM, and the strategy is widely accepted in western countries. Compared with surgery alone, perioperative FOLFOX therapy significantly increased progression-free survival (PFS) in eligible patients or those with resected CRLM. Overall survival (OS) data from the EPOC trial were recently published in *The Lancet Oncology*, 2013. Here, we discussed the findings and recommendations from the EORTC 40983 trial.

Keywords: Colorectal liver metastases (CRLM); perioperative chemotherapy; the European Organization for Research and Treatment of Cancer (EORTC) trial (40983)

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The high rate of recurrence in patients with colorectal liver metastases (CRLM) after curative resection remains an unsettled problem (1-3). The most probable explanation for these recurrences is the persistence of microscopic residual disease after surgery. To reduce postoperative recurrences, combining chemotherapy with resection for CRLM is of major interest.

EORTC 40983 (EPOC) trial and new EPOC trial

The European Organization for Research and Treatment of Cancer (EORTC) intergroup trial 40983 (EPOC) clearly demonstrated that perioperative FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) therapy (six cycles before surgery and six cycles after) significantly increased progression-free survival (PFS) compared with surgery alone in eligible patients or those with resected liver-only CRLM (4). The trial was registered with ClinicalTrials.gov, number NCT00006479. The absolute increase in the rate of PFS at 3 years was 7.3% (from 28.1% to 35.4%, HR 0.79; P=0.058) in randomized patients; 8.1% (from 28.1% to 36.2%, HR 0.77; P=0.041) in eligible patients; and 9.2% (from 33.2% to 42.4%, HR 0.73; P=0.025) in patients who underwent hepatic resection. Thereafter, perioperative chemotherapy became the standard of care for patients with resectable CRLM, especially in western countries (5).

The overall survival (OS) data from the EPOC trial were published in *The Lancet Oncology* in 2013 (1). After a median follow-up of 8.5 years, OS in all randomly assigned patients did not differ significantly between groups (HR 0.88, P=0.34) or among eligible patients (HR 0.87, P=0.30). In intention-to-treat analysis, median overall survival (MST) was 61.3 and 54.3 months in the perioperative chemotherapy and surgery alone groups, respectively. In all randomized patients, the absolute difference between groups in the proportion of patients with 5-year OS was 3.4%; in all eligible patients it was 4.1%. However, a greater proportion of eligible patients were alive at 5 years (50/182) in the perioperative chemotherapy group than in the surgery alone group (42/182). Two reasons can be posited

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to explain the lack of any significant advantage in OS. First, this trial was designed to detect a PFS benefit; therefore, any findings regarding OS constituted a secondary endpoint. Second, the positive long-term outcome in the surgery-only group (MST 73.3 months) proved that demonstrating a treatment benefit for perioperative chemotherapy was more difficult. The 4.1% absolute survival benefit at 5 years in the eligible population was similar to other positive adjuvant trials in stage II or III primary colorectal cancer (1). The MOSAIC trial (6) actually reported a 4.2% OS benefit at 6 years of follow-up. The sample size of 364 (Remark 4) was insufficient to detect a significant difference in OS compared with a relatively large sample size of 1,347 patients with stage II or III colon cancer. In the future, such large numbers of patients will be impossible to enroll in clinical trials entailing resectable CRLM (1).

A new EPOC trial (ISRCTN22944367) was registered to assess whether the combination treatment of cytotoxic chemotherapy with targeted agents could improve the outcome (7). However, the addition of cetuximab to FOLFOX and surgery for patients with resectable CRLM in KRAS exon 2 wild-type resulted in significantly shorter PFS compared with the FOLFOX and surgery group (14.1 *vs*. 20.5 months, HR 1.48; P=0.030).

Perioperative chemotherapy for resectable CRLM in the future

The advantages of preoperative chemotherapy for resectable CRLM include the ability to check chemo-responsiveness before hepatectomy, elimination of micrometastasis, and tumor shrinkage for R0 resection (1,5,8); the disadvantages include unresectable tumor progression, hepatic toxicity that increases morbidity/mortality, and missing tumors by complete radiological response (Remark 5) (1,5,8,9). Although certain tumors became unresectable in some patients with initially resectable CRLM, half of the progression occurred outside the liver. Thus, these patients would have received unnecessary hepatic resection (4). Considering that recurrences are frequently observed in approximately 75% of patients with CRLM, even after curative hepatic resection (3,10), further evaluation of perioperative chemotherapy is definitely required.

The EPOC study demonstrated no significant difference by the addition of perioperative chemotherapy to FOLFOX4 compared with surgery alone in OS for patients with CRLM. Previous clinical trials in a CRLM adjuvant setting were judged using disease-free survival (DFS) or PFS as the primary endpoint; the improvement of which cannot be seen as tantamount to a long-term survival benefit. Future progress in this area will probably have to rely on surrogate endpoints for OS. Oba and Hasegawa *et al*. (11) proposed a new composite endpoint, time to surgical failure (TSF), as a surrogate marker for OS after the resection of CRLM. Their research clearly demonstrated that the first recurrence after an initial hepatic resection does not reflect surgical failure or noncurability; if a surgical approach cannot be selected, any survival time beyond the recurrence is prolonged by appropriate chemotherapy. In contrast, re-resections for recurrences in the remnant liver have been accepted as providing a survival benefit (2,12). As shown by the high repeat resection rate (>40%) for patients with recurrence in the EORTC 40983 trial, the first recurrence-related event does not reflect long-term OS (4). Recently, we reported the predictive value for OS using the half-life of carcinoembryonic antigen (CEA) after induction chemotherapy for CRLM (13). After only three courses of chemotherapy (6 weeks) with oxaliplatin, when the patients in this study were divided into two groups according to the median value of 20 days, significant differences were detected not only in OS but also in the pathological response. The half-life of CEA is easily measured and can contribute to proper decision making, avoiding ineffective treatment.

After assessing long-term OS in the EPOC trial, adequate patient selection should be performed at the time of enrollment. Jones *et al*. (14) reported that patients with liver-only CRLM should be managed in three separate groups as follows: group one, those with easily resectable disease who should be offered immediate surgery followed by adjuvant therapy if considered appropriate; group two, those with borderline resectable or high recurrence risk CRLM who could be offered appropriate systemic neoadjuvant chemotherapy prior to planned liver surgery; and group three, those with unresectable but liver-only CRLM who should be offered the most effective systemic therapy with the primary purpose of achieving maximal disease response with the intention of conversion to curative hepatic resection. An exploratory retrospective analysis (EORTC study 40983) involving perioperative FOLFOX was conducted to identify possibly predictive baseline factors that could prolong PFS (15). Perioperative FOLFOX seems to benefit in particular patients with resectable CRLM with elevated CEA (>5 ng/mL) when PS is unaffected, regardless of the number of liver metastases (1 *vs*. 2-4). Adam *et al*. demonstrated that preoperative chemotherapy does not seem to benefit the outcome of

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patients with solitary metachronous CRLM (16).

We recently demonstrated a nomogram developed by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (HBPS) that predicted the DFS of CRLM patients treated with hepatic resection (3). A total of 727 patients with liver-only CRLM resected without chemotherapy were enrolled. This nomogram can easily calculate the median and yearly DFS rates from only six preoperative variables: synchronous metastases, 3 points; primary lymph node positive, 3 points; two to four tumors, 4 points and ≥5, 9 points; largest tumor diameter >5 cm, 2 points; extrahepatic metastasis at hepatectomy, 4 points; and preoperative carbohydrate antigen 19-9 level >100, 4 points. Estimated median DFS time was calculated as follows: >8.4 years for patients with 0 points, 1.9 years for 5 points, 1.0 year for 10 points; rates were lower than 0.6 years for patients with more than 10 points. The HBPS nomogram is a very useful tool for determining the likelihood of early recurrence and the necessity for perioperative chemotherapy. Patients with over 10 points may be good candidates for perioperative chemotherapy because their DFS is shorter than 1 year.

In Japan, the randomized phase II and III trial "JCOG0603" has been conducted to compare "hepatectomy alone" with "hepatectomy followed by adjuvant 12 courses of FOLFOX" as treatment in patients with curatively resected CRLM to improve survival with intensive chemotherapy (17). Subsequently, "EXPERT trial" is ongoing to evaluate the efficacy and the safety of surgery and perioperative chemotherapy for resectable liver-only and KRAS exon 2 wild-type CRLM patients. This randomized phase III trial compare "surgery plus perioperative 12 courses of FOLFOX plus cetuximab" and "surgery followed by mFOLFOX6 as adjuvant chemotherapy".

In conclusion, perioperative chemotherapy combined with hepatic resection should be tested because the recurrences occurred frequently even in curatively resected CRLM patients. Prospective clinical trials with adequate restriction of enrolled patients and surrogate markers for OS are strongly recommended to determine the optimal protocol.

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