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Phase II Study of Preoperative Capecitabine and Oxaliplatin-based Intensified Chemoradiotherapy With or Without Induction Chemotherapy in Patients With Locally Advanced Rectal Cancer and Synchronous Liver-limited Resectable Metastases

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Objectives: Controversy surrounds the management of patients with locally advanced rectal cancer with synchronous resectable liver metastases (LMs). This study was designed to improve both systemic and local control in these patients.

Methods: Patients with locally advanced rectal cancer (cT3-4N0 or cTanyN1-2) and synchronous resectable liver-limited metastases (cM1a) were randomly assigned to receive either preoperative treatments of induction CapeOx, followed by chemoradiotherapy with CapeOx (CapeOx-RT) (arm A) or CapeOx-RT alone (arm B). Induction CapeOx consisted of oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily on days 1 to 14, every 3 weeks for 2 cycles; CapeOx-RT consisted of radiotherapy with 45 Gy/25 daily fractions ± 5.4 Gy/3 fractions, oxaliplatin 50 mg/m^2 weekly for 5 weeks, and capecitabine 825 mg/m^2 twice daily on days 1 to 38. Total mesorectal excision and simultaneous liver metastasectomy were planned within 6 weeks after completion of preoperative treatments. The primary endpoint was R0 resection rate of both the primary tumor and LMs.

Results: Thirty-eight patients were randomly assigned to the present study, 18 to arm A and 20 to arm B. The overall R0 resection rate for both the primary tumor and LMs was 77.8% in arm A and 70.0% in arm B ($P = 0.72$). The median progression-free survival was 14.2 versus 15.1 months ($P = 0.422$) and the 3-year overall survival rate was 75.0% versus 88.8% ($P = 0.29$), respectively.

Conclusions: Both treatment strategies showed considerable R0 resection rates; however, further study will be warranted to apply these intensified strategies in clinical practice.

Key Words: rectal cancer, liver metastasis, chemoradiotherapy

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Colorectal cancer is the third most common cancer and the fourth leading cause of cancer-related death worldwide, with rectal cancer representing about 40% of cases.[1] Between 15% and 20% of patients have synchronous liver metastasis (LM) at the time of diagnosis.[2,3] It has been reported that 10% to 30% of these patients have a potentially resectable disease, and surgical resection of both the primary tumor and LM may be curative.[4]

Current treatment options for colon cancer with resectable synchronous LM are simultaneous or staged surgical resection of the primary tumor and LM with perioperative chemotherapy.[5] However, management of rectal cancer in this setting is more complicated, because radiotherapy should be considered for local control, especially in locally advanced rectal cancer (LARC). Current treatment options for these patients are preoperative chemoradiotherapy, followed by surgery and adjuvant chemotherapy, with or without induction chemotherapy. One other option is surgery followed by postoperative chemoradiotherapy.[6] However, these treatment guidelines are mainly based on retrospective studies and there have been no prospective trials for the treatment of this group of patients.

After curative-intent resection of the primary tumor and LM in patients with colorectal cancer with synchronous LM,

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recurrences have been reported in up to two thirds of patients, resulting in a poor 5-year survival rate of approximately 40%.[4,7] Recurrences mostly occur at distant sites, probably due to the presence of micrometastases at the time of surgery. Therefore, further improvements in the survival outcome will require integration of more effective systemic chemotherapy into the multimodality therapy.

In an effort to improve the survival outcome of LARC patients, Rodel et al[8] demonstrated that the addition of oxaliplatin to standard preoperative fluorouracil-based chemoradiotherapy was feasible and increased the number of patients achieving a pathologic complete response (pCR). In addition, a number of studies showed that induction chemotherapy with capecitabine and oxaliplatin before preoperative chemoradiotherapy improved exposure to systemic treatment with acceptable toxicity and compliance.[9–11]

Our present multicenter randomized phase II study was conducted to evaluate the efficacy, tolerability, and feasibility of the addition of oxaliplatin to a preoperative chemoradiotherapy regimen (CapeOx-RT), with or without induction chemotherapy also composed of capecitabine and oxaliplatin (induction CapeOx), in LARC patients with resectable LM.

MATERIALS AND METHODS

Patient Population

The eligibility criteria included an age above 20 years and histopathologically confirmed rectal adenocarcinoma, with an inferior tumor border within 12 cm from the anal verge. The tumor had to be confirmed as cT3-4 or cN+ disease on the basis of rectal magnetic resonance imaging (MRI) and judged to be resectable or expected to be resectable after chemoradiotherapy by a multidisciplinary team. All patients underwent liver MRI and positron emission tomography to assess the exact number of LMs and to exclude extrahepatic metastasis. Metastatic liver lesions had to be resectable according to the following criteria: (1) ≤ 5 in number; (2) no invasion of major vessels; (3) considered resectable with respect to their distribution by a multidisciplinary team; and (4) expected to maintain adequate liver function after the surgery. Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, no prior chemotherapy or radiation therapy, and adequate bone marrow, liver, and renal function. We excluded patients with adenocarcinoma arising from inflammatory bowel disease, extrahepatic distant metastasis, synchronous unresected colon cancer, intestinal obstruction or risk of intestinal obstruction, clinically significant cardiovascular disease, or other cancers diagnosed within 5 years. Pregnant or breast-feeding women were also excluded. All patients provided written informed consent and the study protocol was approved by the institutional review boards of the participating institutions. This trial is registered with ClinicalTrials.gov, number NCT 01643070.

Randomization and Treatment

This was a prospective, multicenter, randomized phase 2 study, and patients were randomly allocated in a 1:1 ratio to either preoperative treatments of induction CapeOx followed by CapeOx-RT (arm A) or CapeOx-RT alone (arm B) using the allocation table of the stratified randomized design derived from the number of LMs and the carcinoembryonic antigen level. Induction CapeOx consisted of oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily on days 1 to 14, every 3 weeks for 2 cycles. CapeOx-RT consisted of radiation therapy with 45 Gy delivered in conventional fractionation (daily fractions of 1.8 Gy over a period of approximately 5 wk, excluding weekends) with or without additional 5.4 Gy delivery in daily fractions of 1.8 Gy over 3 days, oxaliplatin 50 mg/m^2 weekly for 5 weeks, and capecitabine 825 mg/m^2 twice daily on days 1 to 38 (during radiation therapy). Surgery was planned with total mesorectal excision and simultaneous liver metastasectomy with or without addition of radiofrequency ablation within 6 weeks after completion of preoperative treatments. Postoperative chemotherapy (postoperative CapeOx) consisted of oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily on days 1 to 14, every 3 weeks for 6 cycles.

Pathologic Examination

R0 and R1 were defined as histologically tumor-free or infiltrated resections margins, respectively, whereas R2 was defined as macroscopic residual tumor. Rectal circumferential resection margins were defined as negative when the distance to the tumor was >1 mm. The regression of the primary tumor was quantified according to the 5-point tumor regression grade proposed by Dworak et al[12]: The pathologic stage (ypT or N) was recorded according to the International Union Against Cancer TNM system. Pathologic complete response (ypCR) was defined as the absence of viable tumor cells in the surgical specimens, of the primary tumor (ypT0). A major pathologic response of the primary tumor was defined as tumor regression grades 3 and 4.

Assessment

We repeated abdominopelvic computed tomography or MRI after completion of induction CapeOx, CapeOx-RT, and adjuvant CapeOx. The tumor response was assessed according to the guidelines of the Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1).

The primary endpoint was the synchronous complete R0 resection rate, defined as the R0 resection rate of both the primary tumor and LMs. Secondary endpoints were the pCR rate of the primary tumor, radiologic response rate after preoperative treatment, progression-free survival (PFS), overall survival (OS), and pattern of treatment failure. PFS was defined as the time from the date of randomization until progression or death from any cause. OS was calculated from the date of randomization until death from any cause or was censored at the last follow-up. Toxicities were evaluated at each cycle of induction or postoperative CapeOx and weekly during CapeOx-RT according to NCI-CTC version 3.0.

Statistical Analysis

Assuming that induction chemotherapy and the addition of oxaliplatin to preoperative chemoradiotherapy would improve both local and systemic disease control, the target of the synchronous complete R0 resection rate was set to 90% and a rate of 60% or below was considered futile. A 2-stage optimal design, as proposed by Simon,[13] was used to allow early termination of any ineffective arm early in the study. With a 1-sided, type I error of 5% and power of 0.9, the planned study was to proceed in 2 steps. In the first step, 8 patients were required per arm and, if synchronous complete R0 resection was observed in 6 or more patients in both arms, the study was to proceed to the second step with 9 additional patients per arm (17 patients per arm). If this condition was not met, the study would be stopped for futility. In the second step, if synchronous complete R0 resection was observed in 14 or more patients in both arms, the treatments were considered effective. Assuming a dropout rate of 10%, 19 patients were required in each arm (a total of 38 patients).

Both PFS and OS were estimated by using the Kaplan-Meier method and were compared between arms by the log-rank test. The categorical variables are presented as number (percentage) and the continuous variables are presented as median (range). The categorical variables were compared with the χ^2 test or Fisher exact test, as appropriate, and the continuous variables were compared with the Mann-Whitney *U* test.

RESULTS

Patients

Between March 2010 and May 2014, 38 patients from 3 centers in Korea were enrolled. The progress of all patients during the trial is shown in Figure 1. They underwent random assignment: 18 patients were assigned to arm A and 20 to arm B. The cutoff date for this report was March 15, 2015. The baseline characteristics of these patients are presented in Table 1, and most of them were well balanced between the 2 arms. The median number of LMs was 2 and cT3N+ was the most common clinical disease stage in both arms.

Treatment Exposure

Treatment exposures are summarized in Supplementary Table S1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A131, which shows the treatment exposure).

Induction Chemotherapy

The median relative dose intensities for both oxaliplatin and capecitabine were 100% for the patients who received induction chemotherapy (arm A).

Chemoradiotherapy

Three patients (16.7%) in arm A did not receive chemoradiotherapy for several reasons (Fig. 1). One patient underwent stent insertion due to intestinal obstruction during induction chemotherapy without evidence of disease progression and proceeded to surgery with no chemoradiotherapy due to risk of bowel perforation. Another 2 patients withdrew consent. Among the patients who received chemoradiotherapy, 14 patients (93.3%) in arm A and 18 patients (90%) in arm B completed the planned radiotherapy. The median relative dose intensity of oxaliplatin was 89.7% in both arms, whereas those of capecitabine were 95.4% versus 98.4% in arms A and B, respectively.

Surgery

A total of 16 patients (88.9%) in arm A and 19 patients (95%) in arm B underwent surgery. The median times from the completion of the radiation therapy to surgery were 5.9 weeks (range, 4.6 to 7.3 wk) in arm A and 6.0 weeks (range, 3.0 to 8.1 wk) in arm B, respectively. Two patients in arm A and 1 patient in arm B did not receive surgery due to consent withdrawal (Fig. 1).

Postoperative Chemotherapy

Of the resected patients, 14 (87.5%) in arm A and 17 (89.5%) in arm B received postoperative chemotherapy, and 2 patients in each arm did not receive adjuvant chemotherapy for several reasons (Fig. 1). One patient died due to sepsis that was unrelated to the treatment, and another patient in arm A withdrew consent. The disease progressed in 2 patients in arm B. The median relative dose intensity of oxaliplatin was 83.8% in arm A and 96.2% in arm B, whereas that of capecitabine was 82.9% and 89.3%, respectively.

Efficacy and Survival

In the intention-to-treat population, the synchronous complete R0 resection rates were 77.8% in arm A and 70.0% in arm B (odds ratio 1.500; 95% confidence interval [CI],

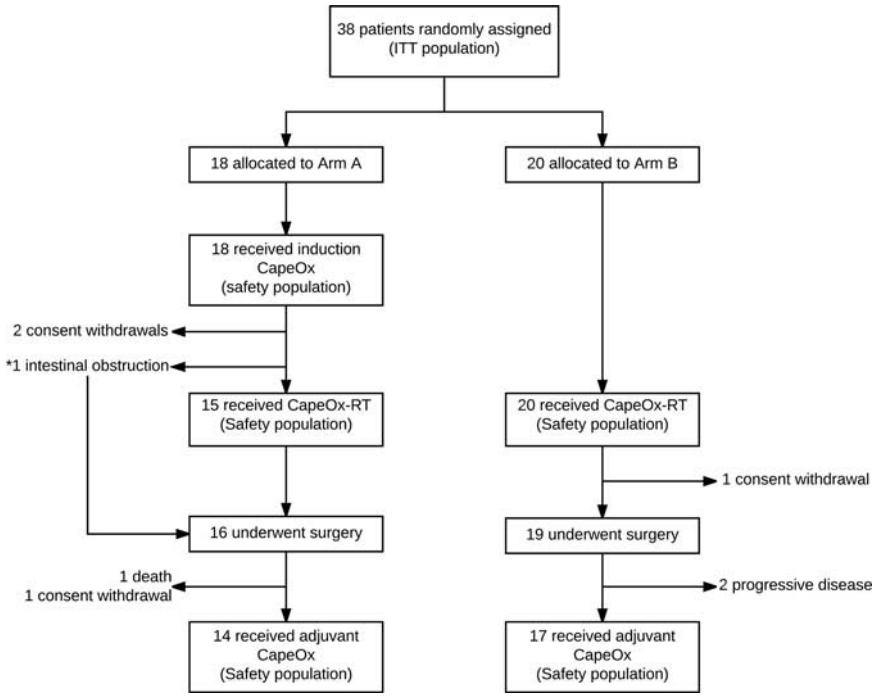

FIGURE 1. CONSORT diagram. *Proceeded to surgery with no chemoradiotherapy due to a risk of bowel perforation. ITT indicates intention-to-treat.

TABLE 1. Patient and Tumor Characteristics

	Arm A (n = 18)	Arm B (n = 20)	*P*
Age (y), median (range)	60 (32-73)	56 (37-76)	0.919
Sex (n [%])			0.328
Male	15 (83)	19 (95)	
Female	3 (17)	1 (5)	
Performance status (n [%])			0.048
0	0 (0)	5 (25)	
1	18 (100)	15 (75)	
Distance of the primary tumor from the anal verge (n [%])			0.222
≤ 6 cm	13 (72)	18 (90)	
> 6 cm	5 (28)	2 (10)	
Tumor differentiation (n [%])			0.360
Well differentiated	3 (17)	3 (15)	
Moderately differentiated	13 (72)	16 (80)	
Poorly differentiated/signet ring cell/mucinous	0 (0)	1 (5)	
Undetermined	2 (11)	0 (0)	
Clinical T stage (n [%])			0.468
cT3	12 (67)	16 (80)	
cT4	6 (33)	4 (20)	
Clinical N stage (n [%])			0.540
cN0	1 (5)	0 (0)	
cN1	5 (28)	5 (25)	
cN2	12 (67)	15 (75)	
No. liver metastases (n [%])			0.959
1	6 (33)	7 (35)	
2	4 (22)	5 (25)	
≥ 3	8 (45)	8 (40)	
Largest size of liver metastases (cm), median (range)	1.8 (1.0-7.4)	2.4 (1.0-6.9)	0.515
Carcinoembryonic antigen (ng/mL), median (range)	7.4 (0.7-548.0)	6.9 (1.4-219.0)	0.874

0.346-6.501; $P = 0.72$); the R0 resection rates for the primary tumor were 83.3% versus 95.0% ($P = 0.33$), whereas those for the LM were 77.8% versus 70.0% ($P = 0.72$), respectively (Table 2). The radiologic response rates were 61.1% in arm A and 70.0% in arm B (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/AJCO/A132, which shows the radiologic evaluation of the responses to preoperative treatments). In addition, the pCR rates were 11.1% versus 5.0%, and the major pathologic response rates of the primary tumor were 22.2% versus 25.0% (Table 3), respectively. At a median follow-up of 32.7 months (range, 3.0 to 57.9 mo), the median PFSs were 14.2 versus 15.1 months, the 3-year PFSs were 25.1% versus 36.3% (hazards ratio 0.707; 95% CI, 0.304-1.646; $P = 0.42$) (Fig. 2), and the 3-year OSs were 75.0% versus 88.8% (hazards ratio 0.379; 95% CI, 0.063-2.283; $P = 0.29$) (Fig. 3), respectively.

TABLE 2. Quality of Surgery

	Arm A (n = 18)	Arm B (n = 20)
Surgery not performed (n [%])	2 (11)	1 (5)
Sphincter-saving surgery (n [%])	13 (72)	16 (80)
Quality of surgery (n [%])		
Primary tumor (rectum)		
R0	15 (83)	19 (95)
R1	1 (6)	0 (0)
Liver metastases		
R0	11 (61)	12 (60)
R0 with intraoperative RFA	3 (17)	2 (10)
R1	1 (6)	3 (15)
R2	1 (6)	2 (10)
Synchronous complete R0 resection rates (%) (95% CI)*	77.8 (58.6-97.0)	70.0 (49.9-90.1)
	OR 1.500 (0.346-6.501), $P = 0.719$	

*By intent-to-treat analysis.

CI indicates confidence interval; OR, odds ratio; RFA, radiofrequency ablation.

Patterns of Recurrence

Recurrence was experienced by 10 patients in arm A (55.6%) and 12 patients in arm B (60.0%) (Supplementary Table S3, Supplemental Digital Content 3, http://links.lww.com/AJCO/A133, which shows the pattern of recurrence). Local recurrence was observed in 2 patients in arm B (10.0%), whereas no patient in arm A experienced local recurrence. Treatment failure was mainly due to distant recurrence in both arms and the most common site of distant recurrence was the lung and liver in arm A (27.8%) and the liver in arm B (40.0%).

Adverse Events

Adverse events related to the treatment are summarized in Supplementary Table S4 (Supplemental Digital Content 4, http://links.lww.com/AJCO/A134, which shows the adverse events). During induction CapeOx, only 1 of 18 patients (5.6%) in arm A experienced grade 3/4 toxicity, specifically grade 3 thrombocytopenia. Grade 3/4 toxicities during CapeOx-RT consisted of thrombocytopenia (6.7%) and diarrhea (6.7%) in arm A and diarrhea (10%) in arm B. The most common grade 3/4 hematologic toxicity during adjuvant chemotherapy was neutropenia in both arms, which was observed in 3 patients (21.4%) in arm A and 2 patients (11.8%) in arm B. The most common grade 3/4 nonhematologic toxicity during adjuvant chemotherapy was hand-foot syndrome or sensory neuropathy (7.1%) in arm A and nausea (17.6%) in arm B. There was no treatment-related mortality.

TABLE 3. Pathologic Outcomes

	Arm A (n = 18)	Arm B (n = 20)
Surgery not performed (n [%])	2 (11)	1 (5)
Pathologic stages (n [%])		
Primary tumor		
ypT0	2 (11)	1 (5)
ypT1	0 (0)	1 (5)
ypT2	2 (11)	3 (15)
ypT3	11 (61)	13 (65)
ypT4	1 (6)	1 (5)
Regional lymph nodes		
ypN0	7 (39)	3 (15)
ypN1	8 (44)	10 (50)
ypN2	1 (6)	6 (30)
Tumor regression grade (primary tumor) (n [%])		
Total regression	2 (11)	1 (5)
Near total regression	2 (11)	4 (20)
Moderate regression	10 (56)	11 (55)
Minimal regression	2 (11)	3 (15)
Pathologic complete response rates (%)	11.1 (0-25.6)	5.0 (0-14.6)
Major response rates (%)	22.2 (3.0-41.4)	25.0 (6.0-44.0)

DISCUSSION

This is the first prospective randomized study to investigate the role of intensified chemoradiotherapy with or without induction chemotherapy for LARC patients with resectable LMs. In this phase II study, we found that preoperative CapeOx-RT, with or without induction CapeOx, was effective in both local and systemic control before surgery in LARC patients with resectable LMs. Although LMs progressed in 3 patients (1 in arm A, 2 in arm B) during preoperative treatments, all 3 patients were able to proceed to total mesorectal excision with liver metastasectomy. Considerable synchronous complete R0 resection rates as well as good 3-year PFS and OS were observed in both arms.

Both treatment modalities were feasible with a median relative dose intensity of all chemotherapy agents >80% in both arms. More than 90% of patients in both arms received the planned dose of radiotherapy. The general level of toxicity observed during preoperative treatment was low in both arms. Thrombocytopenia (6.7%) was the only grade 3/4 hematologic toxicity in arm A, whereas no grade 3/4 hematologic toxicity was observed in arm B. Diarrhea was the only grade 3/4 nonhematologic toxicity in both groups (6.7% in arm A vs. 10.0% in arm B). The incidence of grade 3/4 adverse events during preoperative chemoradiotherapy in this study was relatively lower than those observed in the representative trials in whites (range, 23% to 40%).[8,14–16] There may exist ethnic differences underlying this observation or because the sample size was rather small to represent our population. The most common grade 3/4 toxicity during postoperative chemotherapy was neutropenia (21.4%) in arm A and nausea (17.6%) followed by neutropenia (11.8%) in arm B.

Although direct comparisons are difficult, due to differences in sample size and patient selection, the overall R0 resection rate (77.8% in arm A and 70.0% in arm B) of our study was comparable to that of previous retrospective studies on LARC patients with LM (55% to 80%).[17,18] Furthermore, our 3-year PFS (25.1% in arm A vs. 36.3% in arm B) and OS (75.0% vs. 88.8%) were superior to those studies, which were 19% to 24% for 3-year PFS and 51% to 59% for 3-year OS.[17,18]

The pCR rate of the primary tumor (11.1% in arm A and 5.0% in arm B) was lower than that of LARC patients without

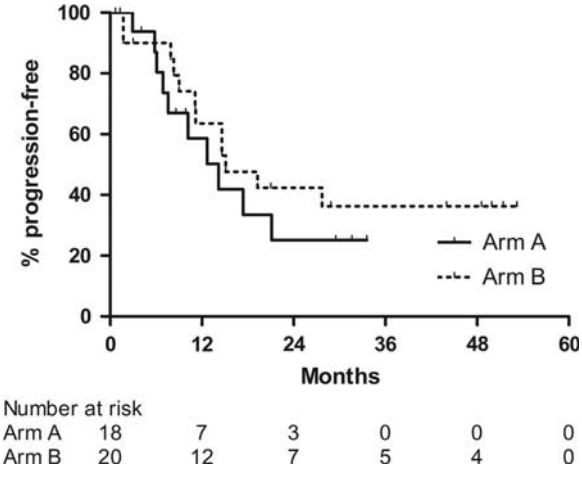

FIGURE 2. Kaplan-Meier curve for progression-free survival time according to treatment arms in the intention-to-treat population.

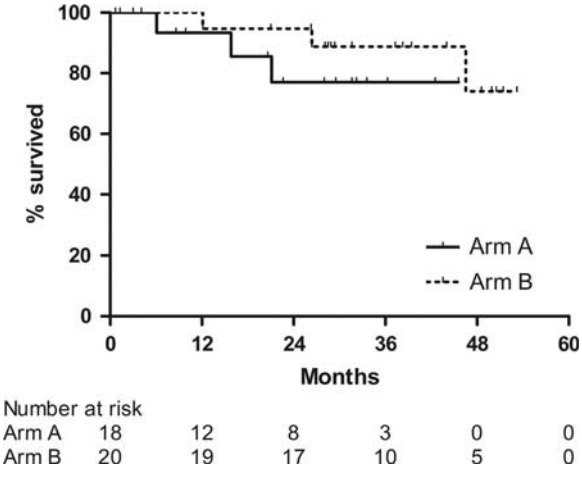

FIGURE 3. Kaplan-Meier curve for overall survival time according to treatment arms in the intention-to-treat population.

distant metastasis (13% to19.5%).[8,14–16] The lower pCR rates of the primary tumor in this study might be related with the shorter interval between completion of chemoradiotherapy and surgery than that in the previous studies for nonmetastatic disease, and also with the selection of patients who had more locally advanced and metastatic disease. Nevertheless, the local recurrence rate (0% in arm A and 10% in arm B) and the rate of sphincter-sparing surgery (72.2% in arm A and 80.0% in arm B) were comparable to those of LARC patients without distant metastasis, with a local recurrence rate of 7.1% to 9.6% and a sphincter-sparing surgery rate of 71% to 79%.[8,16,19,20]

Although local control was satisfactory, more than half of the patients in both arms experienced recurrence, mainly due to distant recurrence, which is in line with previous study results.[20,21] The main cause of treatment failure in rectal cancer is now distant metastasis, and an improvement in OS will require better control of systemic disease while keeping the rate of local recurrence <10%.

The additional 2 cycles of induction CapeOx in arm A did not significantly improve the overall R0 resection rate or any other efficacy outcomes compared with arm B. Thus, the addition of induction chemotherapy may not improve efficacy outcomes in LARC patients with resectable LMs. Nevertheless, a recent phase II study showed that addition of systemic chemotherapy between preoperative chemoradiotherapy and surgery increased the proportion of patients achieving a pCR in LARC without metastasis.[22] Moreover, a randomized phase III trial (the RAPIDO trial) comparing short-course radiotherapy, followed by prolonged preoperative chemotherapy and surgery with standard chemoradiotherapy and surgery in LARC is ongoing. The role of additional systemic chemotherapy for rectal cancer before surgery is expected to be established according to the results of this phase III trial.

It is still controversial whether the addition of oxaliplatin to the standard single fluoropyrimidine-based preoperative chemoradiotherapy regimen is of benefit to LARC patients without metastasis.[8,14–16] However, the addition of oxaliplatin to fluoropyrimidine improved the survival outcomes of metastatic colorectal cancer patients and is now a standard chemotherapy in the metastatic setting.[23] Accordingly, oxaliplatin was added to the preoperative chemoradiotherapy regimen for systemic control of LMs in our study, which may have contributed to the considerable efficacy outcomes. Moreover, this intensified chemoradiotherapy regimen is well tolerated, with a toxicity profile similar to that of the standard single fluoropyrimidine-based chemoradiotherapy.[8,14] Thus, CapeOx-RT can be an additional reasonable approach to LARC patients with resectable metastases who need both local and systemic control.

Recently, the addition of targeted agents such as epidermal growth factor receptor inhibitor or vascular epithelial growth factor receptor inhibitor to the conventional chemotherapy regimen according to the results of companion diagnostics have significantly improved the outcomes of unresectable colorectal cancer patients with metastasis.[24–26] The new EPOC trial, which was conducted to find a benefit of the addition of cetuximab, an epithelial growth factor receptor inhibitor, to chemotherapy in the perioperative setting of resectable colorectal cancer patients with metastasis was stopped early because it met the predefined futility criteria.[27] However, the results of that study are not universally accepted due to several limitations, as recently mentioned by Nordlinger et al,[28] and further confirmatory clinical studies are required to determine the efficacy of the addition of cetuximab to this group of patients.

Bevacizumab is a potent inhibitor of VEGF activity, and it has thus been suggested that its use in a perioperative setting could potentially impact postoperative wound healing.[29] Nevertheless, when bevacizumab was stopped at least 5 weeks before or started at least 28 days after the surgery, there was no increase in wound complications.[30,31] Thus, the addition of bevacizumab can be considered in the treatment of LARC with resectable LMs in future studies in an attempt to improve distant disease control.

Triple combination strategies, FOLFOXIRI (oxaliplatin, irinotecan, and 5-fluorouracil), with or without bevacizumab was proven to bring maximal tumor shrinkage as well as improved survival outcomes.[32,33] The OLIVIA trial, which compared bevacizumab plus FOLFOX with bevacizumab plus FOLFOXIRI for patients with liver-limited metastases, demonstrated that the R0 resection rate was 49% in the bevacizumab plus FOLFOXIRI arm.[34] Thus, triplet combination with or without bevacizumab also can be considered as neoadjuvant strategy for this population.

In conclusion, intensified chemoradiotherapy with or without induction chemotherapy needs more evidence to come into the clinical practice for LARC patients with resectable LMs, although this randomized phase II study demonstrated considerable complete R0 resection rates with manageable adverse events. Further clinical trials with greater numbers of patients are clearly warranted to evaluate the efficacy and safety of this intensified chemoradiotherapy, with or without addition of targeted agents.

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