Preoperative Hepatic and Regional Arterial Chemotherapy in Patients Who Underwent Curative Colorectal Cancer Resection

A Prospective, Multi-center, Randomized Controlled Trial

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Objective: To evaluate the effects of the addition of preoperative hepatic and regional arterial chemotherapy (PHRAC) on prognosis of stage II and III colorectal cancer (CRC) in a multicenter setting.

Summary of Background Data: Our previous single-center pilot trial suggested that PHRAC in combination with surgical resection could reduce the occurrence of liver metastasis (LM) and improve survival in CRC patients.

Methods: A prospective multi-center randomized controlled trial was conducted from December 2008 to December 2012 at 5 hospitals in China. Eligible patients with clinical stage II or III CRC who underwent curative resection were randomized to receive PHRAC plus adjuvant therapy (PHRAC arm) or adjuvant therapy alone (control arm). The primary endpoint was DFS. Secondary endpoints were cumulative LM rates, overall survival (OS), and safety (NCT00643877).

Results: A total of 688 patients from 5 centers in China were randomly assigned (1:1) to each arm. The five-year DFS rate was 77% in the PHRAC arm and 65% in the control arm (HR = 0.61, 95% CI 0.46–0.81; $P = 0.001$). The 5-year LM rates were 7% and 16% in the PHRAC and control arms, respectively (HR = 0.37, 95% CI 0.22–0.63; $P < 0.001$). The 5-year OS rate was 84% in the PHRAC arm and 76% in the control arm (HR = 0.61, 95% CI 0.43–0.86; $P = 0.005$). There were no significant differences regarding treatment related morbidity or mortality between the two arms.

Conclusions: The addition of PHRAC could improve DFS in patients with stage II and III CRC. It reduced the incidence of LM and improved OS without compromising patient safety.

Trial Registration: ClinicalTrials.gov identifier: NCT00643877.

Keywords: colorectal cancer, disease-free survival, hepatic and regional arterial chemotherapy, liver metastasis

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A considerable proportion of colorectal cancer (CRC) patients relapse following potentially curative surgery and standard postoperative adjuvant therapy, and liver metastasis (LM) is the most frequent pattern of recurrence.[1,2] Therefore, a reduction in the incidence of LM may be the most effective method to improve prognosis.

LM originates from micro-metastasis deposits at the time of surgery and is not detectable using modern imaging technique. Such micro-metastases are considered to be an independent prognostic factor.[3,4] Regional chemotherapy to prevent LM, such as intraoperative and postoperative portal vein chemotherapy, is rarely performed, and the outcomes of this procedure remain controversial.[5] Hepatic arterial infusion (HAI) chemotherapy specifically targets the liver and can be effective in preventing liver micro-metastases. Patients with metastatic CRC (mCRC) had higher response rate and more of them converted to resectable with HAI and systemic chemotherapy, compared to those with systemic chemotherapy alone.[6,7] HAI was subsequently shown to reduce hepatic recurrence and improve overall survival (OS) for mCRC in the adjuvant setting.[8,9] However, HAI has not been widely adopted as a first-line treatment for potentially curative CRC.[10]

Given the potential advantages of HAI, we conducted a single-center pilot trial to compare preoperative hepatic and regional arterial chemotherapy (PHRAC) plus adjuvant therapy with adjuvant therapy alone in patients who underwent curative CRC resection, and found that PHRAC could reduce the occurrence of LM and improve survival.[11] The principal goal of this trial was to further investigate the benefit of PHRAC in the treatment of stage II and III CRC in multiple centers.

METHODS

Design and Patients

Participating centers of this study were 5 tertiary hospitals in China (Zhongshan Hospital, Fudan University, the First Affiliated

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Hospital with Nanjing Medical University, the Affiliated Shanghai Ninth People's Hospital of Shanghai Jiao Tong University Medical School, the First Affiliated Hospital, Zhejiang University School of Medicine, and the Second Affiliated Hospital, Zhejiang University School of Medicine). Eligibility criteria included histologically confirmed colorectal adenocarcinoma with clinical stage II or III, Eastern Cooperative Oncology Group performance status 0 or 1, and age 18 to 75 years. Patients were excluded if they had undergone prior cancer therapy for CRC, had other previous malignancy within 5 years, had peripheral neuropathy, or had pathological stage I or IV CRC. Written consent was required for participation in the trial. Ethical approval for the study was given by the local research ethics committee at each hospital.

Categorization of Primary Tumor Location

Primary tumors originating in the appendix, cecum, ascending colon, hepatic flexure or two-thirds of the transverse colon were classified as right-sided CRC. Primary tumors originating in one-third of the transverse colon, the splenic flexure, descending colon, sigmoid colon or rectum were classified as left-sided CRC.

Randomization

In this open-label study, patients were randomly assigned to receive either PHRAC plus adjuvant therapy or adjuvant therapy alone, with a 1:1 allocation ratio. Randomization was done using a central dynamic strategy. Participating centers submitted patient information to the data center at the Department of Biostatistics, Zhongshan Hospital, Fudan University, where central randomization was performed centrally by a computer software program that incorporated a standard procedure for generating random numbers. Subsequently, information on treatment allocation was sent to each participating center.

Procedures

PHRAC were all performed by experienced interventional radiologists approximately 7 days before primary tumor resection, as previously described.[11] First, diagnostic angiography of the celiac trunk and superior mesenteric artery or inferior mesenteric artery was performed selectively with a 4F angiographic catheter (RH catheter; Cook, Bloomington, IN). Then the common hepatic artery and main tumor-feeding artery were identified, and the 4F catheter was advanced into them; when necessary, a 3F microcatheter (SP microcatheter; Terumo, Tokyo, Japan) was used for selective catheterization. After that, fluorodeoxyuridine (650 mg/m^2) and oxaliplatin (75 mg/m^2) were infused continuously, with half dose in common hepatic artery for 30 minutes and half in main tumor-feeding artery for another 30 minutes, and then the arterial catheter was removed. The control arm did not receive preoperative chemotherapy.

Surgery and Adjuvant Therapy

Patients were scheduled to undergo primary surgery approximately 7 days after PHRAC. For both arms, adjuvant chemotherapy with 12 cycles of mFOLFOX6 regimen was regularly administered after the primary surgery, and adjuvant radiotherapy was administered only when necessary. Adverse events were categorized according to the Common Terminology Criteria for Adverse Events version 4.0. Postoperative complications were evaluated with Clavien-Dindo classification.[12]

Follow-up

The follow-up consisted of medical consultation, physical examination, serum carcinoembryonic antigen test and liver ultrasound examination every 3 months for 3 years, then every 6 months for 2 years.[13] The contrast enhanced computed tomography of thorax, abdomen, and pelvic was required annually for 5 years, and also indicated by patient symptoms or laboratory abnormalities. Colonoscopy was performed within 12 months and 3–6 months after resections of non-obstructed CRC and obstructed CRC, respectively.[14] If colonoscopy examination revealed advanced adenoma, the interval was 1 year, and 3 years otherwise. Once patients were diagnosed with recurrence or metastases, further treatments were given and patients were contacted every 3 months to assess survival during follow-up. All of these reports were reviewed centrally.

Statistical Analysis

The primary endpoint was disease-free survival (DFS), defined as the time from randomization to locoregional recurrence or metastasis, second primary cancer, or death from any cause, whichever occurred first. Secondary endpoints included the cumulative incidence of LM, OS, and safety. All analyses were performed according to the intent-to-treat (ITT) principle. ITT patients included all randomized patients regardless of their adherence with the entry criteria and the treatment they actually received. For per-protocol patients, patients with pathological stage I or IV were excluded.

The cutoff date of the analysis was June 30, 2018. The median follow-up was calculated using the inverse Kaplan-Meier method. Survival rates were estimated using the Kaplan-Meier method and compared with a log-rank test. Effects were summarized via the hazard ratios (HR) and 95% confidence intervals (95% CI) using the Cox proportional hazards model. Cumulative LM rates were analyzed using Fine-Gray competing risk model in which death, locoregional recurrence or metastasis at other sites or second primary cancer were used as competing risks.[15] Toxic effects and complication rates were compared with a χ^2 test, or Fisher exact test for cells with $n < 5$. In the subgroup analyses, interaction tests were used to explore the consistency of the treatment effect according to subgroup by including interaction terms between treatment group and subgroup factors in the Cox model. All P values are 2-sided and are considered statistically significant if <0.050.

Target recruitment was at least 321 patients per arm, which would give more than an 80% power to detect a 10% improvement in a 5-year DFS rate (from 65% to 75%) between the control and PHRAC arms with a 2-sided alpha value of 0.050. Assuming a dropout rate of 5%, the planned sample size was 338 patients per arm. Analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL) and R 3.6.2.

RESULTS

Clinical Characterization of Patients

Between December 2008 and December 2012, 688 patients were recruited, 341 to the PHRAC arm and 347 to the control arm. The patients were balanced in baseline characteristics (Table 1). Forty-one patients with pathological stage I or IV were deemed ineligible. Nineteen patients, who were lost to follow-up, were also included in the efficacy analysis. Finally, the eligible patients included 321 patients in the PHRAC arm and 326 in the control arm (Fig. 1). And the pathological information of the 2 arms was shown in Table 2.

At least 1 cycle of adjuvant chemotherapy was received by 313 patients (92%) in the PHRAC arm and 314 (90%) in the control arm. The median cycle number of adjuvant chemotherapy received was 12 in both arms; 304 patients (89%) in the PHRAC arm and 305 (88%) in the control arm received the planned 12 cycles. The median dose of total oxaliplatin received in adjuvant therapy was 767 mg/m^2 and 782 mg/m^2 in the PHRAC and control arm, respectively. In both arms, more than 75% of the planned dose was actually given (76% and 78%, respectively). Ninety-seven (15%) of the eligible patients

TABLE 1. Baseline Clinicopathological Characteristics of the ITT Patients

		PHRAC Arm (n = 341)	Control Arm (n = 347)	*P*
Sex				0.976
	Female	148 (43%)	151 (44%)	
	Male	193 (57%)	196 (56%)	
Age, yr	Median	57.0 (22–75)	59.0 (19–75)	0.407
	<65	259 (76%)	254 (73%)	
	≥65	82 (24%)	93 (27%)	
ECOG PS				0.669
	0	294 (86%)	303 (87%)	
	1	47 (14%)	44 (13%)	
Location of tumor				0.365
	Colon	172 (50%)	187 (54%)	
	Rectum	169 (50%)	160 (46%)	
Primary tumor sidedness				0.117
	Right-sided	73 (21%)	92 (27%)	
	Left-sided	268 (79%)	255 (73%)	
cT stage				0.512
	T3	95 (28%)	89 (26%)	
	T4	246 (72%)	258 (74%)	
cN stage				0.276
	Negative	150 (44%)	167 (48%)	
	Positive	191 (56%)	180 (52%)	
CEA				0.593
	<5 ng/ml	248 (73%)	246 (71%)	
	≥5 ng/ml	93 (27%)	101 (29%)	

CEA indicates carcinoembryonic antigen; cN stage, clinical node stage; cT stage, clinical tumor stage; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat.

received adjuvant radiotherapy (49 PHRAC and 48 control patients with rectal cancer). The median follow-up time was 67.0 months (95% CI: 64.7–69.3).

DFS

In the ITT patients, 78 patients (23%) in the PHRAC arm and 120 (35%) in the control arm had a recurrence event (Table S1, http://links.lww.com/SLA/C674). PHRAC was associated with a reduced hazard of recurrence (HR = 0.61, 95% CI: 0.46–0.81; $P = 0.001$). DFS rate at 3 and 5 years was 80% (95% CI: 76%–84%) and 77% (95% CI: 73%–81%) for the PHRAC arm, respectively, and 70% (95% CI: 65%–75%) and 65% (95% CI: 60%–70%) for the control arm, respectively (Fig. 2A). Eighteen (6 in the PHRAC arm and 12 in the control arm) of 78 patients with LM had a R0 resection; 3 of 24 patients with lung metastasis in the PHRAC arm and 3 of 25 in the control arm had a R0 resection. The results for eligible patients were similar (Table S2, http://links.lww.com/SLA/C674).

Table S3, http://links.lww.com/SLA/C674 showed that among the patients with stage II disease, the DFS at 5 years was 84% (95% CI: 79%–89%) in the PHRAC arm (n = 182) and 77% (95% CI: 70%–84%) in the control arm (n = 170; HR = 0.69, 95% CI: 0.43–1.11; $P = 0.129$; Fig. 2B). Among the patients with stage III disease in the eligible patients group, DFS at 5 years was 68% (95% CI: 60%–76%) in the PHRAC arm (n = 139) and 53% (95% CI: 45%–61%) in the control arm (n = 156; HR = 0.61, 95% CI: 0.42–0.89; $P = 0.011$; Fig. 2C). The *P* value of interaction between stage and PHRAC for DFS was 0.640, indicating that the DFS benefit of PHRAC was consistent across subgroups of different stages.

Among the patients with right-sided CRC, the DFS at 5 years was 74% (95% CI: 64%–84%) in the PHRAC arm (n = 70) and 63% (95% CI: 53%–73%) in the control arm (n = 89; HR = 0.69, 95% CI: 0.39–1.23; $P = 0.204$; Fig. 2D). Among the patients with left-sided CRC in the eligible patients group, DFS at 5 years was 78% (95% CI: 73%–83%) in the PHRAC arm (n = 251) and 66% (95% CI: 60%–72%) in the control arm (n = 237; HR = 0.62, 95% CI: 0.44–0.87; $P = 0.005$; Fig. 2E). The *P* value of interaction between tumor sidedness and PHRAC for DFS was 0.780, indicating that the DFS benefit of PHRAC was consistent across subgroups of different sidednesses.

Cumulative LM Rate

Of the ITT patients, LM occurred in 23 of the 341 patients (6.7%) assigned to the PHRAC arm and in 55 of 347 (15.9%) assigned to the control arm. The cumulative LM rates at 3 years and 5 years were 6% (95% CI: 4%–9%) and 7% (95% CI: 4%–9%) in the PHRAC arm, respectively, and 15% (95% CI: 11%–19%) and 16% (95% CI: 12%–20%) in the control arm, respectively (HR = 0.40, 95% CI: 0.25–0.66; $P < 0.001$; Fig. 3A). The results for eligible patients were also similar.

The cumulative LM rates for patients with stage II disease at 5 years were 5% (95% CI: 2%–8%) and 9% (95% CI: 5%–14%) for the PHRAC and control arms, respectively (HR = 0.55, 95% CI: 0.24–1.26; $P = 0.160$; Fig. 3B). For the eligible patients with stage III disease, the cumulative LM rates at 5 years were 10% (95% CI: 5%–15%) and 24% (95% CI: 17%–31%) for the PHRAC and control arms, respectively (HR = 0.35, 95% CI: 0.19–0.65; $P < 0.001$; Fig. 3C).

The cumulative LM rates for patients with right-sided CRC at 5 years were 7% (95% CI: 2%–13%) and 20% (95% CI: 12%–29%) for the PHRAC and control arms, respectively (HR = 0.34, 95% CI: 0.12–0.91; $P = 0.031$; Fig. 3D). For the eligible patients with left-sided CRC, the cumulative LM rates at 5 years were 7% (95% CI: 4%–11%) and 15% (95% CI: 10%–20%) for the PHRAC and control arms, respectively (HR = 0.44, 95% CI: 0.24–0.77; $P = 0.005$; Fig. 3E).

OS

The OS at 5 years in the ITT patients was 84% (95% CI: 80% to 88%) in the PHRAC arm and 76% (95% CI: 71%–81%) in the control arm, corresponding to an 8% decrease in the rate of death

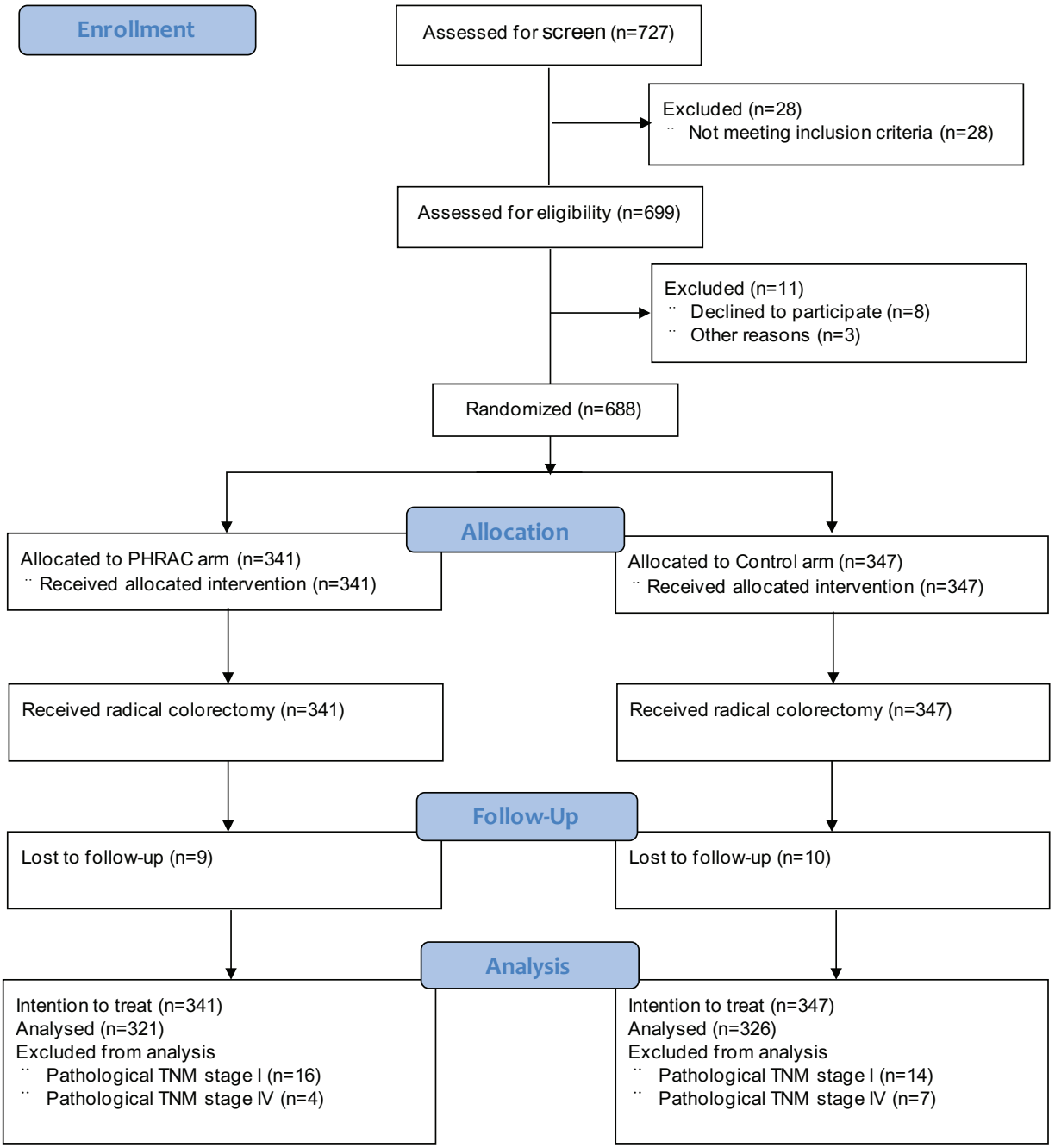

FIGURE 1. The CONSORT diagram. For both arms, adjuvant chemotherapy with 12 cycles of mFOLFOX6 regimen (Oxaliplatin 85 mg/m^2 intravenously on day 1, leucovorin 400 mg/m^2 intravenously on day 1, fluorouracil 400 mg/m^2 intravenously and 2400 mg/m^2 continuous intravenous infusion over 46–48 h every 2 wk) was scheduled to be administered within 4 wk after the primary surgery. Adjuvant long-term radiotherapy for rectal cancer was administered according to Chinese clinical guideline if necessary.

(Fig. 4A). PHRAC was associated with a reduced hazard of death (HR = 0.61, 95% CI: 0.43–0.86; P = 0.005).

For the patients with stage II disease, the 5-year OS rates were 90% (95% CI: 86%–94%) and 86% (95% CI: 81%–91%) in the PHRAC arm and the control arm, respectively (HR = 0.68, 95% CI: 0.37–1.26; P = 0.218; Fig. 4B). For the patients with stage III disease, the 5-year OS rates were 77% (95% CI: 70%–84%) and 66% (95% CI 58%–74%) in the PHRAC and control arms, respectively (HR = 0.60, 95% CI: 0.39–0.94; P = 0.025; Fig. 4C).

For the patients with right-sided CRC, the 5-year OS rates were 84% (95% CI: 75%–93%) and 77% (95% CI: 68%–86%) in the PHRAC and control arm, respectively (HR = 0.68, 95% CI: 0.32–1.41; P = 0.295; Fig. 4D). Among the eligible patients with left-sided CRC, the 5-year OS rates were 85% (95% CI: 80%–90%) and 76%

TABLE 2. Surgical and Pathological Characteristics of the ITT Patients

		PHRAC Arm (n = 341)	Control Arm (n = 347)	*P*
Type of surgery				0.745
	RH	70 (21%)	85 (24%)	
	TE	5 (1%)	7 (2%)	
	LH	22 (6%)	24 (7%)	
	SE	75 (22%)	71 (20%)	
	AR	124 (36%)	112 (32%)	
	Hartmann	4 (1%)	2 (1%)	
	APR	41 (12%)	46 (13%)	
Access of surgery				0.280
	Open	46 (13%)	57 (16%)	
	MIS	295 (87%)	290 (84%)	
Tumor differentiation				0.179
	Well	54 (16%)	45 (13%)	
	Moderate	235 (69%)	232 (67%)	
	Poor or non	52 (15%)	70 (20%)	
pT stage				0.808
	T2	28 (8%)	30 (9%)	
	T3	107 (31%)	101 (29%)	
	T4	206 (60%)	216 (62%)	
pN stage				0.350
	N0	198 (58%)	184 (53%)	
	N1	84 (25%)	101 (29%)	
	N2	59 (17%)	62 (18%)	
Lymphatic/vascular invasion		19 (6%)	26 (7%)	0.308
Nervous invasion		18 (5%)	20 (6%)	0.781
pTNM Stage				0.506
	II	182 (53%)	170 (49%)	
	III	139 (41%)	156 (45%)	
	IV or I	20 (6%)	21 (6%)	

APR indicates abdominoperineal resection; AR, anterior rectal resection; LH, left hemicolectomy; MIS, minimally-invasive surgery; pN stage, pathological node stage; pT stage, pathological tumor stage; pTNM stage, pathological TNM stage; RH, right hemicolectomy; SE, sigmoidectomy; TE, transcolonectomy.

(95% CI: 70%–82%) in the PHRAC and control arms, respectively (HR = 0.60, 95% CI: 0.40–0.90; $P = 0.014$; Fig. 4E).

Surgical-related Complications and Toxicity

The 30-day postoperative mortality was 0 in both arms. No catheter-related complications requiring intervention were reported in the PHRAC arm. There were 36 patients in the PHRAC arm and 34 in the control arm who suffered from surgical-related complications of Clavien-Dindo grade ≥II, with no significant difference ($P = 0.742$). During the therapy period, the most common grade 3 to 4 toxicities were peripheral neuropathy, leucopenia/neutropenia, nausea/vomiting, and increased alanine aminotransferase (Table 3). Grade 3/4 peripheral neuropathy was reported in 35 patients (10%) in the PHRAC arm and 33 (10%) in the control arm.

DISCUSSION

This randomized multi-center trial had reached the primary endpoint, and showed a significant improvement in DFS for patients receiving PHRAC combined with adjuvant chemotherapy compared with those treated with conventional adjuvant therapy alone. The data presented here are also consistent with the evidence of our previous single center trial, which showed that PHRAC could reduce the occurrence of LM and improve survival rate in CRC patients.[11] It should be noted that the DFS rates of the control arm in our trial were poorer than previous trials of oxaliplatin-based chemotherapy, which is likely due to different prognostic factors for baseline characteristics, and there were more T4 patients in our trial (61% in our trial compared with 19% in the MOSAIC trial and 2% in the NSABP C-07 trial).[16,17] Previous studies showed that patients with stage IIB/C (T4N0) colon cancer had significantly worse oncologic outcomes than those with stage IIIA (T1-2N1) colon cancer regardless of adjuvant chemotherapy.[18–20]

Our investigation of PHRAC with an expected survival benefit was based on the potential advantages of delivering composited agents with HAI at an early stage. A meta-analysis including 10 eligible studies of 15,410 patients demonstrated that longer time to adjuvant chemotherapy was associated with worse survival among patients with resected CRC, and a 4-week delay in time to adjuvant chemotherapy was associated with a significant decrease in DFS.[21] For both mCRC and CRC patients, preoperative or perioperative chemotherapy had an apparent advantage in DFS compared with adjuvant chemotherapy.[22,23] An international randomized controlled trial FOxTROT also found that neoadjuvant chemotherapy could improve surgical outcomes of operable colon cancer patients; however, longer follow-up is needed to confirm the long-term benefits.[24,25] Sadahiro et al compared surgery plus perioperative adjuvant HAI with surgery alone, and Ota et al and Feng et al compared adjuvant HAI plus systemic chemotherapy with systemic chemotherapy alone.[10,26,27] All of the above studies found that the addition of HAI improved long-term survival. These results, combined with our findings, suggested that PHRAC could serve as an promising alternative to early-stage chemotherapy, and a complement to adjuvant treatment.

We found that PHRAC significantly reduced postoperative LM rates. Different from the finding in our previous single-center study, no significant differences were observed in extra-hepatic metastasis or recurrences. Therefore, we considered that DFS benefits were mainly attributed to a decrease in the proportion of LM, which depended on the eradication of micro-metastasis foci. Our data on the eligible patients also showed that the cumulative LM rate was the highest in the first 3 years, similar to that of a previous study.[1]

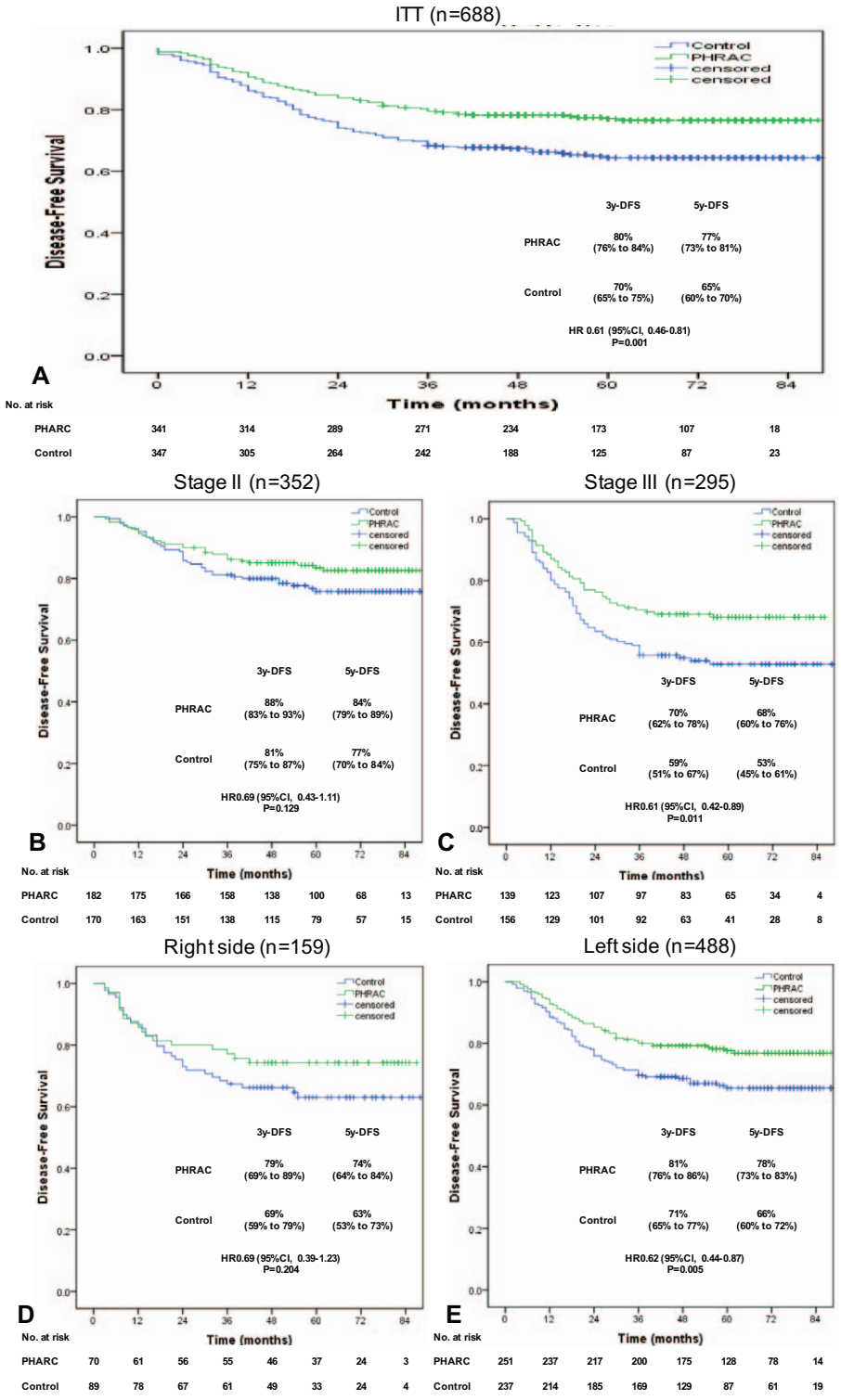

FIGURE 2. Disease-free survival curves. A, In the ITT patients, the DFS of the PHRAC arm was better than that of the control arm ($P = 0.001$). B, In the stage II patients, DFS was not significantly different between the PHRAC and control arms ($P = 0.129$). C, In the stage III patients, differences in DFS between the PHRAC and control arm were significant ($P = 0.011$). D, In the right-sided patients, DFS was not significantly different between the PHRAC and control arms ($P = 0.204$). E, In the left-sided patients, differences in DFS between the PHRAC and control arm were significant ($P = 0.005$). DFS indicates disease-free survival; ITT, intent-to-treat; PHRAC, preoperative hepatic and regional arterial infusion chemotherapy.

However, the incidence of LM was substantially lower in the PHRAC arm during the same period. Currently, the mechanism for this LM-free survival advantage remains to be explored. Some research indicated that preoperative or adjuvant therapy may only postpone recurrence, and late incidence after 5 years could be expected.[28,29]

Sidedness should be considered as a strong prognostic variable and a surrogate predictor of anti-EGFR agents in mCRC, while its role in early stages of resected CRC is still uncertain.[30] Subgroup analysis showed that the observed significant DFS benefits of PHRAC seemed to be driven primarily by the

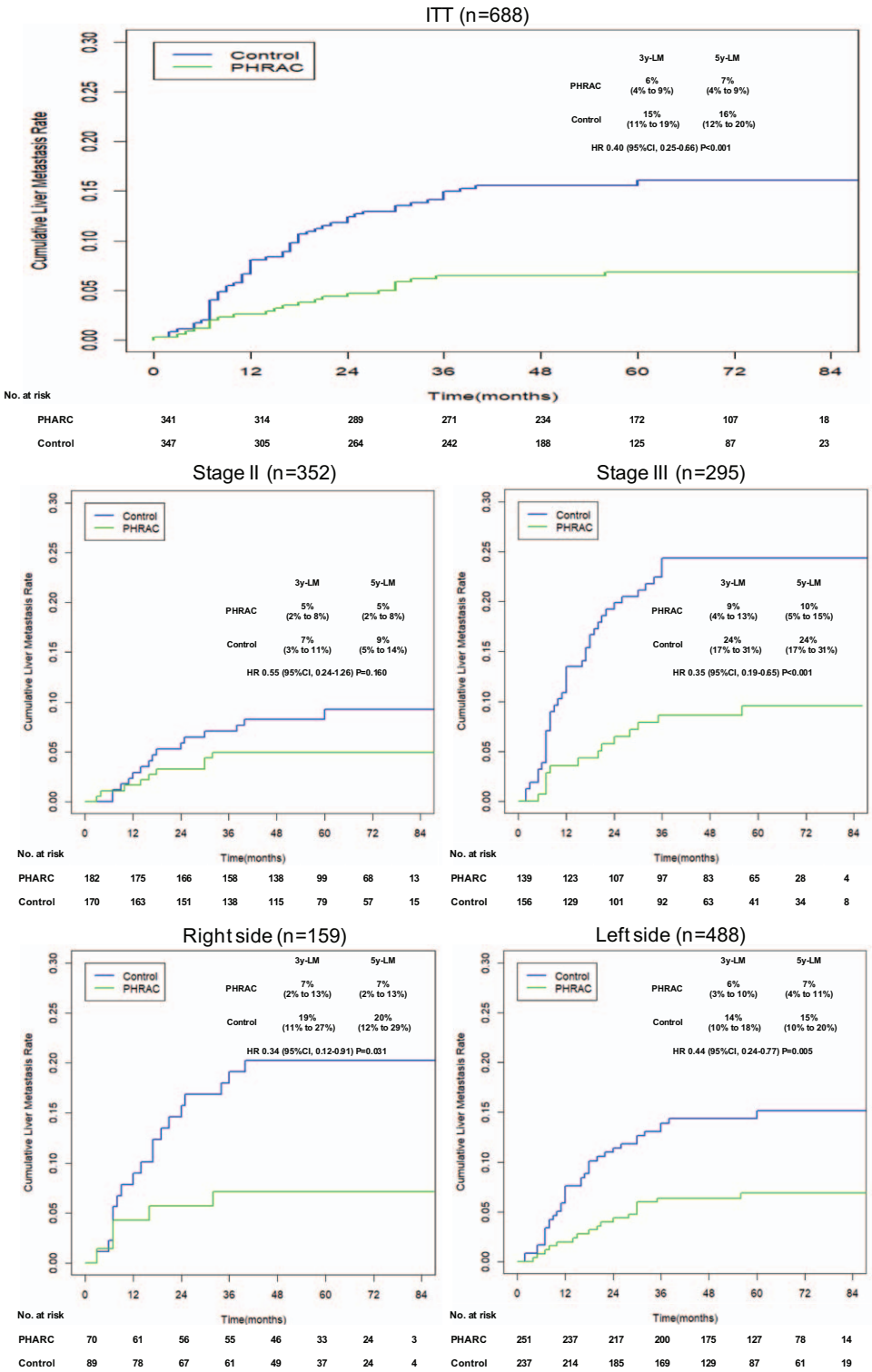

FIGURE 3. Cumulative incidence of LM. A, In the ITT patients, the cumulative LM rate of the PHRAC arm was lower than that of the control arm ($P < 0.001$). B, In the stage II patients, the differences in cumulative LM rates between the PHRAC and control arms were not significant ($P = 0.160$). C, In the stage III subgroup, the differences in cumulative LM rates between the PHRAC and control arms were significant ($P < 0.001$). D, In the right-sided patients, the differences in cumulative LM rates between the PHRAC and control arms were significant ($P = 0.031$). E, In the left-sided subgroup, the differences in cumulative LM rates between the PHRAC and control arms were significant ($P = 0.005$). ITT indicates intent-to-treat; LM, liver metastasis; PHRAC, preoperative hepatic and regional arterial infusion chemotherapy.

favorable effect in stage III or left-sided patients. However, there was no significant difference in the interaction between stage and PHRAC and between tumor sidedness and PHRAC. Therefore, we cannot simply conclude that PHRAC is only useful in stage III or left-sided patients, and, a preoperative predictive model for high risk patients remains to be an important field of further investigation.

There is a strong correlation between DFS and OS.[31] As a secondary endpoint, OS was shown to differ significantly between the 2 arms. However, improved DFS could not always be translated

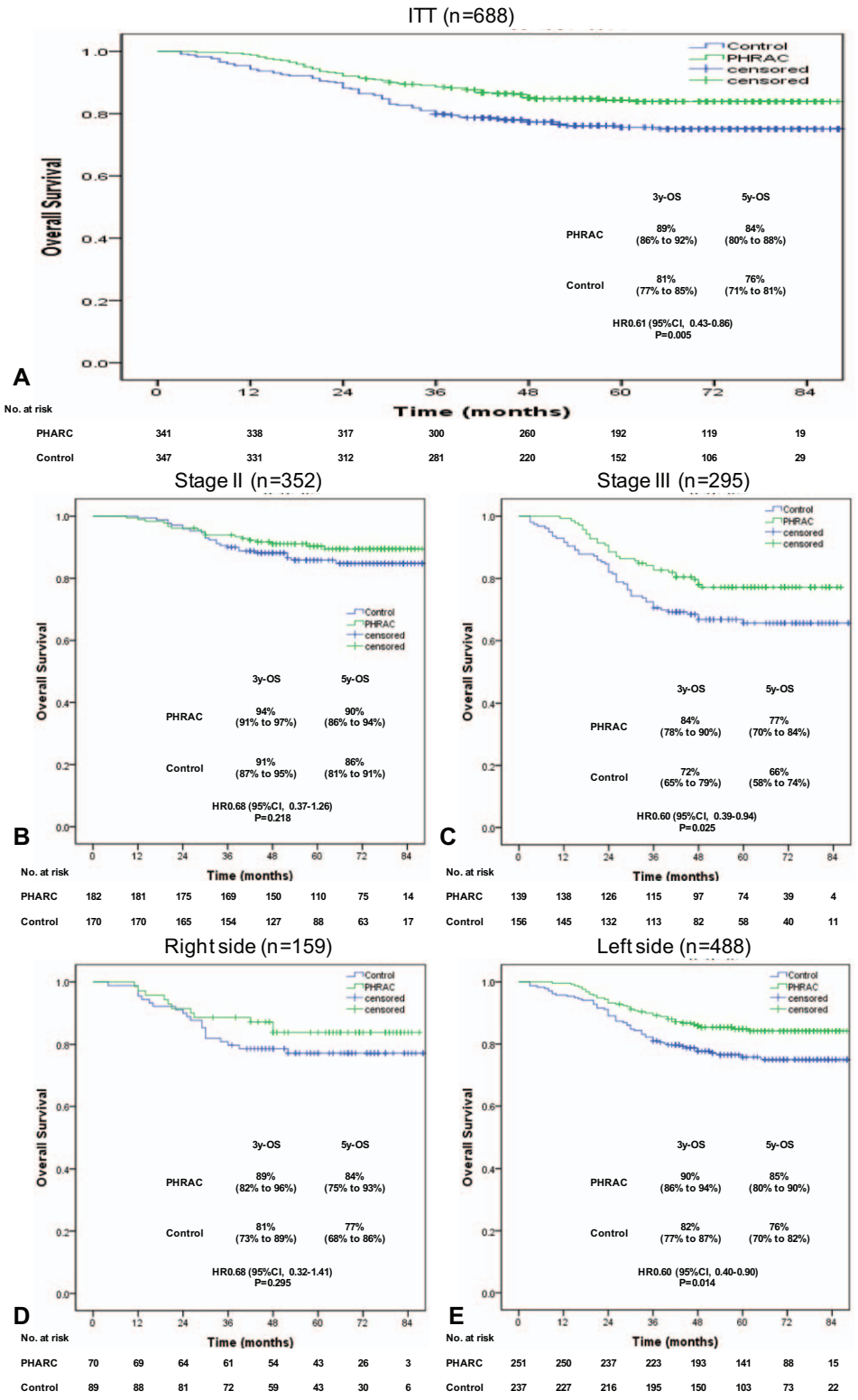

FIGURE 4. Overall survival curves. A, In the ITT patients, the OS at 5 yr was better in the PHRAC arm than in the control arm ($P = 0.005$). B, In the stage II patients, differences in OS were not significant between the PHRAC and control arms ($P = 0.218$). C, In the stage III patients, differences in OS were significant between the PHRAC and control arms ($P = 0.025$). D, In the right-sided patients, differences in OS were not significant between the PHRAC and control arms ($P = 0.295$). E, In left-sided patients, differences in OS were significant between the PHRAC and control arms ($P = 0.014$). ITT indicates intent-to-treat; OS, overall survival; PHRAC, preoperative hepatic and regional arterial infusion chemotherapy.

TABLE 3. Surgical-related Complications and Grade 3/4 Toxicities

	PHRAC Arm (n = 341)	Control Arm (n = 347)	*P*
Surgical-related complications of Clavien-Dindo grade ≥II	36 (11%)	34 (10%)	0.742
Ileus	12 (4%)	10 (3%)	
Wound infection	10 (3%)	8 (2%)	
Anastomotic leakage	4 (1%)	2 (1%)	
Pulmonary infection	3 (1%)	4 (1%)	
Intra-abdominal infection	3 (1%)	3 (1%)	
Anastomotic stenosis	2 (1%)	3 (1%)	
Pulmonary embolism	2 (1%)	1 (0%)	
Bleeding	1 (0%)	3 (1%)	
Others	3 (1%)	2 (1%)	
Grade 3/4 Hematological toxicities	30 (9%)	33 (10%)	0.746
Leucopenia/neutropenia	29 (9%)	32 (9%)	
Thrombocytopenia	1 (0%)	3 (1%)	
Anemia	1 (0%)	0	
Grade 3/4 Non-hematological toxicities	85 (25%)	91 (26%)	0.831
Nausea/vomiting	26 (8%)	14 (4%)	
Increased alanine aminotransferase	16 (5%)	19 (5%)	
Thrombosis or embolism	2 (1%)	3 (1%)	
Diarrhea	10 (3%)	15 (4%)	
Peripheral neuropathy	35 (10%)	33 (10%)	
Others	8 (2%)	12 (3%)	

into an OS benefit because OS after tumor relapse depends on various factors such as physical status, recurrence pattern, second-line therapies and treatment response. Among these factors, the resectability of recurrent diseases was one of the most critical issues.[16,17,32] A prolonged survival after recurrence may reduce the association between DFS and OS, and an imbalance between the 2 arms may indicate no advantage in OS. In the present trial, recurrent diseases were managed by the same way between the 2 arms, and we found that there was a similar resectability rate of LM in both arms.

Despite potential survival advantages, previous experience indicated that PHRAC could cause liver-specific toxicity, increase perioperative morbidity, and might preclude liver resection. However, in our trial with 1 cycle of PHRAC, we observed no significant association between PHRAC and major postoperative complications, and no perioperative mortality. The difference of anastomotic leakage was not significant between the 2 arms and the total incidence was lower than a previous report.[33] There were no catheter-related complications requiring intervention in the PHRAC arm, partly because most of the patients were in good vascular conditions, the interventional radiologists within the multidisciplinary teams were every experienced, and we used relatively thin angiographic catheter. In addition, we found that there was no significant difference in grade 3/4 toxicities of chemotherapy between the 2 arms.

There were several limitations in our study. Our study involved only stage II and III CRC cases; however, due to the current technological limitations of preoperative clinical staging, it was difficult to exclude stage I and IV cases (small LM or limited abdominal dissemination), and the clinical misstaging rate of stage II and III CRC in our study was approximately 15%.[34] The subgroup analysis was based on postoperative pathology, which may introduce bias. PHRAC may have influenced postoperative lymph node staging. As a result, the later exploratory analyses should be interpreted with caution. In addition, the biological characteristics and tumor regression grade of resected CRC specimens should also be considered, which would help in the selection of the most suitable beneficiary patients.

CONCLUSIONS

In summary, this study provided new information on the potential benefits and risks of PHRAC. PHRAC is relatively safe and feasible for the improvement of DFS in stage II and III CRC patients.

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