Perioperative versus Preoperative Chemotherapy with Surgery in Patients with Resectable Squamous Cell Carcinoma of Esophagus

A Phase III Randomized Trial

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Background: Perioperative chemotherapy for resectable squamous cell carcinoma of esophagus remains elusive. Thus, we assessed whether a perioperative regimen of paclitaxel, cisplatin, and 5-fluorouracil (PCF) improved outcomes among patients with curable squamous cell carcinoma of esophagus comparing with preoperative chemotherapy alone.

Methods: Overall, 346 patients with resectable squamous cell carcinoma of esophagus were randomly assigned to receive surgery plus perioperative chemotherapy (175, arm A) or preoperative chemotherapy (171, arm B). Both arms received two preoperative cycles of PCF: intravenous paclitaxel (100 mg per square meter of body surface area) and cisplatin (60 mg per square meter of body surface area) on day 1, and a continuous intravenous infusion of 5-fluorouracil (700 mg per square meter of body surface area per day) for 5 days. Arm A received two added postoperative cycles of PCF. The primary end point was relapse-free survival, and the secondary end point was overall survival.

Results: Compared with preoperative chemotherapy group, perioperative chemotherapy group had a greater likelihood of 5-year relapse-free survival (hazard ratio for relapse, 0.62; 95% confidence interval, 0.49–0.73; 31% versus 17%, $p < 0.001$) and of 5-year overall survival (hazard ratio for death, 0.79; 95% confidence interval, 0.59–0.95; 38% versus 22%, $p < 0.001$). A pathologic complete response rate was achieved in 77 of 320 patients (24.1%) who underwent resection after chemotherapy. The increased PCF-related toxic events were not detected with the addition of two postoperative cycles of PCF.

Conclusion: In patients with operable esophageal squamous cell carcinoma, perioperative regimen of PCF can significantly improve 5-year relapse-free and overall survival comparing with preoperative chemotherapy alone. (The trial has been registered at ClinicalTrials.gov, number NCT01225523.)

Key Words: Perioperative chemotherapy, Preoperative chemotherapy, Squamous cell carcinoma of esophagus, Paclitaxel, Phase III.

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With annual new diagnosis of more than 450,000, esophageal cancer is characterized as the eighth most common cancer worldwide, whereas it is a highly lethal disease because of more than 400,000 deaths per year.[1–3] The incidence of esophageal adenocarcinoma is rapidly increasing, whereas that of squamous cell carcinoma of the esophagus remains unchanged.[1–3] In China, esophageal cancer is the second most common cause of cancer-related deaths in males and the fourth in females.[4] Despite improvement in surgical management in the past two decades, the prognosis of patients with esophageal cancer undergoing resection with curable intent was poor with only approximately 20% survival at 5 years.[5] A huge number of patients with resectable esophageal cancer may shortly develop metastatic disease or local recurrence. The factors contribute to this dismal outlook, including the presence of locoregionally advanced disease, undetected micrometastasis at diagnosis, and inadequate preoperative staging. Because of high rates of locoregional and distant failure, there are increasing interests in the combination of treatments with surgery.

As an alternative to resection for locoregional treatment of esophageal cancer, the evidences are growing to favor neoadjuvant chemotherapy with the potential benefits of increasing the likelihood of curative resection by downstaging the tumor, eliminating micrometastasis, and improving survival.[6,7] In parallel, adjuvant chemotherapy has not been shown to yield an absolute survival benefit comparing with surgery alone for esophageal cancer.[8–10] However, the encouraging results

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with perioperative chemotherapy in two randomized phase III clinical trials were shown to significantly improve overall and progression-free survival in patients with the adenocarcinoma of stomach or esophagus,[11–13] despite a divergent outcome from INT 113 USA trial.[14,15] Conversely, a well-conceived and well-executed clinical trial of perioperative chemotherapy in patients with resectable squamous cell carcinoma of esophagus remains blank.

The regimen of cisplatin and 5-fluorouracil achieved the response rates of 40% to 50% for squamous cell carcinoma and 30% to 40% for adenocarcinoma.[16,17] A higher histopathologic response rate has been detected by using more efficient cytotoxic agents, such as paclitaxel in patients with advanced squamous cell carcinoma of esophagus.[18] In the mid-1990s, there were considerable interests in paclitaxel for treatment of esophageal cancer with concerns on hemotologic toxic effects.[18–20] In patients with advanced squamous cell carcinoma of esophagus, although the efficacy between docetaxel and paclitaxel was not significantly different in overall survival, paclitaxel was a more feasible agent with less febrile neutropenia.[21] Accordingly, the combination of paclitaxel, cisplatin, and 5-fluorouracil (PCF) had substantial antitumor activity with an intriguing complete response rate in patients with the advanced squamous cell carcinoma of esophagus.[18] Despite concerns regarding toxicity, this trial established PCF as an active chemotherapy regimen. Given the positive findings of PCF, we sought to investigate whether perioperative PCF could improve the outcomes of resectable squamous cell carcinoma of esophagus comparing with those receiving preoperative PCF.

PATIENTS AND METHODS

Eligibility

The patients were enrolled at the First Affiliated Hospital and the Second Affiliated Hospital of Xi'an Jiaotong University from January 2005 to April 2007, with no evidences of previous chemotherapy or radiotherapy. Patients aged 18 years and older who had a World Health Organization (WHO) performance status 0 or 1 were eligible if they had histopathologically proven squamous cell carcinoma of esophagus that was considered as suitable for curative resection. The disease had to be confined to primary and regional nodes, although celiac nodal involvement (M1a) was permitted for primary tumor localized in the distal esophagus or gastroesophageal junction. Patients had to be operative candidates without excessive clinical risks and had no evidences of distant disease or involvement of tracheobronchial tree or other structures that would preclude a complete resection. Laboratory parameters included adequate bone marrow reserve consisting of a white blood cell count of more than 3500 cells/ml, platelet count of more than 100,000 cells/ml, normal liver function with total bilirubin of less than 1.5 mg/100 ml, and creatinine clearance of more than 60 ml/min. The protocol was approved by ethics committees. The written informed consents were obtained before randomization.

Pretreatment examinations consisted of the followings: esophagogastroscopy; barium esophagram; helical computed tomography scans of the chest, abdomen, and pelvis; and exploratory laparoscopy with biopsy as indicated to confirm nodal disease. All the procedures were performed by experienced gastroenterologists. Patients in this trial were stratified on the basis of clinical characteristics, including age, sex, WHO performance status, body weight loss, site, and maximum diameter of tumor. Pretreatment staging was not reported in the trial, because endocopic ultrasonography (EUS) was not available at the time of trial.

Treatment Plan

Eligible patients with resectable squamous cell carcinoma of esophagus were randomly assigned to receive surgery plus perioperative chemotherapy (175, arm A) or preoperative chemotherapy (171, arm B). Each 3-week cycle consisted of PCF: paclitaxel (100 mg per square meter of body surface area) by a 3-hour intravenous infusion on day 1, cisplatin (60 mg per square meter of body surface area) intravenously with hydration on day 1, and 5-fluorouracil (700 mg per square meter of body surface area) daily through day 1 to 5 by continuous intravenous infusion with a double-lumen Hickman catheter. Both arms received surgery and two preoperative cycles of PCF. Arm A received two added postoperative cycles of PCF. One milligram of warfarin daily was recommended as prophylaxis against thrombosis. All patients were premedicated intravenously 30 minutes before therapy with 8 to 16 mg dexamethasone, 300 mg cimetidine, and 50 mg diphenhydramine hydrochloride as standard antiemetic and antianaphylaxis. The patients were closely monitored for toxic effects of chemotherapy with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.[22]

Before each cycle of chemotherapy, a complete blood count, blood urea nitrogen, electrolyte, serum creatinine levels, and liver function were required. Dose modifications of PCF regimen were recommended for patients with myelosuppression and thrombocytopenia, and dose modifications of 5-fluorouracil were recommended for those with stomatitis, hand–foot syndrome, and diarrhea. If there was an increase in the serum creatinine level, the creatinine clearance was determined and cisplatin dose was subsequently modified if appropriate. Cisplatin was discontinued in patients with clinically significant sensory neural damage. The performance status was assessed every 3 weeks before each chemocycle. A 1-week treatment delay was permitted to allow recovery from toxicity. Dose modifications were implemented based on the guidelines established in RTOG 113 (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0113).

Surgery and Pathologic Examination

Surgery was scheduled within 2 to 4 weeks after completion of the second cycle of preoperative chemotherapy in the two arms. Postoperative chemotherapy was initiated within 5 weeks after surgery in arm A. Tumors of the gastroesophageal junction and the lower third of esophagus were resected through left side of thoracotomy alone, instead of transhiatal resection. In patients with poor respiratory reserve of forced expiratory volume in one second (FEV_1) less than 80%, transhiatal approach was used. The Lewis-Ivor operation in the patients with tumors at the middle third of

esophagus were preferred, and tumors of the upper third, particularly for the patients with tumors of esophagus above aorta arch, were subject to three-field operation in which anastomosis was performed in the neck. The lymph nodes identified by pathologists were collected in the separate boxes and marked according to locations. Separate sampling of subcarinal and celiac axis lymph nodes was recommended. Surgeons were asked to document the extent of dissection and to state whether the procedure was likely to be curative or palliative. Early postoperative complications were prospectively scored by the study coordinators.

In resected specimens, tumors were classified to pathologic tumor, node, metastasis stages according to American Joint Committee on Cancer 2013 Guideline. The absence of residual tumor in the resected specimen, including lymph nodes, was defined as the pathologic complete response (pCR; stage 0).

Resection Type

Resection was classified as curative when gross tumor tissues were removed, and microscopical examination revealed the surgical margins free of tumor (R0). Resections were considered palliative either when microscopical examination revealed positive margins (R1: defined as tumor tissue at <1.0 mm from the radical, or proximal, or distal margin) or when there was residual local gross disease (R2).

Follow-Up and End Points

All patients were visited at the outpatient clinic at intervals of 3 months during first 2 years and every 6 months for 3 or more years. After 5 years, follow-up data were obtained by telephone from patients or family practitioner. Recurrence of disease was diagnosed at the outpatient clinic. Recurrent disease was classified as locoregional or distant. Whenever a relapse was suspected, radiologic, endoscopic, or histologic confirmation was compulsory. Relapse-free survival was characterized as the main end point of the study, and the secondary end point was overall survival.

Statistical Analysis

On the basis of the results of Medical Research Council (MRC) Oesophageal Cancer Working Party,[23] we estimated that 5-year survival after preoperative chemotherapy and surgery would be 20%. The trial was designed to detect an absolute increase in the survival of 15% in the perioperative chemotherapy group, with a two-sided α level of 5% and a statistical power of 80%, given the enrollment of 350 patients over a period of 3 years and approximately 170 deaths. Relapse-free survival was calculated from randomization to the first event (i.e., local recurrence, distant recurrence, or death from any cause), and overall survival was calculated from randomization to death from any causes. Data on patients who were event free were censored on the date the patient was last seen. Kaplan–Meier curves for relapse-free and overall survival were compared with the log-rank test on the intention-to-treat basis. Hazard ratios were calculated with a Cox regression model including treatment alone (primary analysis) and after adjustment for baseline stratification factors by the software RevMan 5.0 Cochrane Collaboration. Categorical data were compared with chi-square test with a test for trend over ordered categories (e.g., T stage). All tests were two sided and unadjusted for multiple comparisons. The trial was overseen by an independent data monitoring committee that met five times (approximately annually) to review accrual, safety, and efficacy data. The committee recommended continuation at each review.

RESULTS

Characteristics of Patients

Between January 2005 and April 2007, of 358 patients enrolled into the clinical trial, 346 were eligible and randomly assigned to two arms, 175 to perioperative chemotherapy group (arm A) and 171 to preoperative chemotherapy group (arm B). The mean time between randomization and preoperative chemotherapy was 1.5 weeks for both arms. Table 1 showed that two arms were similar in terms of age, sex, body weight, and WHO performance status. Accordingly, the distributions of site and maximum diameter of squamous cell carcinoma of esophagus were also well matched (Table 1) with no significant differences among the two arms.

TABLE 1. Demographic and Clinical Characteristics of the Patients

Characteristics[a]	Arm A (n = 175)	Arm B (n = 171)
Age (yr), *n* (%)		
<60	88 (50.3)	86 (50.2)
60–69	56 (32.0)	53 (31.0)
≥70	31 (17.7)	32 (18.8)
Median	59	59
Range	26–89	23–90
Sex, *n* (%)		
Male	152 (86.8)	145 (84.8)
Female	23 (13.2)	26 (15.2)
WHO performance status, *n* (%)		
0	126 (72.0)	121 (70.8)
1	49 (28.0)	50 (29.2)
Loss of ≥10% body weight, *n* (%)		
≥10%	20 (11.4)	18 (10.5)
<10%	155 (88.6)	153 (89.5)
Tumor site, *n* (%)		
Upper third of esophagus	37 (21.1)	36 (21.0)
Middle third of esophagus	52 (29.7)	50 (29.2)
Lower third of esophagus	84 (48.0)	83 (48.5)
Gastroesophageal junction	2 (1.2)	2 (1.3)
Maximum tumor diameter (cm), *n* (%)		
0.0–3.9	54 (30.9)	57 (33.3)
4.0–7.9	86 (49.1)	82 (48.0)
8.0–11.9	31 (17.7)	23 (13.4)
≥12	4 (2.3)	9 (5.3)
Median	5.5	5.5
Interquartile range	3.0–7.0	3.0–7.0

[a]There were no significant differences between groups.
WHO, World Health Organization.

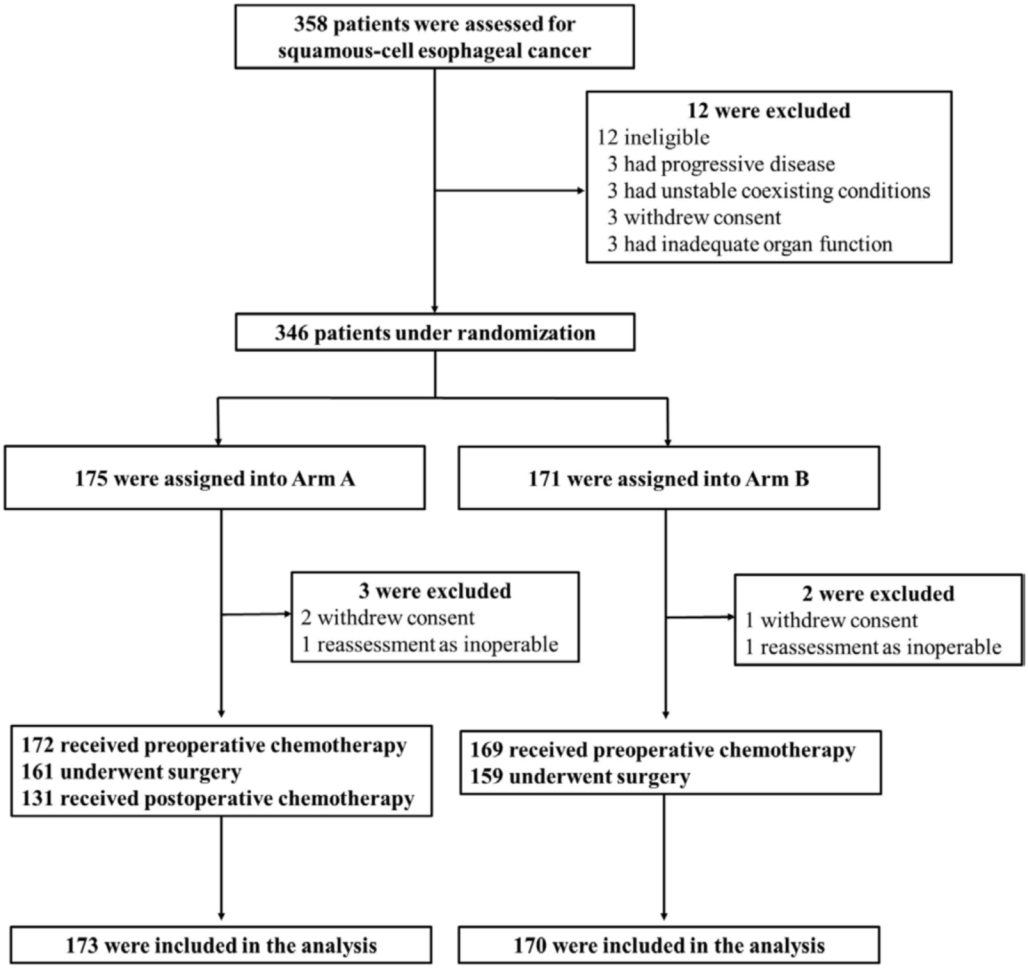

FIGURE 1. CONSORT flow diagram.

Chemotherapy

The CONSORT flow diagram has been displayed in Figure 1. Preoperative chemotherapy details for 346 eligible patients were available in both arms, 175 in arm A and 171 in arm B. In arm A, three patients did not initiate chemotherapy for the following reasons: patient request (two patients) and reassessment as inoperable (one patient). Two patients in arm B did not implement chemotherapy for the following reasons: patient request (one patient) and reassessment as inoperable (one patient). Of 341 who started preoperative treatment (98.5% of patients who were eligible under randomization), 310 (157 in arm A and 153 in arm B) accomplished two preoperative chemotherapy cycles. With regard to not completing two preoperative cycles, the reasons were as follows: toxic effects (19 patients: 9 in arm A and 10 in arm B), patient request (6 patients: 3 in arm A and 3 in arm B), disease progression (3 patients: 1 in arm A and 2 in arm B), early cancer-related death (2 patients: 1 in arm A and 1 in arm B), and detail missing (1 patient in arm A only).

A total of 310 patients (89.7% or 89.5% of patients who were assigned to arm A or arm B, respectively, and 91.3% or 90.5% of those who started chemotherapy in arm A or arm B, respectively) completed two cycles of preoperative chemotherapy, of whom 302 patients (153 in arm A and 149 in arm B) proceeded to surgery. Of 153 patients who proceeded to surgery in arm A, 131 subsequently started postoperative chemotherapy and 121 ultimately completed two postoperative chemotherapy cycles. Reasons for not proceeding to postoperative chemotherapy were disease progression (five patients), unplanned early death (two patients), patient request (five patients), postoperative complications/deaths (seven patients), and worsening coexisting disease (three patients).

One hundred twenty-one (69.1%) of 175 patients in arm A completed all four cycles of chemotherapy, and 121 (92.4%) of 131 patients who underwent two preoperative chemotherapy cycles and surgery completed postoperative treatment. One hundred six (31.8%) of 333 treated patients experienced at least grade 3/4 toxicity under preoperative chemotherapy. The most common grade 3/4 toxicities were granulocytopenia (13.2%) and lymphocytopenia (20.1%), respectively. After surgery, there was no significant increase in the incidence of grade 3 or 4 toxic effects associated with the addition of postoperative chemotherapy (Table 2).

TABLE 2. Adverse Effects Associated with Preoperative and Postoperative Chemotherapy

Adverse Effects[a]	Preoperative (n = 333[b]), n (%)	Postoperative (n = 127), n (%)
Hematologic		
Granulocytopenia		
Grade 0, 1, or 2	289 (86.8)	109 (85.8)
Grade 3 or 4	44 (13.2)	18 (14.2)
Lymphocytopenia		
Grade 0, 1, or 2	266 (79.9)	105 (82.7)
Grade 3 or 4	67 (20.1)	22 (17.3)
Leukopenia		
Grade 0, 1, or 2	294 (88.3)	112 (88.2)
Grade 3 or 4	39 (11.7)	15 (11.8)
Thrombocytopenia		
Grade 0, 1, or 2	330 (99.1)	126 (99.2)
Grade 3 or 4	3 (0.9)	1 (0.8)
Hemoglobinopathy		
Grade 0, 1, or 2	316 (94.9)	121 (95.3)
Grade 3 or 4	17 (5.1)	6 (4.7)
Other hematologic abnormality		
Grade 0, 1, or 2	330 (99.1)	125 (98.4)
Grade 3 or 4	3 (0.9)	2 (1.6)
Nonhematologic		
Nausea		
Grade 0, 1, or 2	310 (93.1)	117 (92.1)
Grade 3 or 4	23 (6.9)	10 (7.9)
Vomiting		
Grade 0, 1, or 2	313 (94.0)	117 (92.1)
Grade 3 or 4	20 (6.0)	10 (7.9)
Neurologic effects		
Grade 0, 1, or 2	319 (95.8)	122 (96.1)
Grade 3 or 4	14 (4.2)	5 (3.9)
Skin effects		
Grade 0, 1, or 2	320 (96.1)	122 (96.1)
Grade 3 or 4	13 (3.9)	5 (3.9)
Stomatitis		
Grade 0, 1, or 2	318 (95.5)	123 (96.8)
Grade 3 or 4	15 (4.5)	4 (3.2)
Diarrhea		
Grade 0, 1, or 2	323 (97.0)	121 (95.3)
Grade 3 or 4	10 (3.0)	6 (4.7)

[a]There were no significant difference between groups.
[b]Three hundred thirty-three patients were consisted of 168 from arm A and 165 from arm B.

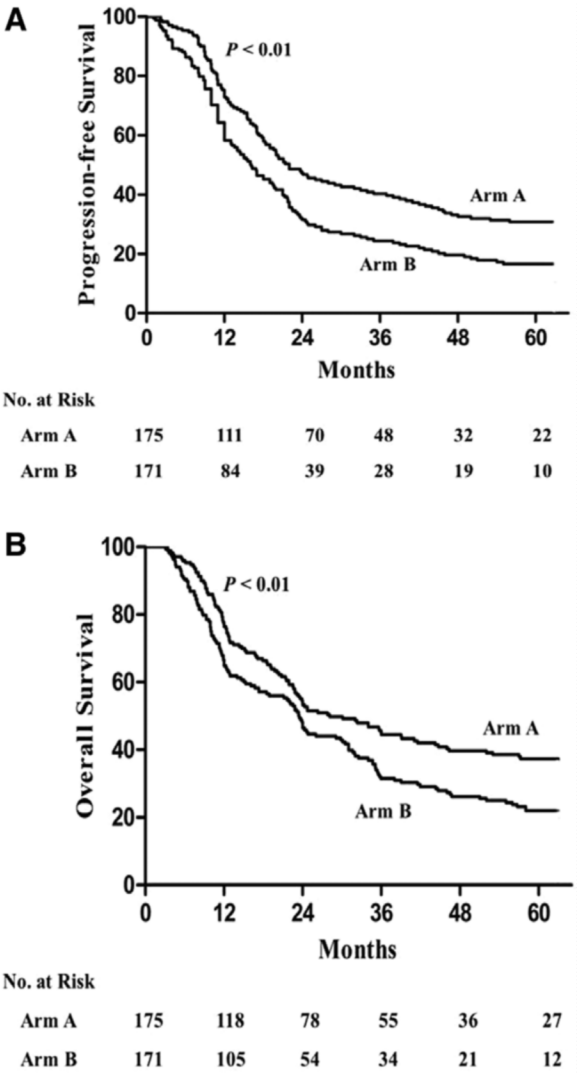

FIGURE 2. Kaplan–Meier estimates of relapse-free survival (*A*) and overall survival (*B*).

Surgery and Pathologic Findings

One hundred sixty-one patients (92.0%) underwent surgery in arm A, including eight patients who did not complete two cycles of preoperative chemotherapy, with a median time from randomization to surgery of 62 days. In parallel, 159 patients (93.0%) underwent surgery in arm B, including 10 patients who did not complete two cycles of preoperative chemotherapy, with a median time from randomization to surgery of 61 days. In Table 3, resections were curative in 264 (82.5%) of 320 patients undergoing esophagectomy. In terms of postoperative pathologic tumor, node, metastasis stage, there was a greater proportion of stage III tumors than other stages ($p < 0.05$ by the chi-square test for trend). Surgical approaches, the incidence of postoperative complications, and the median hospital stay were similar in the two arms (Table 3), as were the number of deaths within 30 days after operations (two patients [1.2%] and three patients [1.9%], respectively, Table 3). Preoperative chemotherapy had the potential benefits of increasing the likelihood of curative resection. Intriguingly, the pCR was achieved in 77 of 320 patients (24.1%) who underwent resection after chemotherapy (Table 3).

Relapse-Free and Overall Survival

The median follow-up was 60 and 61 months in arm A and arm B, respectively. Before deaths, local recurrence was confirmed in 25 patients (14.2%) in arm A and 35 patients

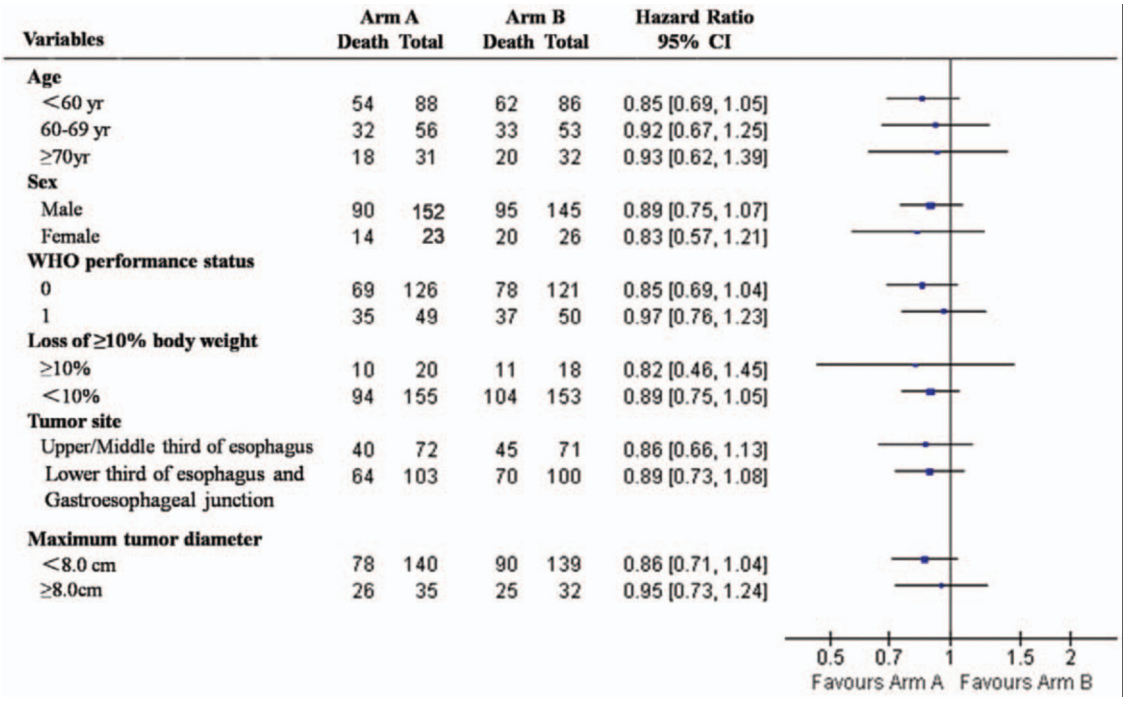

FIGURE 3. Heterogeneity of treatment effects according to the subgroup analysis. CI, confidence interval.

(20.5%) in arm B, and distant metastasis was confirmed in 41 patients (23.4%) in arm A and 62 patients (36.3%) in arm B. The median relapse-free survival and overall survival were 23 and 29 months in arm A versus 15 and 22 months in arm B. Comparing with arm B, arm A had the significantly higher possibility of relapse-free survival (hazard ratio for relapse, 0.62; 95% confidence interval [CI], 0.49–0.73; $p < 0.001$, Fig. 2*A*) and of overall survival (hazard ratio for death, 0.79; 95% CI, 0.59–0.95; $p < 0.001$, Fig. 2*B*). Five-year relapse-free survival rate was 35.0% (95% CI, 26.1–47.2) in arm A compared with 19.1% (95% CI, 15.3–28.7) in arm B. Five-year survival rate was 38.0% (95% CI, 29.5–43.0) in arm A compared with 22.0% (95% CI, 16.6–29.4) in arm B. There was no clear evidence of heterogeneity of treatment effect in terms of the site and maximum diameter of the primary tumor, age, sex, body weight, or WHO performance status (Fig. 3).

DISCUSSION

The recent meta-analysis of the published clinical trials demonstrated no benefit from neoadjuvant chemotherapy for resectable squamous cell carcinoma of esophagus despite a greater benefit for neoadjuvant chemoradiation.[16,17,24] Intriguingly, the largest and latest randomized, controlled trial from UK MRC in the meta-analysis showed that preoperative chemotherapy significantly improved survival in resectable squamous cell carcinoma of esophagus,[7,23] which was supported by a recent randomized, controlled clinical trial of the patients with the squamous cell carcinoma only.[25] There are no clear data to support the survival benefit for adjuvant chemotherapy in the resected squamous cell carcinoma.[8] JCOG 9204 reported that adjuvant chemotherapy significantly improved 5-year disease-free survival up to 55% in patients with lymph node–positive squamous cell carcinoma of esophagus compared with 45% of surgery alone,[8] following a series of clinical trials including JCOG 8806 and JCOG 8807.[26,27] A trend toward improved survival from adjuvant chemotherapy was found in lymph node–positive patients.[9] Given the aforementioned data, perioperative chemotherapy appeared attractive research option for patients with squamous cell carcinoma of the esophagus.

In this randomized phase III trial, patients with resectable squamous cell carcinoma of esophagus, well matched in the terms of clinical characteristics and surgical outcomes, were randomly assigned to receive perioperative or preoperative chemotherapy plus surgery. A significant survival benefit for group receiving perioperative chemotherapy plus surgery had been demonstrated compared with group receiving preoperative chemotherapy plus surgery based on the regimen of PCF. An estimated improvement of 16% in 5-year survival rate was raised corresponding to 28% reduction in the risk of death. Perioperative chemotherapy was proved as efficient to improve relapse-free survival by approximately 16% compared with preoperative chemotherapy alone in the squamous cell carcinoma of esophagus. Because this trial unequivocally implemented the comparison of perioperative versus preoperative chemotherapy, it was reasonable that a statistically significant benefit from the addition of postoperative chemotherapy was associated with the reduced risk of death and progression delay in operable squamous cell carcinoma of esophagus. Our results did a good supplement for the previous reports in the MAGIC[12] and FNCLCC/FFCD trials,[11] which evaluated the impact of perioperative chemotherapy compared with surgery alone in the adenocarcinoma of esophagus. We reported a similar benefit of

5-year overall survival to the MAGIC and FNCLCC/FFCD trials. It suggested that perioperative chemotherapy might be considered as a standard care in both adenocarcinoma and squamous cell carcinoma of esophagus. Intriguingly, INT 0113/RTOG 8911 with 467 patients (53% adenocarcinoma and 47% squamous cell carcinoma) randomized to surgery alone or perioperative chemotherapy plus chemotherapy displayed no difference in overall survival.[14,15] INT 113/RTOG 8911 was initiated two decades ago when the methods for diagnosis, staging, treatment delivery, and trial design issues (effect-size justification, statistical power, sample size, and study duration) that are now mainstream in study planning were not rigorously applied during this time. The divergence from INT 113/RTOG 8911 might result from the trial design, especially for the assignment of postoperative chemotherapy or radiotherapy. A second possible explanation for the negative results of INT 113/RTOG 8911 was that the regimen of chemotherapy was unable to destroy the residual regional and micrometastatic tumors with inadequate amount of cisplatin and fluorouracil owing to the lower rate of curative R0 resection (63% perioperative chemotherapy versus 59% surgery alone) than that in our trial (82%). In most cases of INT 113/RTOG 8911, for patients undergoing an R1 or R2 resection and a portion of patients with R0 resection, chemotherapy was given concurrently with radiation after surgery, so concurrent postoperative chemoradiotherapy in patients receiving the surgery alone might offset the advantage of perioperative chemotherapy. In our trial, concurrent chemoradiotherapy was not recommended for patients with an R1 or R2 resection.

The true potential of chemotherapy might be underestimated in patients with esophageal cancer.[28] Greater survival benefits may be achieved by using more effective drugs combinations.[28–30] Paclitaxel represents a promising new agent with remarkable antineoplastic activity against various human cancers.[31] The activity in esophageal cancer has been described in the squamous cell carcinoma with the concerns of the increased toxicities.[32–34] According to our outcomes, added postoperative PCF chemotherapy did not result in the increased incidence of adverse effects of grade 3/4 associated with chemotherapy, which was relatively lower than previous reports because of dose attenuation.[18] Furthermore, comparing with INT 113/RTOG 8911 (38%), more patients (69.1%) with curable esophageal cancer received a complete postoperative chemotherapy in our trial. It reflected that perioperative PCF was acceptable and feasible in patients with the squamous cell carcinoma of esophagus.

Association between pCR and survival benefit has been confirmed tightly.[35,36] Higher pCR rate could be achieved by using more effective drugs combinations.[28–30] In our clinical trial, a pCR rate was achieved in 77 of 320 patients (24.1%) who underwent resection after two cycles of preoperative PCF. It was partially reasoned that the addition of paclitaxel into the traditional regimen of chemotherapy, cisplatin and fluorouracil, had an improvement of pCR with increased well-tolerated toxicities. The another possibility that the greater portion of clinical early-stage diseases were involved in our trial contribute to an intriguingly high pCR rate. Chemotherapy sensitivity, PCF regimen, remains elusive in the resectable squamous cell carcinoma of esophagus. The genome profiling may do a favor for us to explore the sensitivity of chemotherapy agents in the future. In context, neoadjuvant chemoradiotherapy presents a superiority for pCR with the potential limitations of perioperative mortality/morbidity and toxic effects.[37,38] Coupled with paclitaxel's radiosensitizing, paclitaxel is an ideal agent in chemoradiotherapy. CROSS group released that preoperative chemoradiotherapy consisting of carboplatin/paclitaxel and concurrent radiotherapy improved survival with acceptable adverse effect and in-hospital mortality among patients with resectable squamous cell carcinoma of esophagus.[39,40] A remarkable pCR rate of 29% was achieved in patients who underwent resection after chemoradiotherapy, especially for 45% with squamous cell carcinoma. Presumably, preoperative paclitaxel-based chemotherapy might produce the further improvement in survival and complete response rate with the addition of radiation in our clinical trial. We believe that further improvements in management of squamous cell carcinoma of the esophagus may be achieved through individualization of cytotoxic and targeted agents within combined modality approach.

There are some limitations that need to be acknowledged regarding the present trial. The possible limitation of our trial was that fewer than 70% of patients in arm A completed all protocol treatment, not completing all protocol treatment predominantly owing to early disease relapse, patient request, or postoperative complications. Early disease relapse reflected the malignant biological characteristics of esophageal cancer. Another possible limitation was selection bias because of the recruitment of eligible patients. The patients enrolled into our trial mainly came from four provinces, including Shaanxi, Shanxi, Gansu, and Qinghai, all of which locate in the northwest of China with relatively lower socioeconomic and wealthy status in China. Therefore, this trial is unable to reflect the epidemiological pattern of squamous cell carcinoma of esophagus. Finally, pretreatment staging was not reported in the trial, because EUS was not available at the time of trial in our hospital, which may be a major limitation for preoperative evaluation.

In conclusion, our results showed that perioperative chemotherapy with the regimen of PCF improved 5-year relapse-free and overall survival in patients with resectable squamous cell carcinoma of esophagus compared with preoperative chemotherapy alone. Therefore, this treatment should be considered as an option for patients with resectable squamous cell carcinoma of esophagus.

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