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Neoadjuvant chemotherapy with liposomal paclitaxel plus platinum for locally advanced esophageal squamous cell cancer: Results from a retrospective study

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Abstract

Background: This study analyzed the efficacy and safety of neoadjuvant chemotherapy with liposomal paclitaxel plus platinum in patients with locally advanced resectable esophageal squamous cell carcinoma (ESCC).

Methods: The data of patients with locally advanced resectable ESCC (staging cT2N + M0, cT3-4aNanyM0, IA-IVA) who received preoperative chemotherapy with liposomal paclitaxel plus platinum (cisplatin, nedaplatin or carboplatin) in HuanXing Cancer Hospital from July 2018 to October 2019 were collected. The primary endpoint of this study was R0 resection rate, and secondary endpoints were pathological complete response (pCR) rate, 1- and 2-year overall survival (OS) rate, 1-year and 18-month disease-free survival (DFS) rate, and safety.

Results: A total of 32 eligible patients were included in this study. All patients received neoadjuvant chemotherapy and surgery. The R0 resection rate was 93.8%, the pCR rate was 12.5%, and down-staging was achieved in 14 patients (47.8%). Median follow-up was 31.0 months (95% confidence interval [CI] 30.1–31.9 months). The 1- and 2-year OS rates were 96.9% and 78.1%, and the 1-year and 18-month DFS rates were 86.7% and 76.7%, respectively. The median DFS and OS were not reached. The incidence rate of neoadjuvant chemotherapy related grade 3–4 adverse events was 21.9%, including neutropenia (21.9%) and leukopenia (9.4%).

Conclusions: The results of this study suggest that liposomal paclitaxel combined with platinum as neoadjuvant chemotherapy can provide satisfactory R0 resection rate and survival rate, and significant tumor down-staging effect for patients with locally advanced resectable ESCC, with safety profile.

KEYWORDS
esophageal squamous cell cancer, liposomal paclitaxel, neoadjuvant chemotherapy, platinum

INTRODUCTION

Esophageal cancer is one of the most aggressive malignant tumors, ranking as the seventh most common cancer and the sixth most common cause of cancer death globally in 2018.[1] Asia represents 75% and China accounts for almost half of esophageal cancer cases worldwide.[2,3] In Asia, esophageal squamous cell carcinoma (ESCC) is the most common histological subtype.[2,3] After surgery resection alone, the 5-year overall survival (OS) rate of locally advanced esophageal cancer was only 25%.[4] It has been demonstrated that multidisciplinary treatment can significantly improve survival of patients with locally advanced esophageal cancer in contrast to surgery alone.[5]

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However, the prognosis of patients with locally advanced ESCC remains unsatisfactory.

Various studies have shown that neoadjuvant chemoradiotherapy (nCRT) combined with surgery can significantly decrease tumor size and recurrence rate, increasing the R0 resection rate and prolonging OS.[5–8] The pathological complete response (pCR) rate of nCRT ranged between 13% and 22% for esophageal adenocarcinoma, and the pCR rate was approximately 40% for ESCC.[9–12] However, concurrent chemoradiotherapy also increased adverse events (AEs). A previous study has reported that the incidences of postoperative complications such as peritreatment mortality (2.2% vs. 0.4%; $p = 0.212$) were higher in the nCRT group compared with surgery resection alone.[12] Similar results were also observed in the FFCD9901 study, where nCRT did not improve the R0 resection rate or the 3-year OS rate, but increased the postoperative mortality (11.1% vs. 3.4%, $p = 0.049$) in esophageal cancer patients compared with surgery alone.[13]

Encouragingly, neoadjuvant chemotherapy (nCT) alone has also been shown to have efficacy in increasing OS and the R0 resection rate for locally advanced esophageal cancer. In The Medical Research Council trial for oesophageal cancer (OEO2) study, preoperative chemotherapy of cisplatin plus 5-fluorouracil increased the 5-year OS rate (23% vs. 17%, $p = 0.03$) and the R0 resection rate (60% vs. 54%, $p < 0.0001$) compared with surgery alone.[14] However, the pCR rate of cisplatin plus 5-fluorouracil was unsatisfactory in esophageal cancer patients.[11,14,15] A previous study reported that neoadjuvant chemotherapy with DCF (docetaxel, cisplatin, and fluorouracil) achieved an objective response rate (ORR) of 64.3% for ESCC patients and no treatment-related deaths.[16] In addition, paclitaxel has efficacy in neoadjuvant chemotherapy for locally advanced esophageal cancer. Zhao et al.[17] reported that preoperative chemotherapy with a paclitaxel, cisplatin, and 5-fluorouracil regimen increased the pCR (24.1%) and R0 resection (82.5%) rates of patients with resectable locally ESCC, and the perioperative mortality was only 1.9%. However, paclitaxel has low water solubility and is insoluble in many solvents. Polyoxyethylene castor oil, the traditional solvent of paclitaxel, can produce many adverse reactions, including hypersensitivity, neurotoxicity, and nephrotoxicity.[18–20] As a solvent-free form of paclitaxel, liposomal paclitaxel increases the solubility of paclitaxel and reduces the incidence of adverse reactions, including allergic reactions.[21] Liposomal paclitaxel is effective in a variety of tumors, including breast cancer and esophageal cancer.[22–24] In addition, liposomal paclitaxel plus nedaplatin has been reported as a first-line chemotherapy regimen for advanced ESCC.[22]

Therefore, considering that neoadjuvant chemotherapy regimens for esophageal cancer have not been well established, we conducted a retrospective study to analyze the efficacy and safety of neoadjuvant chemotherapy with liposomal paclitaxel plus platinum in locally advanced ESCC patients treated in Beijing HuanXing Cancer Hospital.

METHODS

Study design and participants

wThis was a retrospective study, and the data of all eligible patients with locally advanced ESCC from 6 July 2018 to 20 October 2019 in Beijing Huanxing Cancer Hospital were collected retrospectively, including age, gender, tumor stage, surgical resection, Eastern Cooperative Oncology Group (ECOG) performance status (PS) before neoadjuvant chemotherapy, treatment efficacy after neoadjuvant chemotherapy, OS, disease-free survival (DFS), and AEs during chemotherapy. The inclusion criteria were (1) histologically confirmed locally advanced ESCC; (2) clinical TNM staging of cT1-2N+M0, cT3-4aNanyM0 according to the American Joint Committee on Cancer (AJCC 8th edition); (3) an ECOG score of 0–1; and (4) patients who received at least one cycle of neoadjuvant chemotherapy with liposomal paclitaxel plus platinum. The exclusion criteria were (1) nonsquamous cell carcinoma confirmed by histology; (2) cervical esophageal cancer; (3) has received chemotherapy or radiotherapy for esophageal lesions; (4) distant metastatic (M1) diseases; and (5) other malignancies within the past 5 years, while radically treated cutaneous squamous or basal cell carcinoma and cervical carcinoma in situ were excluded.

Chemotherapeutic regimen

All patients were treated with a liposomal paclitaxel plus platinum regimen as neoadjuvant chemotherapy (triweekly or biweekly regimen). The choice of liposomal paclitaxel plus platinum regimen was determined by clinicians. Liposomal paclitaxel was administered at dose of 150 mg/m^2 (biweekly) or 175 mg/m^2 (triweekly) intravenously on day 1; both cisplatin and nedaplatin were administered at dose of 50 mg/m^2 (biweekly) or 75 mg/m^2 (triweekly). The dose of carboplatin was calculated as area under the curve (AUC) = 4 (triweekly). Radical esophagectomy was performed within 4–6 weeks after the last dose of neoadjuvant chemotherapy. Postoperative radiotherapy was permitted and decided by the radiation therapist.

Evaluation of disease

During and after neoadjuvant chemotherapy, the antitumor efficacy was evaluated by cervical, thoracic, and abdominal plain or enhanced computed tomography (CT) every 6 weeks. Surgical treatment was performed after two to four cycles of chemotherapy, and radical esophagectomy was performed 4–6 weeks after the last dose of neoadjuvant chemotherapy. Clinical and pathological staging was performed according to AJCC TNM staging criteria, 8th edition.

Toxicity evaluation

All AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Blood biochemistry and standard complete blood count results of patients before each cycle of neoadjuvant chemotherapy were collected. The AEs were monitored throughout the study treatment.

Follow-up

Cervical, chest, and abdominal CT (plain or enhanced) was performed every 3–6 months in the 1–2 years after surgery, and every 6 months in the 3–5 years. All patients were followed up to 21 October 2021. Disease recurrence was defined as local recurrence (esophageal or anastomotic site or regional lymph node) or distant metastasis (nonregional lymph node or distant organ). Physical examination, and chest and abdominal CT were completed each time.

Endpoints and statistical analysis

The primary endpoint of the study was radical resection rate (R0 resection rate). An R0 resection was defined as complete tumor excision with all margins histologically free of tumor, R1 resection as macroscopically complete with microscopically positive margins, and R2 resection as macroscopically incomplete excision. The secondary endpoints were pCR rate, 1-year and 2-year OS rates, 1-year and 18-month DFS rates, and safety. The pCR was defined as no residual tumor cells found in the surgical specimens of primary esophageal lesions and drainage lymph nodes. Patients with residual high-grade dysplasia/carcinoma in situ without invasive carcinoma were also included in pCR. OS was defined as the time period between the start of the neoadjuvant chemotherapy and death of any cause, censored for patients alive at data cut-off. DFS was defined as the time period between surgical treatment and the first documented disease recurrence or death of any cause, with censoring for patients alive and progression-free at data cut-off.

The safety analysis was assessed in all patients who received at least one dose of liposomal paclitaxel or platinum. The Kaplan–Meier method was used to estimate time-to-event variables. The differences in rate were compared using Fisher's exact test. We used SPSS (version 22) for statistical analyses.

RESULTS

Patient characteristics

A total of 32 patients with resectable locally advanced ESCC treated in Beijing Huanxing Cancer Hospital between 6 July 2018 and 20 October 2019 were included in this study.

TABLE 1 Baseline characteristics of patients ($n = 32$)

Characteristics	Number of patients (cases [%])
Age, year (median [range])	62.5 (48–71)
<60	7 (21.9)
≥60	25 (78.1)
Gender	
Male	26 (81.3)
Female	6 (18.7)
ECOG PS score	
0	22 (68.8)
1	10 (31.2)
Histologic grade	
G1	0 (0.0)
G2	21 (65.6)
G3	9 (28.1)
Unknown	2 (6.3)
Clinical T stage	
T2	4 (12.5)
T3	21 (65.6)
T4a	7 (21.9)
Clinical N stage	
N0	10 (31.2)
N1	18 (56.3)
N2	4 (12.5)
N3	0 (0.0)
cTNM staging	
II	10 (31.3)
III	15 (46.9)
IVA	7 (21.9)
Neoadjuvant chemotherapy regimen	
Liposomal paclitaxel plus cisplatin	5 (15.6)
Liposomal paclitaxel plus nedaplatin	26 (81.3)
Biweekly	18 (56.3)
Triweekly	8 (25.0)
Both liposomal paclitaxel plus carboplatin and liposomal paclitaxel plus nedaplatin	1 (3.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

The baseline characteristics of the patients are summarized in Table 1. All patients underwent pathological biopsies before treatment, and all were noncervical ESCC patients. The median age was 62.5 years (range 48–71 years) and 26 of the patients (81.3%) were male (Table 1). Twenty-six patients (65.6%) belonged to T3, T4a accounted for 21.9% (7/32), and 22 patients (68.8%) had lymph node metastasis. There were 21 (65.6%) and nine (28.1%) patients with G2 and G3 histological grade, respectively, and two (6.3%) patients with unknown histological grades. The numbers of patients with stage II, III and IVA disease were 10 (31.3%), 15 (46.9%), and seven (21.9%), respectively. All 32 patients

were followed up after surgery, with a median follow-up time of 31.0 months (95% CI 30.1–31.9 months) as of the data cut-off date (21 October 2021).

Treatment compliance

Among the 32 patients, five patients received triweekly liposomal paclitaxel combined with cisplatin regimen. Twenty-six patients received liposomal paclitaxel plus nedaplatin treatment, of which 18 cases received a biweekly regimen and eight patients received a triweekly regimen. In addition, one patient received triweekly liposomal paclitaxel combined with carboplatin (AUC = 4) for one cycle followed by two cycles of triweekly liposomal paclitaxel plus nedaplatin for personal reasons. The chemotherapy regimen and dose for all patients were determined by clinicians.

The median number of neoadjuvant chemotherapy cycles in patients with cisplatin plus liposomal paclitaxel was two (range two to four). For patients who received liposomal paclitaxel plus nedaplatin, the median number of preoperative treatment cycles for the biweekly and triweekly regimens were three (range two to five) and two (range one to three), respectively. The median duration from last dose of neoadjuvant chemotherapy to surgical treatment was 4.8 weeks (range 2.1–10 weeks) and 32 patients underwent surgical resection. Fifteen patients received postoperative adjuvant chemotherapy, of which 14 patients received the same regimen as neoadjuvant chemotherapy and one patient received capecitabine. Four patients received local adjuvant radiotherapy after surgery (two patients with R2 resection, one case with ypT3N0 disease, and one with ypT3N1 disease).

Efficacy outcomes

None of the patients had progression disease after neoadjuvant chemotherapy. Twenty-four patients achieved various degrees of tumor shrinking after neoadjuvant chemotherapy. All 32 patients received surgical treatment and the R0 resection rate was 93.8% (30/32). Two patients received R2 resection (hilar splenic lymph node metastasis in one case, and close relationship between primary tumor and thoracic aorta in one case), then received local radiotherapy. In addition, pCR was achieved in four of 32 patients (12.5%). The downstaging rate was 43.8% (14/32), five patients were reduced to stage I (ypT0–2N0M0), 15 patients (46.9%) were N0 stage,

TABLE 2 Efficacy outcomes of post-surgery with neoadjuvant chemotherapy regimen ($N = 32$)

	Number of patients (cases [%])
R0 resection rate	2/32 (93.8)
pCR rate	4/32 (12.5)
Downstaging rate	14/32 (47.8)
Pathological stage	
pCR (ypT0N0)	4/32 (12.5)
Stage I (ypT1-2 N0)	5/32 (15.6)
Stage II (ypT3N0)	5/32 (15.6)
Stage IIIA (ypT0-2 N1)	4/32 (12.5)
Stage IIIB (ypT3N1/T0-3N2/T4a N0)	9/32 (28.1)
IVA (ypT3N3/T4aN1–2)	4/32 (12.5)
IVB (ypTanyNanyM1)	1/32 (3.1)
ypT stage	
T0	5/32 (15.6)
T1	4/32 (12.5)
T2	5/32 (15.6)
T3	15/32 (46.9)
T4	3/32 (9.4)
ypN stage	
N0	15 /32 (46.9)
N1	11/32 (34.4)
N2	3/32 (9.4)
N3	3/32 (9.4)
Post-surgical morbidities anastomotic leak	2/32 (6.3)

Abbreviation: pCR, partial complete response.

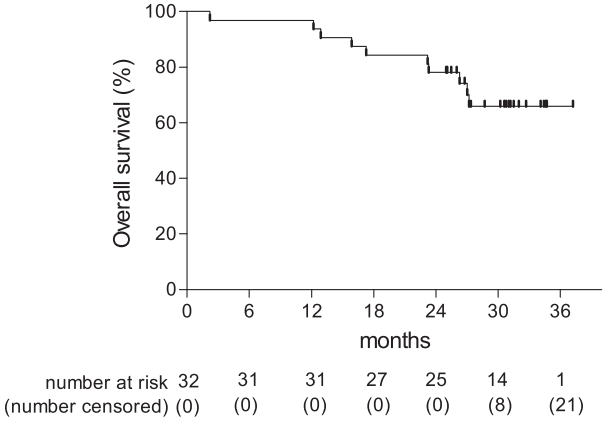

FIGURE 1 The OS rates at 1 and 2 years

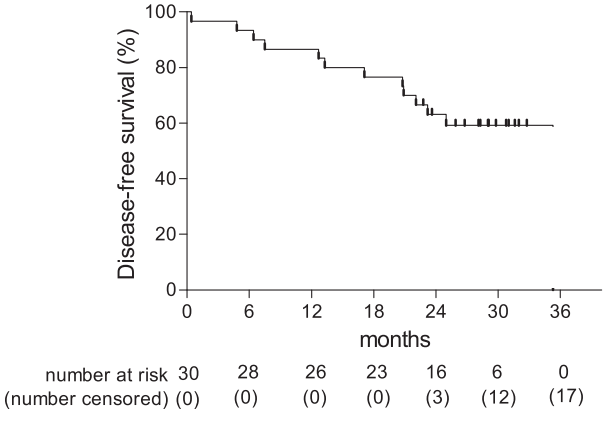

FIGURE 2 The DFS rates at 1 year and 18 months

TABLE 3 Treatment-related adverse events (TRAEs)

Events	Total	Number of patients (cases [%])			
		Grade 1	Grade 2	Grade 3	Grade 4
Nausea	24 (75.0)	23 (71.9)	1 (3.1)	0 (0.0)	0 (0.0)
Vomiting	9 (28.1)	9 (28.1)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy	4 (12.5)	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	2 (6.3)	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)
Leukopenia	19 (59.4)	10 (31.3)	6 (18.8)	3 (9.4)	0 (0.0)
Neutropenia	19 (59.4)	6 (18.8)	6 (18.8)	6 (18.8)	1 (3.1)
Thrombocytopenia	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)

Note: TRAEs observed in patients; there were no grade 5 TRAEs.

and 17 patients were lymph node metastasis (11 patients were N1, three patients were N2, three patients were N3) (Table 2).

By 21 October 2021, the median follow-up time was 31.0 months (95% CI 30.1–31.9 months) in our study, 10 (31.2%) patients had died, and 22 (68.8%) patients were still alive. In addition, of the surviving patients, 17 were without disease relapse. The OS rates at 1 and 2 years were 96.9% and 78.1% (Figure 1), and the DFS rates at 1 year and 18 months were 86.7% and 76.7%, respectively (Figure 2). The median DFS and OS were not reached.

Safety outcomes

Safety analyses were based on the total 32 patients (Table 3). Treatment-related AEs, as determined by the investigators, occurred in 30 patients (93.8%). The most common chemotherapy-related AEs occurring during neoadjuvant chemotherapy were nausea, leukopenia, and neutropenia, most of which were grade 1–2. The incidence rate of neoadjuvant chemotherapy related grade 3–4 AEs was 21.9%, including neutropenia (21.9%) and leukopenia (9.7%). Only one (3.1%) patient had grade 4 neutropenia. AEs led to dose reductions of chemotherapy in two patients (one case of grade 3 neutropenia and one case of treatment-unrelated grade 1 edema face and edema limbs). One patient refused to continue chemotherapy due to treatment-unrelated grade 3 pneumonia after the first cycle of preoperative chemotherapy. All AEs were managed with proper medical care and did not result in suspension of the chemotherapy.

No neoadjuvant chemotherapy-related deaths occurred. Significant surgery-related complications after surgery occurred in two patients, both of whom were anastomotic fistula (2/32, 6.3%). One patient was still disease-free until the data cut-off date.

DISCUSSION

In the present study, we explored liposomal paclitaxel plus platinum as neoadjuvant chemotherapy for locally advanced resectable ESCC patients. Our study including 46.9% (15/32) stage III and 21.9% (7/32) stage IVA patients. The rates of R0 resection and pCR were 93.8% and 12.5%, respectively. The rates of DFS and OS were also encouraging, the 1- and 2-year OS rates were 96.9% and 78.1%, and the 1-year and 18-month DFS rates were 86.7% and 76.7%, respectively. The toxicity profile was tolerable.

To our knowledge, some studies have shown that neoadjuvant chemotherapy or concurrent chemoradiotherapy improved prognosis of locally advanced esophageal cancer patients.[25–29] A previous study reported that preoperative chemotherapy with cisplatin plus 5-fluorouracil can improve the survival of esophageal cancer patients,[13] and an update of this study further reported a 5-year OS rate of 23% in the neoadjuvant chemotherapy group, which was higher than that in the surgery group (17.1%).[14] In addition, a meta-analysis showed that the efficacy of neoadjuvant chemotherapy was not inferior to neoadjuvant concurrent chemoradiotherapy.[5] However, the optimal neoadjuvant chemotherapy regimen for patients with resectable locally advanced ESCC has not been established. Paclitaxel plus platinum has been used in the treatment of advanced or locally advanced ESCC patients.[30,31] Liposomal paclitaxel has many advantages over conventional paclitaxel. Compared with taxol, loading in liposomes achieves a significant increase in the maximum tolerated dose of paclitaxel, greater transport of paclitaxel into tumor cells, and fewer side effects,[32,33] and liposomal paclitaxel plus platinum has been used in the treatment of advanced ESCC.[22,34] As we know, JCOG9907 included resectable stage II/III ESCC patients, and two cycles of preoperative cisplatin plus 5-fluorouracil chemotherapy significantly increased the 5-year OS rate compared with postoperative chemotherapy (55% vs. 43%, $p = 0.04$).[15] Based on these results, neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil is the current standard treatment for clinical stage II/III ESCC in Japan.

The RTOG 8911 and OEO2 studies, as well as other studies of patients with resectable esophageal cancer with preoperative chemotherapy, have shown that OS remains poor unless R0 resection is performed.[35–38] In our study the R0 resection rate reached 93.8% and the 1- and 2-year OS rates were 96.9% and 78.1%, and 1-year and 18-month DFS rates were 86.7% and 76.7%, both better those in the

INT0113 and Medical Research Council Oesophageal Cancer Working Group (MRC) studies.[14,39] In addition, the R0 resection rate (93.8% vs. 95.8%) was also comparable to that observed in a retrospective study which locally enrolled ESCC patients received preoperative chemotherapy with albumin-bound paclitaxel plus cisplatin and capecitabine, while the pCR rate (12.5% vs. 66.7%) was better than ours.[40] In the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) study, the R0 resection rate for resectable esophageal cancer patients in the chemoradiotherapy group was 92%,[6] which is similar to that reported in our study, the OS rates at 1 and 2 years were 82% and 67% in the nCRT-surgery group, as compared with 70% and 50% in the surgery group,[6] and the 1- and 2-year OS rates in the two groups were inferior to ours. In the French Francophone de Cancerologie Digestive (FFCD) 9901 study, the R0 resection rate of both the chemoradiotherapy (93.8%) and surgery (92.1%) groups was comparable to that observed in our study, while the pretreatment disease was stage I in 19.0%, IIA in 53.3%, and IIB in 27.7% of all patients,[13] suggested the stage of disease was earlier than in our study (III-IVA, 68.8%). The proportion of stage III-IVA patients in our study was also higher than that in Japan Clinical Oncology Group trial (JCOG9907) study (68.8% vs. 51%), and patients with IVA stage accounted for 21.9% in our study. The 1- and 2-year OS rates in our study were also better than those in a prospective study including ESCC patients receiving nab-paclitaxel plus cisplatin as the neoadjuvant chemotherapy regimen (1-year, 96.9% vs. 83.3%; 2-year, 78.1% vs. 63.3%),[41] while the R0 resection rate was superior to ours (93.8% vs.100%). In addition, both the R0 resection rate and the 2-year OS rate in our study were higher than that observed in the UK MRC study (33% ESCC), in which neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil increased the R0 resection rate from 54% to 60% and the 2-year OS rate from 34% to 43%.[38] Additionally, in a previous study including stage IIA-IIIC ESCC patients receiving neoadjuvant chemotherapy with nab-paclitaxel and cisplatin, the rates of R0 resection (100%) and pCR (13.3%) were slightly higher than found in our study, and the downstaging rate was also superior to that in our study (43.8% vs. 63.3%).[42] However, the rates of 1- and 2-year OS (1-year, 96.9% vs. 90.0%; 2-year, 78.1% vs. 70.0%) and DFS (1-year, 86.7% vs. 83.3%) were reduced in comparison to our study.

Additionally, previous studies have confirmed that pCR rate is associated with longer DFS and OS.[36–38] The RTOG 8911 study also showed significant improvement of DFS in patients who achieved pCR on preoperative treatment compared to non-pCR patients.[35] The pCR rate of 12.5% in our study exceeds that reported for other cisplatin-based regimens (0–7.7%).[43–45] The randomized-controlled CROSS study reported a pCR rate of 29% in the chemoradiotherapy–surgery subgroup,[6] while the DFS and OS were not better than ours. Recently, immune checkpoint combined with chemotherapy has been tried for neoadjuvant treatment of locally advanced esophageal cancer. In a retrospective study, 12 patients with locally advanced ESCC received programmed death-1 blockade camrelizumab plus nab-paclitaxel and S1, and as a result pCR rate was 30%.[46] However, in the INT0113 study, 49% of ESCC patients were enrolled and no statistical difference in OS between neoadjuvant chemotherapy and surgery alone was found.[39]

Although some researchers favored preoperative concurrent chemoradiotherapy, neoadjuvant chemotherapy appears to be safer and may reduce postoperative mortality.[13,47] In our study, the toxicity profile was also tolerable, and all patients completed at least one cycle of neoadjuvant chemotherapy; AEs led to dose reductions in two patients. The incidence rate of 3–4 neutropenia in a prospective study with nab-paclitaxel plus cisplatin as neoadjuvant chemotherapy for ESCC patients was 11.4%.[41] In a retrospective study, albumin-bound paclitaxel plus cisplatin and capecitabine resulted in more common grade 3–4 neutropenia (35.5%) and leukopenia (9.7%) than in our study.[40] In addition, the DCF regimen (docetaxel, cisplatin, and fluorouracil) can also generate increased grade 3–4 neutropenia (83%) and leukopenia (45.2%).[16] Compared with phase 2 concurrent chemoradiotherapy using paclitaxel plus cisplatin in patients with unresectable ESCC,[48] the incidence rate of grade 3–4 neutropenia was reduced (21.9% vs. 61.9%). In the CROSS study (23% ESCC),[6] postoperative anastomotic fistula occurred in 36 (22%) patients, and 10 (6%) patients died in the preoperative concurrent chemoradiotherapy group.[6] In a previous study, surgery-related mortality was increased in patients with preoperative concurrent chemorradiation versus surgery alone (10.2% vs. 3.8%).[49] In our study, there were no chemotherapy-related deaths before and after surgery, and only two patients (6.3%) had anastomotic fistula as surgical complication; one patient was still alive without disease relapse until the data cut-off date. Some studies, such as JCOG9907 and OEO2, have demonstrated the advantage of preoperative chemotherapy for locally advanced resectable esophageal cancer without increasing surgical complications or postoperative mortality,[7,14,38,50] which was consistent with our results. Therefore, our results suggest that liposomal paclitaxel plus platinum as neoadjuvant chemotherapy is safe in locally advanced ESCC patients.

To the best of our knowledge, this is the first study to report the efficacy and safety of liposomal paclitaxel combined with platinum as neoadjuvant chemotherapy in patients with locally advanced resectable ESCC. However, compared with other similar studies, the disadvantage of our study is that it is a retrospective study with a small sample size. The single-arm design is another limitation, therefore we cannot compare liposome paclitaxel plus platinum with other chemotherapy regimens. In addition, the follow-up period was short, so this study cannot provide data related to 5-year survival rate at present. Additionally, three platinum drugs were used in our study, and some patients received a triweekly regimen, while others received a biweekly regimen, which put certain limitations on our analysis of the efficacy of neoadjuvant chemotherapy.

In summary, liposomal paclitaxel plus cisplatin as neoadjuvant chemotherapy showed encouraging antitumor

activity and a favorable safety profile in locally advanced ESCC patients. It therefore seems that liposomal paclitaxel plus platinum as a neoadjuvant chemotherapy for locally advanced ESCC might be a promising alternative. However, the value of preoperative chemotherapy needs further substantiation.

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