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ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 401−407

www.jcma-online.com

Original article

Phase II study of preoperative concurrent chemoradiotherapy with oxaliplatin for locally advanced esophageal cancer

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Received August 12, 2016; accepted December 7, 2016

Abstract

Background: We investigated preoperative concurrent chemoradiotherapy (CCRT) with oxaliplatin for locally advanced, potentially operative esophageal cancer in this Phase II study.
Methods: Between October 2009 and October 2011, 35 consecutive patients with newly diagnosed esophageal cancer clinical stage T3-4, N0-1, M0 were enrolled into this study. One dose of chemotherapy with oxaliplatin (35 mg/m^2) on Day 1 and Day 2, leucovorin (200 mg/m^2) on Day 1, and 5-fluorouracil [5-FU; 2400 mg/m^2 intravenously (i.v.) administered continuously for 48 hours] on Day 1 was administered 2 weeks before preoperative CCRT. During preoperative CCRT, radiation dose of 4500 cGy in 25 fractions was administered to the clinical target volume and 5000 cGy to 5040 cGy in 25 fractions was administered to the gross tumor volume; chemotherapy is administered concomitantly with oxaliplatin (45 mg/m^2) on Day 1 of radiation therapy (R/T) every 14 days; 5-FU (400 mg/m^2 i.v. bolus for 1 hour) for 5 days on Weeks 1 and 5 of R/T. Operation was performed 4−6 weeks after preoperative CCRT. Acute toxicity profile, overall survival rate, disease-free survival rate, distant metastasis failure-free survival rate, and local recurrence rate were evaluated.
Results: Four patients withdrew from the study. The total number of patients in this analysis was 31. The resection rate was 64.5%. The pathologic complete response rate was 15%. The overall median survival was 19.3 months. The 5-year overall survival rate was 37.8%. The 5-year disease-free survival rate was 31.1%. The 5-year distant metastasis failure-free survival rate was 40.7% (50.56% for patients with operation; 27.2% for patients without operation, $p = 0.0298$). The acute toxicities were mild, and no Grade 3 or above hematologic toxicity was noted. There was only one patient with Grade 3 esophagus toxicity. Grade 3 lung toxicity occurred in only three patients.
Conclusion: Preoperative chemoradiotherapy with oxaliplatin in the treatment of locally advanced, potentially resectable esophageal cancer is feasible and safe.

Keywords: chemoradiotherapy; esophageal cancer; oxaliplatin; preoperative

1. Introduction

In Asia, the predominant histological type of esophageal cancer is squamous cell carcinoma, accounting for over 90% of all cancers of the esophagus. Most squamous cell carcinomas are located in the midportion of the esophagus, with early local invasion and regional lymph node spreading. Because the early symptoms of esophageal cancer are subtle and nonspecific, patients usually present with obvious

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2017.03.004

difficulty swallowing and body weight loss, which indicate advanced disease. Only a minority of affected patients have a tumor confined to the mucosa, requiring treatment by surgical management alone. Multidisciplinary modalities should be considered to achieve a higher local control and overall survival in the treatment of advanced esophageal cancer. From 1981 to 1999, there were over 46 nonrandomized clinical trials that analyzed over 2700 patients with advanced esophageal cancer who were treated by neoadjuvant chemoradiotherapy. Taken together, the results suggested that the overall survival and local control of advanced esophageal cancer could be improved by neoadjuvant chemoradiotherapy followed by surgery. At least two randomized clinical trials[1,2] and two meta-analyses[3,4] demonstrated the benefits of neoadjuvant chemoradiotherapy in improving the overall survival of patients with advanced esophageal cancer.

The most popular chemotherapy regimens investigated in previous studies of neoadjuvant chemoradiotherapy contained 5-fluorouracil (5-FU) and cisplatin. One of the severe side effects of cisplatin is renal function impairment. Oxaliplatin, a platinum-based chemotherapeutic agent with a 1,2-diaminocyclohexane carrier ligand, has shown *in vitro* and *in vivo* efficacy against many tumor cell lines, including some that are resistant to cisplatin and carboplatin. Oxaliplatin also lacks ototoxicity and nephrological toxicities that are caused by cisplatin. Preclinical studies have shown that oxaliplatin is a radiation-sensitizing agent and is synergistic with 5-FU.[5] Furthermore, oxaliplatin in combination with capecitabine resulted in a 35% tumor response rate and acceptable toxicities in a Phase II study when used as a first-line therapy for metastatic esophageal cancer.[6] To maximize the treatment effect without compromising the general condition of patients before surgery, we designed this Phase II study to assess the efficacy and safety of one cycle of loading chemotherapy plus preoperative concurrent chemoradiotherapy (CCRT) with oxaliplatin and 5-FU/leucovorin followed by surgery, if possible, in patients with locally advanced esophageal cancer.

2. Methods

2.1. Patient population

Between October 2009 and October 2011, 35 consecutive patients with newly diagnosed esophageal cancer were enrolled into this study. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital and informed consent was obtained from each participant. The imaging studies included positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (CT) scan, liver sonography, gastroendoscopy, and bronchoscopy. The histology of the tumors was proved by endoscopic biopsy. The inclusion criteria included Eastern Cooperative Oncology Group performance scores less than 2, age between 20 years and 75 years, American Joint Committee on Cancer stage T3-4 N0-1 M0, and histology of squamous cell carcinoma. Patients who had other histology, previous chemotherapy/radiotherapy, synchronous double cancers, or medical disease likely to require surgery were excluded from this study.

2.2. Loading chemotherapy

One dose of chemotherapy with oxaliplatin [35 mg/m^2 intravenously (i.v.) for 2 hours] on Days 1 and 2, leucovorin (200 mg/m^2 i.v. for 2 hours) on Day 1, and 5-FU (2400 mg/m^2 i.v. continuously for 48 hours) on Day 1 was administered 2 weeks before preoperative CCRT.

2.3. Radiotherapy in preoperative CCRT

Radiotherapy was administered using an intensity-modulated radiation therapy treatment plan. All patients underwent CT simulation in a supine position with their arms above their heads, and a customized vacuum bag was used for immobilization. The CT images were taken at a 5-mm thickness throughout the neck and the entire thorax for the upper and the middle thoracic tumors or the entire thorax and the abdomen for the lower thoracic tumors. The gross tumor volume (GTV), clinical target volume (CTV), planning target volume, and the organs at risk were outlined on the CT images. The GTV included the tumor mass and the enlarged lymph node found from the images of PET scan and CT scan. CTV included the tumor in the esophagus plus 5 cm superiorly and inferiorly, 1 cm radially surrounding the tumor, and possible lymph nodes spreading in the mediastinum, supraclavicular area, and retroperitoneal area, which depended on the position of the tumor in the thoracic esophagus. The total radiation dose of 4500 cGy in 25 fractions was administered to CTV and 5000 cGy to 5040 cGy in 25 fractions was administered to GTV.

2.4. Chemotherapy in preoperative CCRT

Chemotherapy was given concurrently with oxaliplatin (45 mg/m^2 i.v. for 2 hours) on Day 1 of radiation therapy (R/T) every 14 days, and 5-FU (400 mg/m^2 i.v. bolus for 1 hour) for 5 days on Weeks 1 and 5 of R/T.

2.5. Tumor response assessment before the operation

Tumor response assessments were performed 3 weeks after preoperative CCRT was completed by PET scan, and gastroendoscopy. Biopsy of the tumor lesion was performed to assess the clinical tumor response.

2.6. Surgery after preoperative CCRT

Operation was performed 4−6 weeks after preoperative CCRT if the tumor was operable. Esophagectomy was performed by video-assisted thoracoscopy through a three-phase incision with extensive two-field lymph node dissection of the mediastinum and abdomen. The stomach was mobilized to the neck via the retrosternal route, and a cervical esophageal anastomosis was performed.

2.7. Toxicity assessment

Acute toxicities such as radiation pneumonitis and hematologic toxicity (leukopenia, anemia, and thrombocytopenia) were evaluated each week during the treatment and every 2 weeks after radiotherapy for 3 months. All treatment-related toxicities were assessed according to the toxicity criteria of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), version 3, 2003.

2.8. Follow-up and evaluation

The primary end points were resection rate, pathologic complete response rate, and acute toxicity profile. The secondary end points were median survival, overall survival rate, disease-free survival rate, and local recurrence rate. The pathologic response was graded by the Mandard tumor regression grading system. Analyses of the efficacy variables were conducted using both the evaluable and intent-to-treat data sets. The primary analysis was presented using descriptive statistics, point estimates, and 95% confidence interval for the primary efficacy variable. Time to progression and overall survival were described by the same method as for the primary efficacy variable, and were evaluated by the Kaplan–Meier method.

3. Results

Four patients withdrew from the study due to elevated liver function, allergy to oxaliplatin, refusal of surgery, and refusal of chemotherapy, respectively. The total number of patients included in the final analysis was 31. The patients' characteristics are presented in Table 1. Most of the patients had Stage III disease (30/31, 96.7%). Median follow-up time was 61.2 months. The resection rate was 64.5% (20/31). Five patients were found with progressive disease (distant metastasis including brain, lung, stomach, and bone metastasis). Two patients refused to receive surgery. Three patients were found to have pneumonitis/pneumonia and one patient had elevated liver function. Those who were not fit for operation were scheduled to finish the treatment by definite chemoradiotherapy (adding two cycles of adjuvant chemotherapy). Dose and regimens of adjuvant chemotherapy were cisplatin (20 mg/m^2/d) during Days 1–4, with continuous daily oral uracil–tegafur (Ufur) every 3 weeks for two cycles in one patient and epirubicin (50 mg/m^2) on Day 1, cisplatin (60 mg/m^2) on Day 1, and 5-FU (600 mg/m^2/d) during Days 1–4 every 4 weeks for two cycles in one patient. The remaining nine patients did not receive any adjuvant chemotherapy. The pathologic complete response rate was 15% (3/20). The complete resection (R0 resection) rate was 75%. In those patients who did not receive surgery, we used PET/CT scan and gastroendoscopy to evaluate post-CCRT response. The clinical complete response rate was 18% (3/11). Other pathologic findings are presented in Table 2. The overall median survival was 19.3 months (19.95 months with operation; 19.3 months without operation). The 5-year overall survival rate was 37.8%

Table 1
Patients' characteristics ($n = 31$).

Variables	*n*	%
Age (mean)	52	
<52 y	13	41.9
≥52 y	18	58.1
Sex		
Male	31	100
Median follow-up time (mo)	61.2	
Clinical stage		
II	1	3.2
IIA	1	3.2
III	30	96.7
IIIA	20	64.5
IIIB	8	25.7
IIIC	2	6.5
Tumor grade		
1	1	3.2
2	15	48.4
3	15	48.4
Surgery		
Yes	20	64.5
No	11	35.5
Pathological response		
Complete response	3	15
Incomplete response	17	85
Resection status		
R0 (complete resection)	15	75
R1 (microscopic residual tumor)	3	15
R2 (macroscopic residual tumor)	2	10
Clinical response		
Progressive disease	6	55
Partial response	3	27
Complete response	2	18

(Fig. 1). The 5-year progression-free survival rate was 31.1% (Fig. 2). There was a significant difference in distant failure-free survival between the patients who did and did not receive surgery ($p = 0.0298$; Fig. 3). No statistical difference was found in the overall survival rate between the patients who did and did not receive the operation ($p = 0.517$; Fig. 4). The acute toxicities (Table 3) were mild, and there were no Grade 3 or above hematologic toxicities. There were no neuropathy toxicities. There was only one patient with Grade 3 esophagus toxicity. Grade 3 lung toxicity occurred in only three patients.

4. Discussion

The combination of cisplatin and 5-FU is a standard regimen of chemoradiotherapy for esophageal cancer. However, toxicities such as renal insufficiency and bone marrow suppression may lead to an adjustment of the chemotherapy dose or a delayed prescription schedule. To overcome this deadly side effect, the patient must be hydrated with a large amount of water, which will further impact cardiac function. Shinoda et al[7] designed a study to decrease cisplatin and 5-FU dose for reducing toxicity without prejudice to survival. However, the study found there were no differences in toxicities (including hematologic toxicities and esophagitis) in either arm. Furthermore, the lower-dose cisplatin and 5-FU arm did not improve survival.

Table 2
Pathologic findings ($n = 20$).

Patient No.	TRG[a]	Resection status	Margin	ALI	PNI	Lymph nodes[b]
1	G1	R0	−	−	−	1/25
2	−[c]	R2[d]	−	−	−	0/1
3	G2	R0	5 mm	−	−	0/5
4	G2	R0	<1 mm	−	−	0/18
5	G3	R1	+	−	−	0/53
6	G4	R2	+	+	−	5/8
7	−[c]	R0	2 mm	+	+	2/28
8	G3	R0	−	+	−	3/40
9	G2	R0	−	−	−	1/38
10	G5	R0	−	−	−	0/40
11	G5	R0	−	−	−	0/22
12	G3	R1	+	+	+	6/22
13	G4	R0	−	+	−	1/22
14	G3	R0	2 mm	+	−	10/27
15	G3	R0	4 mm	+	−	0/7
16	G5	R0	−	−	−	0/26
17	G4	R0	<1 mm	−	−	0/33
18	G5	R1	+	+	+	2/19
19	G1	R0	−	−	−	0/29
20	G4	R0	−	+	−	41/64

ALI = angiolymphatic invasion; PNI = perineural invasion; TRG = tumor regression grade.

[a] TRG 1 (complete regression) showed absence of residual cancer and fibrosis extending through the different layers of the esophageal wall; TRG 2 was characterized by the presence of rare residual cancer cells scattered through the fibrosis; TRG 3 was characterized by an increase in the number of residual cancer cells, but fibrosis still predominated; TRG 4 showed residual cancer outgrowing fibrosis; and TRG 5 was characterized by absence of regressive changes.

[b] *Lymph nodes:* positive metastatic lymph nodes/total resection lymph nodes.

[c] Without description in pathology report.

[d] Unresectable celiac lymph node fibrosis though negative margin.

Prior experience of preoperative chemoradiotherapy with oxaliplatin in locally advanced rectal cancer showed that the treatment was well-tolerated and achieved an excellent pathologic complete response.[8] This result demonstrated the role of oxaliplatin as a radiosensitizer. Thus, we investigated preoperative CCRT with oxaliplatin for locally advanced esophageal cancer.

To reduce the incidence of distant metastatic disease, recent trials have added additional loading doses of chemotherapy before CCRT.[9–12] One of the obstacles to adding neoadjuvant chemoradiotherapy is the introduction of systemic toxicity before surgery.

The resection rate increased to 73%, and up to 38% of the patients who had surgery achieved a pathologic complete response to the treatment.[1] The locoregional recurrence rate decreased from 29% by surgery alone to 15% by neoadjuvant chemoradiotherapy plus surgery.[13] In this study, the pathologic complete response rate was 15% (3/20) and complete resection (R0 resection) rate was 75%, showing promising results of surgery.

In our study, acute toxicities were mild, and there were no Grade 3 or above hematologic toxicities. Only one patient (3.2%) had Grade 3 esophagus toxicity and three patients (9.7%) had Grade 3 lung toxicity. Compared with studies that investigated regimens of oxaliplatin and 5-FU/leucovorin, the prevalence of Grade 3 or above hematologic toxicities ranged from 0% to 10%. Grade 3 or above gastrointestinal toxicity was noted in 25% to 43% of patients.[14–17] Burmeister et al[14] reported the best median overall survival (32.6 months), but Grade 3 or above gastrointestinal toxicity also increased to 43% compared with other studies. Thus, the study found that weekly oxaliplatin in combination with infusional 5-FU was

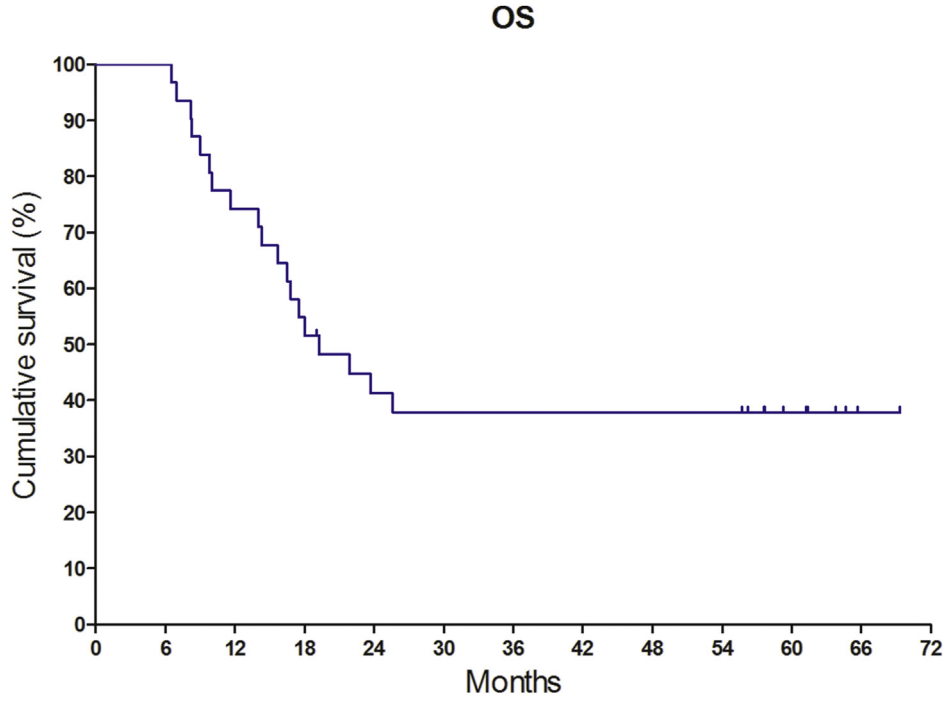

Fig. 1. Overall survival (OS) rate for all patients (5-year OS, 37.8%).

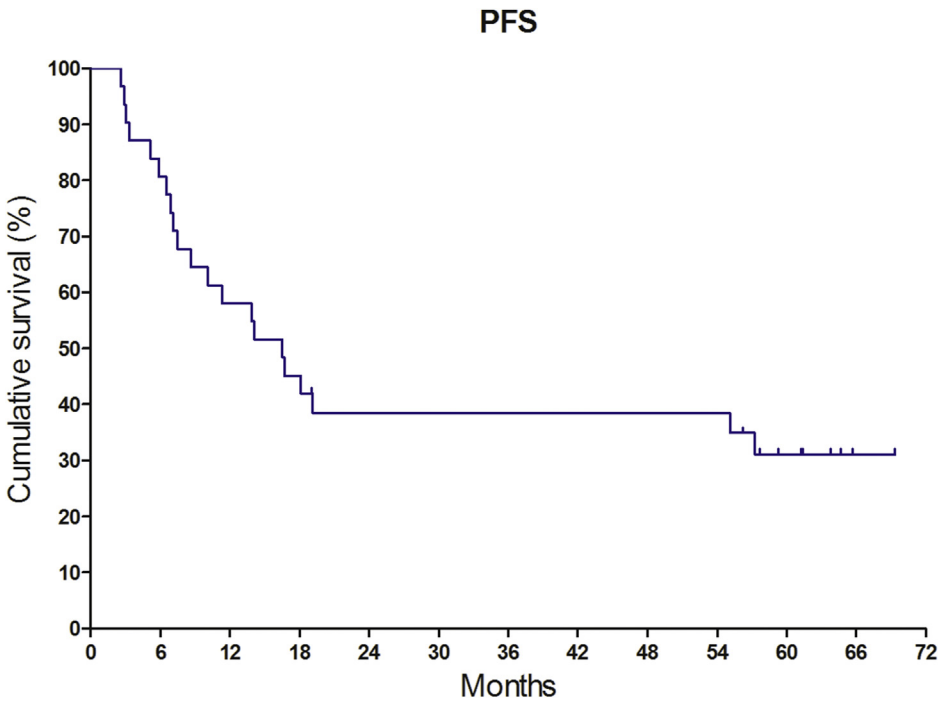

Fig. 2. Progression-free survival (PFS) rate for all patients (5-year PFS, 31.1%).

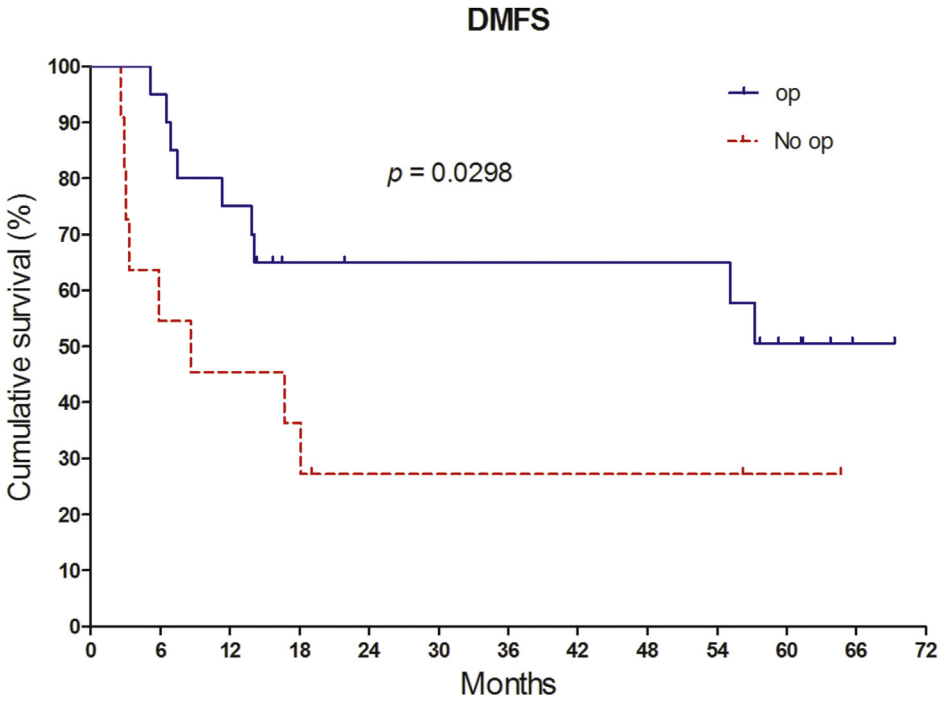

Fig. 3. Distant metastasis failure-free survival (DMFS) rate for nonoperative and operative groups (5-year DMFS of the operative group, 50.56%; 5-year DMFS of the nonoperative group, 27.2%).

not acceptable for routine use. Although oxaliplatin can be used as a radiosensitizing chemotherapy, it may increase the rate of esophagitis. After adjusting the dose and timing of oxaliplatin according to our design, gastrointestinal toxicity was lower than levels reported in the aforementioned studies. In this study, median overall survival rate, local control rate, and distant metastasis rate were not inferior to those of previous randomized trials. Comparing a meta-analysis[4] and our study, 5-year overall survival rates were 38.8% and 37.8%, respectively. In addition, during chemoradiotherapy, there was also no need to adjust the dose of chemotherapy or withhold radiotherapy due to adverse effects.

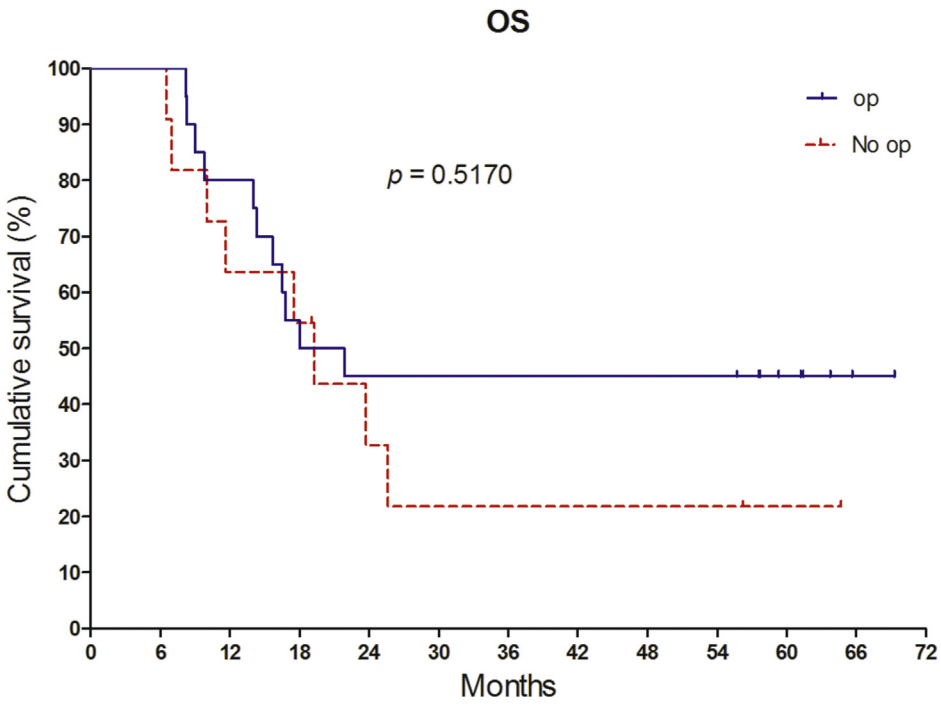

Fig. 4. Overall survival (OS) rate for nonoperative and operative groups (5-year OS of the operative group, 45%; 5-year OS of the nonoperative group, 21.8%).

Table 3
Treatment-related toxicities.

	Esophagitis, *n* (%)	Hematologic toxicity, *n* (%)	Pulmonary toxicity, *n* (%)
Grade 0	20 (64.5)	19 (61.3)	21 (67.7)
Grade 1	9 (29)	8 (25.8)	3 (9.7)
Grade 2	1 (3.2)	4 (12.9)	2 (6.5)
Grade 3	1 (3.2)	0 (0)	3 (9.7)
Grade 4	0 (0)	0 (0)	0 (0)

Oxaliplatin and cisplatin were demonstrated to damage DNA via different pathways.[18–20] One study showed that squamous cell carcinoma cells of the esophagus died via apoptosis due to cell-cycle arrest during the G_2 phase after oxaliplatin treatment.[21] Thus, oxaliplatin treatment still had noninferior efficacy in the treatment of locally advanced esophageal cancer in our study. Furthermore, cisplatin has a higher rate of hematologic toxicity, such as neutropenia and thrombocytopenia, and may damage renal function in the event of renal insufficiency or inadequate hydration. According to our investigation, oxaliplatin may provide an alternative choice for patients who are not suited to treatment with cisplatin.

A better regimen of chemotherapy when used concurrently with radiotherapy is needed to improve survival and decrease toxicity. Oxaliplatin with capecitabine,[22] and oxaliplatin with S1[23] were evaluated for the treatment of esophageal cancer. Unfortunately, there were no significant improvements in survival rates compared with those achieved using a cisplatin-based regimen.

There were some limitations in this study, including a small patient population and the fact that not all patients received surgery. Thus, there was the potential for bias in the evaluation of survival rates, though the difference in overall survival rate between the surgery and nonsurgery groups was not statistically significant. Another drawback was that there was no control arm (cisplatin with 5-FU or different dose of oxaliplatin) in our study. In addition, all patients were male, so there may be a bias for analysis, though female patients have better prognosis than males.

In conclusion, preoperative chemoradiotherapy with oxaliplatin in the treatment of locally advanced, potentially resectable esophageal cancer is feasible and shows efficacy with lower toxicities than cisplatin-based chemotherapy.

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