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Clinical Trial Results

Endostatin and Oxaliplatin-Based Chemoradiotherapy for Inoperable Esophageal Squamous Cell Carcinoma: Results of a Phase II Study

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02745561
- **Sponsor(s):** None
- **Principal Investigator:** Shixiu Wu
- **IRB Approved:** Yes

Lessons Learned

- Definitive concurrent chemoradiotherapy based on oxaliplatin and endostatin was effective with the objective response rate exceeding 80%, and the treatment-related toxicities were acceptable.
- The treatment compliance of the current combination was much higher, without significant reduction in survival outcomes, than historical reports.

Abstract

Background. This phase II trial aimed at assessing the efficiency and safety of definitive concurrent chemoradiotherapy (dCRT) using oxaliplatin (OHP) and endostatin in patients with inoperable esophageal squamous cell carcinoma (ESCC).

Methods. Radiotherapy was delivered with a daily fraction of 2.0 Gy to a total dose of 60.0 Gy over 6 weeks. Endostatin and OHP were both intravenously administered at doses of 7.5 mg/m^2 daily for 2 weeks and 135 mg/m^2 on day 1, respectively, every 3 weeks. The primary endpoint was the objective response rate (ORR).

Results. The analysis included 37 patients. The median age was 63 years (range: 49–71 years), and all patients were stage III–IVA. Of these patients, 97.3% (36/37) completed the dCRT course with an ORR of 83.8%, including 10 (27.0%) patients with complete response and 21 (56.8%) patients with partial response. The median overall survival (OS) time was 18.5 months (95% confidence interval [CI]: 10.6–26.4) with a 2-year OS rate of 39.6% (95% CI: 0.202–0.590). The median progression-free survival (PFS) time was 11.5 months (95% CI: 7.6–15.4) with a 2-year PFS rate of 20.2% (95% CI: 0.049–0.355). Grade 3 toxicities included esophagitis (five patients) and leukocytopenia (three patients). Grade 4 leukopenia was observed in one patient. Late toxicity was infrequent, and no treatment-related death occurred. Posttreatment dysphagia scores were significantly improved when compared with baseline ($p < .001$).

Conclusion. dCRT based on OHP and endostatin resulted in high treatment compliance with manageable toxicities. This combination resulted in encouraging ORR without compromising survival outcomes. It should be validated in future clinical studies. ***The Oncologist*** 2019;24:461–e136

Discussion

Endostatin, a novel artificially synthesized antiangiogenesis drug, has been tested as a potential therapeutic strategy to overcome tumor resistance in many types of solid tumors, including non-small cell lung cancer, colorectal cancer, bone soft tissue sarcoma, and metastatic malignant melanoma, in combination with different regimens of chemotherapy. However, it has been rarely tested in combination with chemoradiotherapy for patients with ESCC.

To our knowledge, this is the first study to evaluate oxaliplatin in combination with endostatin as first-line treatment for inoperable ESCC.

The primary endpoint of this study was set to evaluate the efficiency of oxaliplatin and endostatin on the ORR of patients with ESCC. A Simon's optimal two-stage design was required to accept the hypothesis that the true ORR was greater than 80% with 80% power and to reject the hypothesis that the ORR was less than 60% with a type I error of 0.05. After testing the combination on 13 patients

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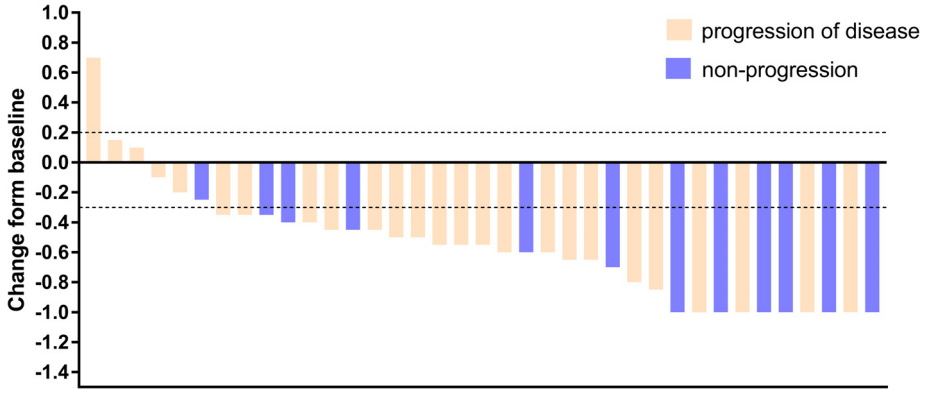

Figure 1. Waterfall plot of responses to definitive concurrent chemoradiotherapy.

with ESCC in the first stage, the trial would be terminated if 8 or fewer had an overall response. If the trial proceeded to the second stage, a total of 35 patients with ESCC would be enrolled. Considering some deviant cases, the preplanned accrual number was set to 37 patients.

Based on our findings, the current treatment regimen was effective, with the primary endpoint (ORR) exceeding 80% for unresectable ESCC. Toxicities of this combination were quite acceptable, with only one patient recorded with grade 4 leukopenia; 97.3% of the patients completed treatment without changing treatment plan, with a median OS and PFS of 18.5 (95% CI: 10.6–26.4) and 11.5 (95% CI: 7.6–15.4) months, respectively. This treatment combination should be validated in future large sample clinical studies.

Trial Information	
Disease	Esophageal cancer
Stage of Disease/Treatment	Primary
Prior Therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Toxicity
Secondary Endpoint	Overall survival
Secondary Endpoint	Progression-free survival

Additional Details of Endpoints or Study Design

This trial was conducted from January 2016, and the last follow-up date was July 31, 2018. Patients are still in follow-up.

Eligibility Criteria

The key inclusion criteria were as follows: (A) Patients with cytopathologically confirmed ESCC who were referred to receive dCRT after careful evaluation or based on the patient or physician choice. (B) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and aged 18 years or older. (C) Clinical stages according to the sixth edition of the TNM classification, with the exception of stage IVb. (D) Adequate bone marrow, renal, hepatic, and respiratory function (leukocytes ≥3000/mm^3, neutrophil ≥1.5 × 109/L, hemoglobulin level ≥9 g/dL, platelets ≥100 × 109/L, aspartate aminotransferase and alanine aminotransferase lower than double of the upper normal limit, total serum bilirubin ≤1.5 mg/dL, serum creatinine ≤1.2 mg/dL, creatinine clearance ≥50 mL/min, pulmonary function (FEV1 >1L), and no major electrocardiogram abnormalities.

Major exclusion criteria were as follows: (A) Prior treatments of chemotherapy or vascular endothelial growth factor inhibitors and infection or other diseases contraindicating dCRT. (B) Prior radiotherapy with field overlapping the proposed esophageal irradiation field. (C) Poor bone marrow, liver, kidney, and respiratory functions, which would make dCRT intolerable. (D) Tracheo-esophageal fistula or biopsy-proven invasion of the trachea-bronchial tree. (E) Dyscrasia needing immediate treatment. (F) Weight loss of 20% or more of normal body weight within 3 months.

Pretreatment Evaluation

Complete history collection, physical examination, electrocardiography, and blood test were routinely performed for all the enrolled patients. The extent of disease evaluation included endoscopic ultrasound of the esophagus, barium swallowing, and enhanced computed tomography (CT) of the neck, chest, and abdomen. Bone scintigraphy and brain magnetic resonance imaging were additionally performed if clinically indicated for the determination of individual staging. Positron emission tomography (PET) with CT was encouraged but not compulsory. Treatment schedule and dose modification of radiotherapy (RT) delivery was performed by intensity-modulated radiation therapy using the step-and-shoot technique in all patients. Previously, we had introduced the methods of gross tumor volume, clinical target volume, planning target volume, and dose-volume constraints of normal tissue delineations for patients with esophageal cancer [1, 2]. The total radiation dose was set to 60.0 Gy, which was given in 30 fractions of 2.0 Gy once-daily fractions for 5 consecutive days each week. The maximum dose to

the spinal cord was 45 Gy. For the lungs, V20 Gy and V30 Gy should be less than 25% and 20%, respectively. Thirty percent of the heart was limited to 50 Gy, and 60% of liver tissue was limited to 30 Gy. OHP 135 mg/m^2 was administered as a 2 h intravenous infusion in 500 mL of 5% glucose on day 1 and day 22, concurrently with 7.5 mg/m^2 endostatin over 3 h infusion between days 1 and 14 and between days 22 and 35. The first course began on the first day of concurrent radiotherapy. The treatment modifications were identical to those of our previous report. If patients received more than two dose reductions or there was a treatment delay of over 2 weeks because of intolerable adverse effects, OHP would be terminated, and RT and endostatin would be continued during the dCRT phase.

Study Assessments

Tumor response (primary endpoint) was evaluated 4–8 weeks after completion of dCRT and was recorded according to RECIST, version 1.1. Complete response (CR) was defined as the complete disappearance of any tumor ulceration with no new lesion and no progression on enhanced CT scan. Biopsies were optional when feasible. Acute treatment toxicity was evaluated according to the Common Toxicity Criteria for Adverse Events, version 4.0, and was recorded according to the worst score achieved during treatment. Late toxicity was defined as an adverse event occurred more than 6 months after dCRT initiation. Treatment failure was defined as any sign of recurrent disease. Follow-up modalities included physical examination, blood tests, gastrointestinal endoscopy, and enhanced CT. PET/CT was performed based on the patient's choice. Patients were followed up every month in the first half of the year, every 2 months in the second half of the year, 3 months for the second year, and then on a yearly basis. Additionally, dysphagia score before and after dCRT was measured according to the following scale: 0, able to consume a normal diet; 1, able to swallow certain solid foods; 2, able to swallow only semisolid foods; 3, able to swallow liquids only; and 4, unable to swallow anything.

Statistical Considerations

We postulate that the current combination could increase the treatment compliance and further improve the short-term response to dCRT. Thus, the primary endpoint was set to the ORR (CR + partial response [PR]), and secondary endpoints were PFS, OS, and treatment-related toxic reactions. This trial used an optimal two-stage design. A sample size of 35 was required to accept the hypothesis that the true response rate was greater than 80% with 80% power and to reject the hypothesis that the response rate was less than 60% with an α error of 5%. Initially, we planned to enroll 13 patients in the first stage. If eight or more responses were observed, we planned to continue to the second stage for a total of 35 patients for the analysis. Considering some deviant cases, the preplanned accrual number was set to 37 patients. The follow-up duration was calculated from the entry date to the end of the study on July 31, 2018. OS was defined as the time that elapsed from the date of treatment initiation to the date of death or the last follow-up (censored). PFS was defined as the interval between the first day of treatment and the first appearance of disease progression, death, or the last follow-up (censored). Survival curves were determined using the Kaplan-Meier method, and the difference of dysphagia scores between baseline and after dCRT was evaluated with the Mann-Whitney *U* test. All the statistical analyses were performed using SPSS software (version 22.0, IBM Corporation, Armonk, NY), and 95% CIs were calculated for all relevant estimates. All statistical tests were two-sided, and the significance level was set at $p < .05$.

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	Oxaliplatin
Trade Name	Eloxatin
Company Name	Sanofi-Aventis
Drug Type	Small molecule
Drug Class	Platinum compound
Dose	135 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Oxaliplatin 135 mg/m^2 was administered as a 2 h intravenous infusion in 500 mL of 5% glucose on day 1 and day 22 during the treatment
Drug 2	
Generic/Working Name	Endostatin
Trade Name	Endostar
Company Name	Simcere-Medgenn Bio-Pharmaceutical
Drug Type	Antibody
Dose	7.5 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Endostatin, 7.5 mg/m^2 over 3 h infusion between days 1 and 14 and between days 22 and 35

Patient Characteristics	
Number of Patients, Male	31
Number of Patients, Female	6
Stage	21 (56.8%) patients had clinical stage III; 16 (43.2%) patients with ESCC were diagnosed with clinical stage IVa
Age	Median (range): 63
Number of Prior Systemic Therapies	Median (range): 0
Performance Status: ECOG	0 — 14 1 — 23 2 — 0 3 — 0 Unknown — 0
Other	Detailed patient characteristics are presented in Table 1
Cancer Types or Histologic Subtypes	Esophageal squamous cell carcinoma, 37

Primary Assessment Method	
Title	New Assessment
Title	Total Patient Population
Number of Patients Screened	37
Number of Patients Enrolled	37
Number of Patients Evaluable for Toxicity	37
Number of Patients Evaluated for Efficacy	37
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 10 (27.0%)
Response Assessment PR	*n* = 21 (56.8%)
Response Assessment SD	*n* = 5 (13.5%)
Response Assessment PD	*n* = 1 (2.7%)
Response Assessment Other	*n* = 0 (0%)
(Median) Duration Assessments PFS	11.5 months, CI: 7.6–15.4
(Median) Duration Assessments OS	18.5 months, CI: 10.6–26.4
Outcome Notes	

Patient Characteristics

A total of 37 patients with ESCC were accrued in the present trial from January 2016 to March 2018 at Hangzhou Cancer Hospital. The median age of the patients was 63.0 years (range, 49–71 years), and 31 (83.8%) patients were male. The upper and middle thirds of the esophagus (78.4%) were the most common primary tumor sites. Twenty-one (56.8%) patients had clinical stage III, and 16 (43.2%) patients with ESCC were diagnosed with clinical stage IVa. Most (73.0%) patients had dysphagia grade ≥ 3, with only three (8.1%) patients being free of dysphagia. Other baseline characteristics of the patients with ESCC are summarized in Table 1.

Tolerance and Efficiency

Based on the study protocol, 10 out of the 13 patients with ESCC were considered to have disease response (ORR) in the first stage, and we continued to the second stage for a total of 37 patients with ESCC. All patients completed the full course of RT without radiation delay. One patient required a 20% dose reduction in the second cycle of OHP for developing grade 4 leukopenia. Thus, a total of 36 (97.3%) patients completed dCRT without changing treatment plan.

In the intention-to-treat analysis, CR was observed in 10 (27.0%) patients, PR in 21 (56.8%) patients, stable disease in five (13.5%) patients, and progressive disease in one (2.7%) patient, yielding an ORR rate of 83.8% based on the RECIST system (Fig. 1).

Acute and Late Toxicities

At the last follow-up, all patients were applicable for the evaluation of acute toxicities. The toxicity profiles are presented in the Adverse Events table. The most common hematological toxicity was leukopenia, including 3 (8.1%) patients with grade 3 and one (2.7%) patient with grade 4. Grade 3 anemia was observed in one (2.7%) patient, and another one (2.7%) patient experienced grade 3 thrombocytopenia. The main grade ≥3 nonhematologic toxicity was esophagitis (13.5%). Other grade 3 nonhematological toxicities included pneumonitis (5.4%), peripheral neuropathy (5.4%), fatigue (5.4%), anorexia (5.4%), diarrhea (5.4%), and

nausea/vomiting (5.4%). In terms of late toxicities, applicable in 30 patients, 3 (10.0%) patients exhibited grade 3 esophageal stenosis, and two (6.7%) patients were diagnosed with severe pneumonitis. No patients died of toxicities during dCRT.

Survival

At the time of this report (July 2018), the median follow-up time was 16.0 months (range: 2.5–30.0 months) with no one lost to follow-up. Twenty-five (67.6%) patients had experienced treatment failure, of which 10 (40.0%) were local-regional, 12 (48.0%) distant metastasis, and three (12.0%) considered as both local-regional and distant metastasis.

The median OS and PFS were 18.5 (95% CI: 10.6–26.4) and 11.5 (95% CI: 7.6–15.4) months, respectively. The 1- and 2-year OS rates were 62.3% (95% CI: 0.460–0.786) and 39.6% (95% CI: 0.202–0.590), respectively. The 1- and 2-year PFS rates were 44.3% (95% CI: 0.272–0.614) and 20.2% (95% CI: 0.049–0.355), respectively (Fig. 2).

Dysphagia Relief

The distribution of dysphagia score at baseline and after dCRT is shown in Figure 3. The dysphagia score had improved in 24 (64.9%) patients after dCRT. Twelve of the 37 patients (32.4%) reported no change of dysphagia score, and one (2.7%) patient reported worsening of dysphagia. The median dysphagia score (graded 0 to 4) was 3 (able to swallow liquids foods) at baseline and 2 (able to swallow only semisolid foods) after dCRT, with this change being statistically significant ($p < .001$). Results of the quality-of-life analyses will be reported elsewhere.

Adverse Events

Factor	Grade 0, *n* (%)	Grades 1–2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Acute toxic reactions (*n* = 37)				
Leukocytopenia	8 (21.6)	25 (67.6)	3 (8.1)	1 (2.7)
Anemia	31 (83.8)	5 (13.5)	1 (2.7)	–
Thrombocytopenia	28 (75.7)	8 (21.6)	1 (2.7)	–
Esophagitis	10 (27.0)	22 (59.5)	5 (13.5)	–
Pneumonitis	15 (40.5)	20 (54.1)	2 (5.4)	–
Peripheral neuropathy	28 (75.7)	7 (18.9)	2 (5.4)	–
Fatigue	21 (56.8)	14 (37.8)	2 (5.4)	–
Hepatotoxicity	31 (83.8)	5 (13.5)	1 (2.7)	–
Anorexia	27 (73.0)	8 (21.6)	2 (5.4)	
Diarrhea	22 (59.5)	13 (35.1)	2 (5.4)	–
Nausea/vomiting	20 (54.1)	15 (40.5)	2 (5.4)	–
Arrhythmia	36 (97.3)	1 (2.7)	–	–
Late toxic reactions (*n* = 30)				
Esophagitis	23 (76.7)	4 (13.3)	3 (10.0)	–
Pneumonitis	25 (83.3)	3 (10.0)	2 (6.7)	–
Pleural effusion	27 (90.0)	2 (6.7)	1 (3.3)	–
Pericardial effusion	30 (100)	–	–	–

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

The present study was designed to evaluate the efficacy and toxicity of oxaliplatin (OHP)-based definitive concurrent chemoradiotherapy (dCRT) combined with endostatin for patients with esophageal squamous cell carcinoma (ESCC). Our results demonstrated that the current combination was effective, with the primary endpoint (objective response rate, ORR) exceeding 80.0%; the treatment-related toxicities were quite acceptable with only one patient recorded with grade 4 leukocytopenia. Additionally, compliance with this treatment regimen was much higher than historical reports in the setting of double-regimen dCRT without markedly sacrificing survival outcomes.

Unsatisfactory treatment outcomes had driven physicians to further explore potential treatment combinations to improve the dismal situation for the management of ESCC. According to the landmark results of the RTOG 85-01 trial, the combination of cisplatin and fluorouracil (5-FU) resulted in substantial toxicity with all cycles of chemotherapy, and the combination could only be administered as planned in 33 of 61 (54%) patients with esophageal cancer (EC) [3]. In another trial, RTOG 0436 [4], patients with EC were randomly assigned to receive concurrent cisplatin and paclitaxel with or without weekly cetuximab in combination with radiotherapy. Results indicated that the grade

3 or higher hematologic toxic effects were 45% in the dCRT plus cetuximab group and 44% in the dCRT group. The 2- and 3-year overall survival (OS) rates for the dCRT plus cetuximab group were 45% and 34% versus 44% and 28% for the dCRT group (hazard ratio, 0.90; 95% confidence interval, 0.70–1.16; p = .47). Moreover, 109 (69%) patients treated in the dCRT plus cetuximab group and 127 (75%) in the dCRT group received chemotherapy per protocol, with dose modifications were recorded in 87 (55%) and 85 (50%) in each group, respectively. This trial failed to demonstrate any survival improvement for patients with locally advanced EC treated with dCRT plus targeted therapy. Insignificant results were also seen in the SCOPE-1 trial, which evaluated the addition of cetuximab to 5-FU and cisplatin-based chemoradiation treatment scheme [5]. As for bevacizumab, another vascular endothelial growth factor inhibitor, a former phase II trial had indicated that the addition of bevacizumab and erlotinib to neoadjuvant chemoradiation also did not demonstrate any survival benefit or improved pathologic complete response rate over similar regimens without targeted therapies [6]. Thus, the rationale of combining doublets chemotherapy with targeted inhibitors for unselected patients with EC seems impracticable in a series of prospective studies. To date, few studies have evaluated the efficacy of single-agent chemoradiotherapy for non-age-selected EC patients. In a phase II study evaluating the feasibility and efficiency of dCRT with single-agent chemotherapy of S-1, 93.3% (28/30) patients with EC completed the full course of radiotherapy with no grade 4 toxicity or treatment-related death. Survival analysis demonstrated that the median progression-free survival (PFS) and OS time was 19 and 24 months, respectively [7]. This treatment combination showed favorable efficacy with acceptable toxicity in elderly patients with EC. But the suitability of single-agent dCRT for non-age-selected patients with EC still remains uncertain at the current stage.

As a potent radio-sensitizing drug that could overcome resistance to cisplatin, OHP had also been assessed for the management of EC with different combinations in a series of studies. In the PRODIGE5/ACCORD17 trial [8], 133 patients with EC were assigned to receive FOLFOX regimen; results showed that combined chemoradiotherapy was delivered as planned in 93% patients in the FOLFOX group. Although survival analysis indicated no significant difference between the FOLFOX group and the 5-FU and cisplatin group, the FOLFOX regimen was associated with a marginally significant reduction of treatment-related death compared with the 5-FU and cisplatin regimen (1 vs. 6; p = .066). The authors concluded that although dCRT with FOLFOX did not increase PFS and OS compared with dCRT based on 5-FU and cisplatin, the FOLFOX regimen might be a more convenient treatment option for patients with unresectable EC. Previously, we also reported a phase II clinical trial evaluating the efficiency and safety of dCRT based on OHP and paclitaxel for patients with EC [2]. Our results indicated that 26 (76.5%) of 34 patients finished dCRT on schedule with a median OS of 23.7 months. Toxic effects were acceptable, with grade 3 and 4 leukocytopenia recorded in eight (23.5%) and five (14.7%) patients, respectively.

Regarding improvement in the dysphagia score, which was another important indicator of functional status for patients with EC, our results indicated that 24 (64.9%) patients experienced improvement of dysphagia score after dCRT by at least one grade when compared with baseline. This result was consistent with the findings of Ueda et al. [9]. In their report, the dysphagia score was improved after dCRT in 36 (72%) patients with metastatic esophageal cancer and did not change between before and after treatment in 14 (28%) patients. Because dysphagia score has been confirmed as having a substantial impact on the quality of life, we might consider that this treatment could also bring improved quality of life for patients with ESCC.

In conclusion, this pilot study demonstrated that the combination of OHP and endostatin in the setting of dCRT could be safely delivered in patients with unresectable ESCC. Patients with ESCC highly complied with this treatment regimen, and the toxicities associated with therapy were quite manageable. No significant reduction in survival was noted. It should be validated in future large sample clinical studies.

Acknowledgments

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Disclosures

The authors indicated no financial relationships.

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Figures and Table

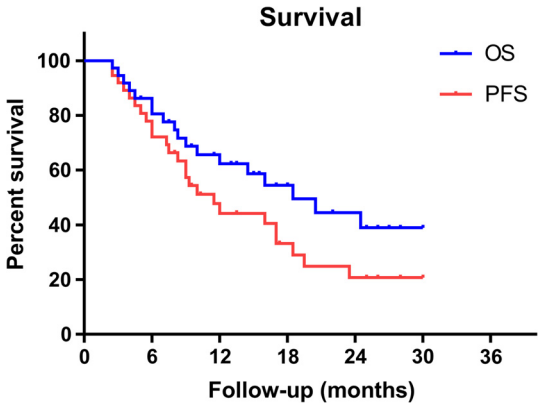

Figure 2. Kaplan-Meier curves of OS and PFS.
Abbreviations: OS, overall survival; PFS, progression-free survival.

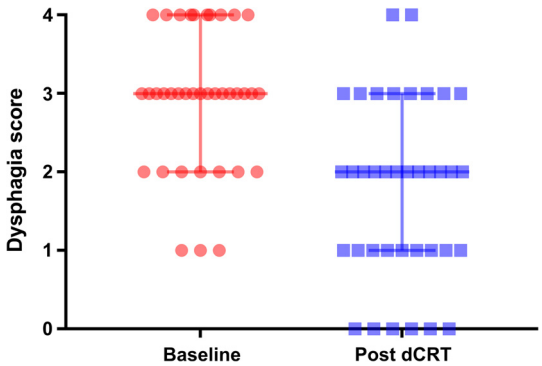

Figure 3. Distribution of dysphagia score at baseline and after dCRT.
Abbreviation: dCRT, definitive concurrent chemoradiotherapy.

Table 1. Patients' characteristics (n = 37)

Characteristic	dCRT, *n* (%)
Age, median (range), years	63 (49–71)
Sex	
Female	6 (16.2)
Male	31 (83.8)
ECOG PS	
0	14 (37.9)
1	23 (62.1)
Location	
Upper third	14 (37.9)
Middle third	15 (40.5)
Lower third	8 (21.6)
Tumor length, cm	
<5	15 (40.5)
≥5	22 (59.5)
Dysphagia score	
1–2	11 (29.7)
3–4	26 (70.3)
T stage	
T3	15 (40.5)
T4	22 (59.5)
N stage	
N0	8 (21.6)
N1	29 (78.4)
TNM stage	
Stage III	21 (56.8)
Stage IVa	16 (43.2)
Smoking status	
Current	17 (45.9)
Former/never	20 (54.1)
Alcohol consumption	
Regular drinkers	16 (43.2)
Occasional/never	21 (56.8)
Reasons for no surgery	
Inoperable tumor	26 (70.3)
Unsuitable for surgery	9 (24.3)
Refused surgery	2 (5.4)

Abbreviations: dCRT, definitive concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status.