Evaluation of Definitive Chemoradiotherapy Versus Radical Esophagectomy in Clinical T1bN0M0 Esophageal Squamous Cell Carcinoma

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Abstract

Background: The standard treatment for patients with clinical T1bN0M0 esophageal squamous cell carcinoma is radical esophagectomy. Definitive chemoradiotherapy is regarded as a treatment option, and good clinical outcome of this treatment has been reported. This study compared the efficacy of definitive chemoradiotherapy with radical esophagectomy.

Methods: From January 2011 to December 2019, this study enrolled 68 consecutive patients. Patients were classified into two groups whether treated by surgery or definitive chemoradiotherapy. Survival outcome were compared and subsequent therapies after recurrence were also investigated.

Results: Surgery was performed to 39 patients, and 29 patients received definitive chemoradiotherapy. No significant difference was noted in overall survival between two groups. However, the rate of 5-year recurrence free survival was significantly lower in definitive chemoradiotherapy group than that of surgery group (91.1% vs. 62.7%, Hazard ratio 3.976, 95% Confidence interval 1.076-14.696, $p = 0.039$). Patients who had local recurrence after definitive chemoradiotherapy received endoscopic submucosal dissection or photodynamic therapy as salvage therapies, and resulted in no disease progression and a good prognosis.

Conclusions: Definitive chemoradiotherapy may become a promising alternative therapy comparable with radical esophagectomy in patients with clinical T1bN0M0 esophageal squamous cell carcinoma. Early detection of recurrence by frequent follow-up after definitive chemoradiotherapy is important to control disease within local recurrence, and salvage therapy for local lesions could contribute to long-term survival.

Background

Esophageal cancer is currently the sixth cause of cancer-related mortality in the world [1]. Although multidisciplinary treatments have been developed for esophageal squamous cell carcinoma (ESCC), the high degree of recurrence and poor prognosis remain significant challenges [2, 3]. The postoperative 5-year survival rate in American Joint Committee on Cancer stage I esophageal cancer is approximately 90%; this rate decreases to 45% in patients with stage II disease, to 20% in stage III disease and to 10% in stage IV disease [4].

According to the 2017 esophageal cancer practice guidelines in Japan, promulgated by the Japan Esophageal Society, radical esophagectomy with regional lymph node (LN) dissection is a standard treatment for patients with clinical stage I, II, or III ESCC [5, 6]. However, esophagectomy is a highly invasive procedure with a high risk of postoperative complications [7]. Definitive chemoradiotherapy (dCRT) is a treatment option when esophagectomy is contraindicated. Good clinical outcomes of dCRT for patients with clinical stage I ESCC have been reported [8].

We hypothesized the efficacy of dCRT is equivalent to that of esophagectomy in patients with clinical T1bN0M0 ESCC, and therefore, dCRT may become a promising alternative treatment. In this study, the treatment results of dCRT and esophagectomy were compared.

Methods

Patients

From January 2011 to December 2019, the authors retrospectively investigated 109 consecutive patients with clinical T1bN0M0 esophageal cancer. All patients underwent esophagoduodenogastroscopy (EGD), computed tomography

(CT) from the neck to the pelvis, ultrasound evaluation of the neck and the abdomen, and positron emission tomography. Endoscopic ultrasound was performed to support the diagnosis of tumor depth. Diagnosis of clinical stage was determined based on the Union for International Cancer Control TNM classification of malignant tumors 8th edition [9]. All procedures were conducted in accordance with institutional and national standards on human experimentation, as confirmed by the Ethics Committee of Shizuoka Cancer Center, and with the Declaration of Helsinki of 1964 and its subsequent versions.

Patient eligibility for study enrolment was based on the following inclusion criteria: (1) histologic diagnosis of ESCC by endoscopic biopsy; (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1; (3) primary lesion site in the thoracic esophagus; (4) no prior chemotherapy or radiotherapy; and (5) irradiation dose > 50 Gy.

Among 109 patients with clinical T1bN0M0 ESCC, patient ineligibility for study enrolment was based on the following exclusion criteria: adenocarcinoma (11 patients); location at cervical esophagus (2 patients) and esophagogastric junction (10 patients); salvage surgery (6 patients); radiation dose < 50 Gy (16 patients) and radiation therapy alone (4 patients). Some patients were excluded due to multiple factors. The final study population was 68 patients and they were classified into two groups, 39 patients were surgery group and 29 patients were dCRT group (Fig. 1). All patients received medical information by the oncologists and surgeons and decided treatment.

Treatment and follow-up

Surgical treatment consisted of subtotal esophagectomy with 2- or 3-field LN dissection and reconstruction using gastric tube or pedicled jejunum with microvascular anastomosis. The standard LN dissection comprised removal of mediastinal LNs with bilateral recurrent nerve LNs and abdominal LNs, including the pericardial LNs and LNs along the lesser curvature and left gastric artery in 2-field LN dissection (Fig. 2a). In addition, bilateral supraclavicular LNs were also dissected in 3-field LN dissection (Fig. 2b). In transthoracic approach, video-assisted thoracoscopic surgery in the left decubitus position was generally performed. The abdominal approach was typically laparotomy. Postoperative complications were categorized using the Clavien–Dindo classification [10, 11].

For the first choice of dCRT regimen, the dose of cisplatin and 5-FU was selected from Japan Clinical Oncology Group (JCOG) 0303 protocol [12]. If cisplatin was not suitable for use because of insufficient renal function, nedaplatin was used. Radiation was planned to deliver a total of 60 Gy / 30 Fr using a linear accelerator with a 6-, 10-, or 18-MV photon beam. Before patients underwent planning CT, esophageal lesions were marked with metallic clips at the oral and the anal margin. From planning CT, radiation field was designed to cover these clips (Fig. 2c). Follow-up evaluation was performed by EGD and CT. Tumor response was defined according to the Response Evaluation Criteria in Solid Tumor guidelines [13, 14]. Adverse events were evaluated by Common Terminology Criteria for Adverse Events v5.0 [15].

Post-treatment follow-up was EGD and CT every 6 months for 5 years after esophagectomy in surgery group. In dCRT group, post-treatment follow-up was EGD and CT every 3 months for 1 year and every 4 months in the next 1 year. After 2 years, both EGD and CT were performed every 6 months. Selective investigations such as cervical ultrasound evaluation, magnetic resonance imaging, and positron emission tomography were performed when recurrence was suspected. Overall survival (OS) and recurrence free survival (RFS) were calculated from the start of initial treatment.

Statistical analysis

All statistical analyses were conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Categorical data were analyzed using Fisher's exact test or the chi-squared test as appropriate. Means and standard deviations

were calculated, and differences were identified using the *t* test. The Mann–Whitney U test was used in nonparametric analysis. Survival outcomes were analyzed using the Kaplan–Meier method and log–rank tests. Hazard ratio (HR) was calculated using Cox proportional hazards regression models. The threshold for significance was $p > 0.05$.

Results

Patient characteristics

The characteristics of all study participants were shown in Table 1. The median age of the study population was 69 (37–81) years in surgery group and 71 (44–81) years in dCRT group. The median duration of follow-up was 44.9 (3.9–112.2) months in surgery group and 50.2 (4.2–109.1) months in dCRT group. Clinical characteristics such as age, gender, the population of smoker and drinker, ECOG PS, comorbidities of diabetes mellitus, old myocardial infarction, arrhythmia and chronic hepatitis, history of gastrectomy and lung resection, renal and respiratory function were similar between two groups. There was also no significant difference in tumor location and depth (Table 1).

Treatment outcomes

Clinical outcomes in surgery group were shown in Table 2. The number of patients who underwent 2-field LN dissection was 12 (30.8%) and that of 3-field LN dissection was 27 (69.2%). The approach of reconstruction was gastric tube via the retrosternal route in 36 patients (92.3%). Another patient who had a high risk of anastomotic leakage because of accompanied immunosuppressive therapy to rheumatoid arthritis used gastric conduit via anterior sternal route. Pedicled jejunum with microvascular anastomosis via anterior sternal route was performed in 2 patients; 1 patient was had a history of distal gastrectomy due to gastric ulcer, and the other underwent composite resection of the stomach. Postoperative complications such as pneumonia, anastomotic leakage, and surgical site infection of Clavien–Dindo grade II or higher and recurrent laryngeal nerve palsy of Clavien–Dindo grade I or higher were observed in 17 (43.6%), 6 (15.4%), 7 (17.9%) and 4 patients (10.3%), respectively. Median postoperative hospital stay was 14 (11–59) days. No instances of postoperative mortality were observed. Pathologic findings showed 5 patients (12.8%) were T1a, 32 (82.1%) were T1b and 2 (5.1%) were T2. LN metastases were found in 8 patients (20.5%). Of these patients, 7 received postoperative adjuvant chemotherapy by intravenous infusion of 80 mg/m² of cisplatin and 800 mg/m² of 5-FU [16]. The other 1 patient with LN metastasis at left supraclavicular region received chemoradiotherapy consisted of 70 mg/m² of cisplatin and 700 mg/m² of 5-FU and irradiation of 50.4Gy.

Clinical outcomes in dCRT group were shown in Table 3. 28 of 29 (96.6%) patients completed two courses of chemotherapy and irradiation at 60 Gy. Only 1 patient stopped radiation by 58 Gy because of pneumonia. Adverse events were as follows: leukopenia in 5 (17.2%), neutropenia in 5 (17.2%), thrombocytopenia in 2 (6.9%) and esophagitis in 5 (17.2%) patients. Febrile neutropenia was shown in 1 patient (3.4%). 27 patients (93.1%) achieved complete response (CR) after dCRT and 2 (6.9%) was stable disease. Of these 27 patients, the median duration until achieve CR was 121 days (42–485). No treatment related mortality had occurred.

Patient survival and disease recurrence

No statistically significant difference was found in OS between two groups (Fig. 3a). The rate of 3-year OS was 92.9% in surgery group and 96.4% in dCRT group (HR 0.571, 95% Confidence interval (CI) 0.052–6.299, $p = 0.65$) and the rate of 5-year OS was 92.9% in surgery group and 77.8% in dCRT group (HR 2.471, 95% CI 0.451–13.522, $p = 0.29$). On the other hand, the rate of 3-year RFS was similar between the groups with 91.1% in surgery group and 78.7% in dCRT group (HR 2.59, 95% CI 0.647–10.363, $p = 0.18$). However, the rate of 5-year RFS was significantly lower in

dCRT group at 62.7% than that of surgery group at 91.1% (HR 3.976, 95% CI 1.076–14.696, $p = 0.039$) (Fig. 3b). The causes of mortality were primary tumor for 1 patient and pneumonia for 2 patients in surgery group. In dCRT group, the causes of mortality were primary tumor for 1 patient and other malignancies for 3 patients.

Table 4 showed clinical strategies for the patients with recurrence. In surgery group, 1 patient received chemotherapy consisted of 80 mg/m² of cisplatin and 800 mg/m² of 5-FU (Patient 1, Table 4). The other patient with brain metastasis received stereotactic radiotherapy (Patient 2, Table 4). In dCRT group, local recurrence was occurred in 2 patients and regional LN recurrence was in 4 patients, and distal organ metastasis was in 2 patients. 2 patients with local recurrence underwent salvage therapies; photodynamic therapy (PDT) was conducted for 1 patient (Patient 3, Table 4) and endoscopic submucosal dissection (ESD) was conducted for the other (Patient 4, Table 4). None of these patients experienced recurrence after salvage therapy, and both achieved long-term survival. 2 patients who could not reach CR experienced recurrence at the regional LN and distant organ (Patient 5 and 6, Table 4). Of those patients, 1 received 6 courses chemotherapy with paclitaxel (Patient 5, Table 4); the other patient could not receive chemotherapy because of grade 3 leukopenia, neutropenia, febrile neutropenia and thrombocytopenia following dCRT (Patient 6, Table 4). The relationship between the sites of LN metastasis and location of primary tumor was shown in Table 4. The upper-mediastinal LN metastasis was found in middle-thoracic ESCC and the abdominal LN metastasis was found in in all 3 regions. The LN recurrences were shown outside the radiation field. The recurrence of distal organ was found in middle- and lower-thoracic ESCC. The LN recurrence for 1 patient occurred > 5 years after the initial therapy at the left paracardial region (Patient 8, Table 4).

Discussion

This study revealed that OS of dCRT was equivalent to that of radical esophagectomy in patients with clinical T1bN0M0 ESCC, despite the rate of RFS being lower in dCRT than esophagectomy. In addition, patients who experienced local recurrence after dCRT showed a better prognosis after salvage therapies. These results suggested patients after dCRT have a risk for recurrence, and early detection within a local recurrence and successful subsequent therapy is important to prolong survival.

The standard treatment for cT1bN0M0 ESCC is radical esophagectomy in Japan [5, 6]. However, esophagectomy is associated with higher rates of postoperative complications, such as pneumonia, anastomotic leakage and recurrent laryngeal nerve palsy [17]. We previously reported the correlation between postoperative complications and poor long-term survival [18]. However, minimal invasive esophagectomy is expected to reduce the degree of surgical invasiveness and postoperative complications [19]. In addition, the progress of perioperative care is reported as another cause of reduced mortality [20–22]. Therefore, esophagectomy has become less invasive and the postoperative mortality rate at 90 days decreased from 3.2–1.9% from 2011 to 2018 [7]. In this study, surgery provided excellent OS, and this result confirmed the substantial status of radical esophagectomy as a standard treatment with clinical T1bN0M0 ESCC.

In general, dCRT is regarded as a treatment option when esophagectomy is contraindicated because of serious comorbidities or denials from the patient. A phase II trial (JCOG9708) revealed better outcomes in terms of the 4-year OS and RFS rates (80.5% and 68.1%, respectively) [8]. Several retrospective trials compared dCRT to esophagectomy were reported. Zhao et al. reported survival outcomes of dCRT are noninferior to those of esophagectomy after introduction of three-dimensional radiation with CT-guided planning [23]. Motoori et al. reported no significant difference was found between dCRT and esophagectomy in OS, however, the esophagectomy group displayed significantly better PFS than that of dCRT group [24]. Recently, a nonrandomized prospective trial (JCOG0502) reported no significant difference for OS was shown between surgery and dCRT (5-year OS; 86.5% versus 85.5%, 5-

year RFS; 81.7% versus 71.6%) [25]. The results of this study were consistent with those studies and suggested dCRT may become a promising alternative treatment with cT1bN0M0 ESCC.

In this study, salvage therapy to the local recurrence led to improvement of clinical outcomes after dCRT. Makazu et al. reported no recurrence was detected after salvage endoscopic resection for 54% of patients and the 5-year survival rate was 41.6% [26]. Regarding PDT, a multicentre phase II study reported that salvage PDT using talaporfin and a diode laser showed an excellent high local CR rate (88.5%) for local failure after dCRT [27]. The results of this study suggested early detection of local recurrences by frequent follow-up after dCRT enabled successful treatment by ESD or PDT, and ultimately, OS after dCRT could be prolonged to be comparable to that achieved after esophagectomy.

On the other hand, treatment results of LN recurrence after dCRT were poor. From the result of JCOG0502, the most frequent sites of LN metastasis were the upper mediastinal region in upper thoracic ESCC and the mediastinal or abdominal region in lower thoracic ESCC, although LN metastasis from middle thoracic ESCCs was observed in all 3 regions [28]. However, in this study, patients in upper-thoracic ESCC showed no recurrence at upper-mediastinal LN. In upper-thoracic ESCC, the radiation area includes thoracic paratracheal LN and radiation to this region can contribute to the prevention of upper-mediastinal LN recurrence.

One patient who experienced LN recurrence > 5 years after dCRT in this study. This result advocated long-term follow-up after dCRT was necessary even with a superficial lesion. No study has been conducted to compare OS between esophagectomy and dCRT > 5 years after initial treatment. Late toxicities have occurred and are a serious concern after dCRT, potentially leading to a decline in the survival rate [8, 29, 30].

This study has some limitations. First, selection bias regarding patient background may exist because the study was retrospective and nonrandomized study at a single institution. However, this study included consecutive patients to minimize selection bias. Second, some patients stopped follow-up (self-suspended) in both groups.

Conclusions

In conclusion, dCRT can become a promising alternative treatment comparable to esophagectomy in patients with clinical T1bN0M0 ESCC. Early detection of recurrence by frequent follow-up after definitive chemoradiotherapy is important to control disease within local recurrence, and salvage therapy for local lesions could contribute to long-term survival.

List Of Abbreviations

ESCC, Esophageal squamous cell carcinoma; LN, Lymph node; dCRT, Definitive chemoradiotherapy; EGD, Esophagoduodenogastroscopy; CT, Computed tomography; ECOG, Eastern Cooperative Oncology Group; PS, Performance status; JCOG, Japan Clinical Oncology Group; OS, Overall survival; RFS, Recurrence free survival; HR, Hazard ratio; CR, Complete response; CI, Confidence interval; PDT, Photodynamic therapy; ESD, Endoscopic submucosal dissection

Declarations

Ethics approval and consent to participate

All procedures were conducted in accordance with institutional and national standards on human experimentation, as confirmed by the Ethics Committee of Shizuoka Cancer Center, and with the Declaration of Helsinki of 1964 and its

subsequent versions.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analyzed during the present study is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflicts of interest associated with this study.

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Author's contributions

Conception and design: Ryoma Haneda, Eisuke Booka, Yasuhiro Tsubosa, Hiroya Takeuchi. Acquisition of data: Ryoma Haneda, Eisuke Booka, Kenjiro Ishii. Analysis and interpretation of data: Ryoma Haneda. Writing, review, and/or revision of the manuscript: Ryoma Haneda, Eisuke Booka, Hirotoishi Kikuchi, Yoshihiro Hiramatsu, Kinji Kamiya, Hirofumi Ogawa, Hirofumi Yasui, Hiroya Takeuchi. Study supervision: Eisuke Booka, Yasuhiro Tsubosa. All authors read and approved the final manuscript.

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Tables

Table 1
Patient characteristics

Characteristics	all patients (n = 68)	surgery group (n = 39)	dCRT group (n = 29)	p-value
Age, years*	69 (37–81)	69 (37–81)	71 (44–81)	0.54
Gender				0.75
Male (%)	56 (82.4%)	33 (84.6%)	23 (79.3%)	
Female (%)	12 (17.6%)	6 (15.4%)	6 (20.7%)	
PS (ECOG)				0.27
0 (%)	50 (73.5%)	31 (78.4%)	19 (65.5%)	
1 (%)	18 (26.5%)	8 (21.6%)	10 (34.5%)	
Smoker (%)	64 (94.1%)	38 (97.4%)	26 (89.7%)	0.31
Drinker (%)	63 (92.6%)	36 (52.9%)	27 (93.1%)	1.00
Previous operation				
Gastrectomy (%)	5 (7.4%)	1 (2.6%)	4 (13.8%)	0.16
Lung resection (%)	2 (2.9%)	0 (0%)	2 (6.9%)	0.19
Comorbidities				
DM (%)	5 (7.4%)	4 (10.3%)	1 (3.4%)	0.38
OMI (%)	3 (4.4%)	1 (2.7%)	2 (6.9%)	0.57
Arrhythmia	3 (4.4%)	2 (5.4%)	1 (3.4%)	1.00
Chronic hepatitis (%)	8 (11.8%)	2 (5.4%)	6 (20.7%)	0.07
Serum creatinine, mg/dl*	0.75 (0.43–1.39)	0.77 (0.46–1.39)	0.7 (0.43–1.19)	0.17
CCr, ml/min*	75 (44–137)	75 (45–137)	74 (44–124)	0.46
Respiratory function*				
VC, L	3.27 (1.6-5.0)	3.36 (2.1–4.43)	3.04 (1.6-5.0)	0.13
%VC, %	106.1 (64.2-146.4)	106.2 (66.9-146.4)	98.8 (64.2-131.9)	0.34
FEV1.0, L	2.37 (1.09–3.35)	2.45 (1.39–3.25)	2.28 (1.09–3.35)	0.19
FEV1.0%, %	73.1 (44.5–94.9)	74.1 (53.6–90.8)	70.4 (44.5–94.9)	0.66

*Values are presented as median (range)

dCRT, definitive chemoradiotherapy; PS, performance status; ECOG, Eastern Cooperative Oncology Group; DM, diabetes mellitus; OMI, old myocardial infarction; CCr, creatinine clearance calculated by Cockcroft-Gault formula; VC, vital capacity; FEV 1.0, forced expiratory volume in 1 second; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; sm, submucosa

Characteristics	all patients (n = 68)	surgery group (n = 39)	dCRT group (n = 29)	p-value
Location				0.18
Ut (%)	11 (16.2%)	5 (12.8%)	6 (20.7%)	
Mt (%)	37 (54.4%)	25 (64.1%)	12 (41.4%)	
Lt (%)	20 (29.4%)	9 (23.1%)	11 (37.9%)	
Tumor depth				0.62
sm1 (%)	8 (11.8%)	4 (10.3%)	4 (13.8%)	
sm2 (%)	55 (80.9%)	33 (84.6%)	22 (75.9%)	
sm3 (%)	5 (7.3%)	2 (5.1%)	3 (10.3%)	
*Values are presented as median (range)				
dCRT, definitive chemoradiotherapy; PS, performance status; ECOG, Eastern Cooperative Oncology Group; DM, diabetes mellitus; OMI, old myocardial infarction; CCr, creatinine clearance calculated by Cockcroft-Gault formula; VC, vital capacity; FEV 1.0, forced expiratory volume in 1 second; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; sm, submucosa				

Table 2
Surgical and pathologic outcomes of surgery group

Characteristics	surgery group (n = 39)
Approach (Thoracotomy / VATS)	
Thoracotomy (%)	8 (20.5%)
VATS (%)	31 (79.5%)
Operation time, min*	445 (252–654)
Blood loss, ml*	223 (38–1066)
LNs dissection	
2-field (%)	12 (30.8%)
3-field (%)	27 (69.2%)
Reconstruction organ	
Gastric conduit (%)	37 (94.9%)
Pedicled jejunum conduit (%)	2 (5.1%)
Reconstruction route	
Posterior sternal route (%)	36 (92.3%)
Anterior sternal route (%)	3 (7.7%)
Pathological tumor depth (UICC TNM 8th)	
T1a (%)	5 (12.8%)
T1b (%)	32 (82.1%)
T2 (%)	2 (5.1%)
LNs metastasis (UICC TNM 8th)	8 (20.5%)
N0 (%)	31 (79.5%)
N1 (%)	7 (17.9%)
N2 (%)	1 (2.6%)
Pathological stage (UICC TNM 8th)	
IA (%)	4 (10.3%)
IB (%)	25 (67.6%)
IIA (%)	2 (5.1%)
IIB (%)	7 (15.4%)

*Values are presented median (range)

VATS, video-assisted thoracoscopic surgery; LN, lymph node; UICC TNM 8th, Union for International Cancer Control TNM classification of malignant tumors 8th edition; CD, Clavien–Dindo classification; RLNP, recurrent laryngeal nerve palsy

Characteristics	surgery group (n = 39)
IVB (%)	1 (2.6%)
Lymphatic invasion	
Positive (%)	11 (28.2%)
Negative (%)	28 (71.8%)
Vascular invasion	
Positive (%)	17 (43.6%)
Negative (%)	22 (56.4%)
Postoperative complications	
Pneumonia, CD $\geq$ 2 (%)	11 (28.2%)
Anastomotic leakage, CD $\geq$ 2 (%)	6 (15.4%)
Surgical site infection, CD $\geq$ 2 (%)	7 (17.9%)
RLNP, CD $\geq$ 1 (%)	4 (10.3%)
Postoperative hospital stays, days*	14 (11–59)
Mortality	0
Adjuvant therapy	
Chemotherapy (%)	7 (17.9%)
Chemoradiotherapy (%)	1 (2.6%)
*Values are presented median (range)	
VATS, video-assisted thoracoscopic surgery; LN, lymph node; UICC TNM 8th, Union for International Cancer Control TNM classification of malignant tumors 8th edition; CD, Clavien–Dindo classification; RLNP, recurrent laryngeal nerve palsy	

Table 3
Clinical features of definitive chemoradiotherapy group

Characteristics	dCRT group (n = 29)
Chemotherapy	
CDDP + 5-FU (%)	25 (86.2%)
CDGP + 5-FU (%)	4 (13.8%)
Response	
CR (%)	27 (93.1%)
SD (%)	2 (6.9%)
Adverse events	
Leukopenia, Grade ≥ 3 (%)	5 (17.2%)
Neutropenia, Grade ≥ 3 (%)	5 (17.2%)
Febrile neutropenia, Grade ≥ 3 (%)	1 (3.4%)
Thrombocytopenia, Grade ≥ 3 (%)	2 (6.9%)
Esophagitis, Grade ≥ 3 (%)	5 (17.2%)
Appetite loss, Grade ≥ 3 (%)	1 (3.4%)
Nausea, Grade ≥ 3 (%)	1 (3.4%)
Pericardial effusion, Grade ≥ 1	5 (17.2%)
Radiation pneumonitis, Grade ≥ 1 (%)	12 (41.4%)
Radiation pneumonitis, Grade ≥ 2 (%)	1 (3.4%)
Renal failure, Grade ≥ 2 (%)	1 (3.4%)
Treatment-related death	0
dCRT, definitive chemoradiation therapy; CDDP, cisplatin; 5-FU, 5-fluorouracil; CDGP, nedaplatin; CR, Complete response; SD, Stable disease	

Table 4
Distribution of recurrence site and strategies of subsequent therapy

No	Group	age	site	Clinical Tumor depth	Site of recurrence	Subsequent therapy	RFS (days)	OS (days)	Status
1	S	64	Mt	sm2	Local, bone	CDDP + 5-FU	177	476	Death
2	S	71	Mt	sm2	Brain	SRT (3.6 Gy/10Fr)	225	289	Alive
3	C	69	Lt	sm2	Local	Salvage PDT (talaporfin)	549	1472	Alive
4	C	49	Mt	sm1	Local	Salvage ESD	510	1554	Alive
5	C	73	Lt	sm1	Lesser curvature LN para-aorta LN	Paclitaxel	83	277	Death
6	C	62	Mt	sm3	Lesser curvature LN, Lung	BSC	125	125	Alive
7	C	71	Lt	sm2	Bone	FOLFOX	276	430	Alive
8	C	63	Ut	sm2	Left paracardial LN	Follow-up	2163	2277	Alive
9	C	73	Mt	sm2	Cervical paraesophageal LN	Lymphadenectomy	213	515	Alive
RFS, recurrence free survival; OS, overall survival; S, surgery group; C, definitive chemoradiotherapy; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ut, upper thoracic esophagus; sm, submucosa; LN, lymph node; CDDP, cisplatin; 5-FU, 5-fluorouracil; SRT, stereotactic radiotherapy; PDT, photodynamic therapy; ESD, endoscopic submucosal dissection; BSC, best supportive care; FOLFOX, folinic acid and fluorouracil and oxaliplatin									

Figures

Figure 1

Flow diagram of the study inclusion and exclusion criteria

Figure 2

Number of retrieved lymph nodes. Area encircled by red line was two field lymphangiography (a), and area of three field lymphangiography (b). Radiation area was set from oral margin to anal margin marked by metallic clips (c).

Figure 3

Kaplan–Meier curves of overall survival between surgery group and definitive chemoradiotherapy (dCRT) group (a) and recurrence free survival between surgery group and dCRT group (b). The threshold for significance was $p < 0.05$.