Evaluation of definitive chemoradiotherapy versus radical esophagectomy in clinical T1bN0M0 esophageal squamous cell carcinoma

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Running head

Chemoradiotherapy versus esophagectomy for early esophageal cancer

Keywords

esophageal squamous cell carcinoma, esophagectomy, chemoradiotherapy

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.

Conflict of interests

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

Informed consent

Informed consent was obtained from all individual participants included in the study.

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 recently, good clinical outcomes of this treatment have been reported. This study compared prognosis after definitive chemoradiotherapy with radical esophagectomy.

Methods: From January 2011 to December 2019, 68 consecutive patients who were diagnosed clinical T1bN0M0 squamous cell carcinoma were enrolled and investigated retrospectively. Patients were classified into two groups whether treated by surgery or definitive chemoradiotherapy. Survival outcomes were compared and subsequent therapies after recurrence were also investigated.

Results: Among 68 patients, 39 patients underwent surgery and 29 patients received definitive chemoradiotherapy. No significant difference was noted in overall survival between the 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.

Introduction

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 rate 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 and the National Comprehensive Cancer Network (NCCN) guidelines, radical esophagectomy with regional lymph node (LN) dissection is a standard treatment for patients with clinical T1bN0M0 ESCC [5, 6, 7]. However, esophagectomy is a highly invasive procedure with a high risk of postoperative complications [8]. 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 [9].

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 recurrence free survival (RFS) and overall survival (OS) after

dCRT were compared to those of esophagectomy.

Material and Methods

Patients

From January 2011 to December 2019, 93 consecutive patients with clinical T1bN0M0 esophageal cancer were retrospectively investigated at Shizuoka Cancer Center. Smokers included both current smokers and former smokers. Patients who regularly drink more than 14 grams of alcohol were defined as drinkers from National Institutes on Alcohol Abuse and Alcoholism. 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 (PET). Endoscopic ultrasound (EUS) was performed to support the diagnosis of tumor invasion. Pathological findings were cited from pathological report. Diagnosis of clinical and pathological stage was determined based on the Union for International Cancer Control TNM classification of malignant tumors 8th edition [10]. 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. Informed consent was obtained from all individual participants included in the study.

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; (5) curative resection.

Among 93 patients with clinical T1bN0M0 ESCC, patient ineligibility for study enrolment was based on the following exclusion criteria: adenocarcinoma (12 patients); location at cervical esophagus (2 patients); incomplete resection (1 patient); salvage surgery (6 patients) and radiation therapy alone (4 patients). The final study population for investigation was 68 patients (Fig. 1). Medical information was provided by both the medical and surgical oncologists. In accordance with the 2017 esophageal cancer practice guidelines in Japan, surgery was proposed and dCRT was conducted due to patient denial or tolerance.

Surgical procedure

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 (Supplementary Fig 1a, Online Resource 1). In

addition, bilateral supraclavicular LNs were also dissected in 3-field LN dissection (Supplementary Fig 1b, Online Resource 1). 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 [11, 12].

Definitive Chemoradiotherapy

Chemoradiotherapy consisted of 70 mg/m^2 of cisplatin, 700 mg/m^2 of 5-FU, and irradiation of 60Gy [9]. If cisplatin was not suitable 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 planning CT, metallic clips were placed as markings on the cranial and the caudal margin of the lesion (Supplementary Fig 1c, Online Resource 1). Tumor response was defined according to the Response Evaluation Criteria in Solid Tumor guidelines v1.1 radiologically [13, 14]. Tumor regression grade was classified by the Mandard's classification histologically [15]. Adverse events were evaluated by Common Terminology Criteria for Adverse Events v5.0 [16].

Follow-up

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. According to the Japanese classification of esophageal cancer, to confirm histologically, biopsy was performed another 2 times when clinical response reached complete response (CR) by EGD [17]. Selective investigations such as cervical ultrasound evaluation, magnetic resonance imaging, and PET were performed when recurrence was suspected.

The invasiveness of each treatment to patients was investigated. The rates of patients with gastroesophageal reflux disease (GERD) classified by Los Angeles (LA) classification, stenosis, and proton-pump inhibitor (PPI) medication over 6 months were compared between the two groups.

OS was calculated from initial treatment to death or until the end of study (May 31, 2020). RFS was defined as the date from initial treatment to the detection of recurrence by PET or the end of study (May 31, 2020).

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

Sixty-eight patients who enrolled in this study were stratified into 2 groups–39 patients underwent surgery and 29 patients received dCRT–and compared (Fig. 1). In dCRT group, 4 patients did not tolerate surgery due to comorbidity; 2 patients had alcoholic-related liver cirrhosis; 1 patient had a history of coronary artery bypass grafting; and 1 patient had low pulmonary function. The median follow-up period was 49.6 (3.9–112.2) months in all patients, 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, prior myocardial infarction, arrhythmia and chronic hepatitis, history of gastrectomy and lung resection, renal and respiratory function were similar between the two groups. Patients with chronic hepatitis tended to be more in dCRT group. Furthermore, patients with alcoholic liver disorder also tended to be more in dCRT group (2.6% in surgery group vs 17.6% in dCRT group, p=0.076), however, no patient had cirrhosis. There was also no significant difference in tumor location, length, and invasion (Table 1).

Treatment outcomes

Clinical outcomes of surgery group were shown in Table 2. Subtotal esophagectomy with 2-field LN dissection was performed for 12 patients (30.8%) and 27 patients (69.2%) underwent 3-field LN dissection. At the point of the reconstruction, the gastric tube via the retrosternal route was adopted in 36 patients (92.3%). Pedicled jejunum with microvascular anastomosis via anterior sternal route was performed in 2 patients; 1 patient had a history of distal gastrectomy due to gastric ulcer and another patient underwent composite resection of the stomach. The other patient with immunosuppressive therapy for rheumatoid arthritis used gastric conduit via anterior sternal route, considering a risk of anastomotic leakage. 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 90-day mortality were observed. Pathologic findings showed 5 patients (12.8%) were T1a (muscularis mucosa), 32 (82.1%) were T1b and 2 (5.1%) were T2. LN metastasis was found in 8 patients (20.5%). Of these patients, 7 received postoperative adjuvant chemotherapy by intravenous infusion of 80 mg/m^2 of cisplatin and 800 mg/m^2 of 5-FU [18]. The other 1 patient with LN metastasis at the left supraclavicular region received chemoradiotherapy consisted of

70 mg/m^2 of cisplatin, 700 mg/m^2 of 5-FU, and irradiation of 50.4Gy.

Clinical outcomes in dCRT group were shown in Table 3. Twenty-eight (96.6%) patients completed two courses of chemotherapy and irradiation until 60 Gy. Only 1 patient stopped receiving radiation by 58 Gy due to pneumonia. Adverse events were as follows: leukopenia in 5 (17.2%), neutropenia in 5 (17.2%), thrombocytopenia in 2 (6.9%), esophagitis in 5 (17.2%), and febrile neutropenia in 1 (3.4%). Twenty-seven patients (93.1%) achieved CR after dCRT and 2 (6.9%) was stable disease. According to the Mandard's classification, 27 (93.1%) patients was classified as TRG1 (complete regression), and 2 (6.9%) was TRG 5 (tissue of tumor without changes of regression). The median duration until achieve CR was 121 days (42–485). No treatment related mortality of 90-day after initial treatment had occurred.

Table 4 showed the invasiveness of each treatment to patients. The rates of patients with GERD of LA classification grade A or higher, stenosis, and PPI medication over 6 months were significantly lower in dCRT group than in surgery group ($p = 0.016$, <0.001, <0.001, respectively). Nutritional status and rehabilitation were compared. Although some patients had no data of posttreatment body weight and restarting work, patients in dCRT group (n=25) had significantly less weight loss than that of surgery group (n=38) (+0.5kg vs -6.1kg, $p<0.001$). Regarding the rehabilitation, although some patients had no work when each treatment had

started (20 patients in surgery group, 18 patients in dCRT group) and other patients had no information about restarting their work, the rate of patients who restart their work after dCRT was similar to those of surgery groups (54.5% vs 57.9%, p=1.000).

Patient survival and disease recurrence

There was no significant difference in OS between the two groups (Fig. 2a). 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). 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. 2b). The causes of mortality were as follows; 1 patient had recurrence of the primary tumor and 2 patients had pneumonia in surgery group. In dCRT group, the causes of mortality were recurrence of the primary tumor in 1 patient and other malignancies in 3 patients.

Table 5 showed clinical strategies for patients with recurrence. In surgery group, 1 patient received chemotherapy consisted of cisplatin and 5-FU (Patient No.1). The other patient with

brain metastasis received stereotactic radiotherapy (Patient No.2). Local recurrences, regional LN recurrences, and distal organ metastases in dCRT group occurred in 2, 4, and 3 patients, respectively. Two patients with local recurrences underwent salvage therapies; 1 patient underwent photodynamic therapy (PDT) (Patient No.3) and the other underwent endoscopic submucosal dissection (ESD) (Patient No.4). None of these patients experienced recurrence after salvage therapy, and both achieved long-term survival. Two patients who could not reach CR recurred at the regional LN and distant organ (Patient Nos.5 and 6). Of those patients, 1 received 6 courses chemotherapy with paclitaxel (Patient No.5), and the other could not receive chemotherapy because of grade 3 leukopenia, neutropenia, febrile neutropenia and thrombocytopenia following dCRT (Patient No.6). In the dCRT group, regional LN recurrence was observed in 4 patients (Patient Nos.5, 6, 8 and 9). The LN recurrences were outside the radiation field in all 4 patients. 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 No.8).

Discussion

This study revealed that OS of dCRT is potentially 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 indicated that although patients could have a risk for recurrence after dCRT, early detection within a local recurrence and successful subsequent therapy is important for patients after dCRT to prolong survival.

The standard treatment for clinical T1bN0M0 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 [19]. We previously reported the correlation between postoperative complications and poor long-term survival [20]. However, minimal invasive esophagectomy is expected to reduce the degree of surgical invasiveness and postoperative complications [21]. In addition, the progress of perioperative care is reported as another cause of reduced mortality [22-24]. Therefore, esophagectomy has become less invasive and the postoperative mortality rate at 90 days decreased from 3.2% to 1.9% from 2011 to 2018 [8]. In this study, surgery provided excellent OS, and this result confirmed the substantial status of radical esophagectomy as a standard

treatment for clinical T1bN0M0 ESCC.

According to the 2017 esophageal cancer practice guidelines in Japan and the NCCN guidelines, dCRT is regarded as a treatment option when esophagectomy is contraindicated due to serious comorbidities or patient denials [5, 6, 7]. In this study, the rates of patients with GERD, stenosis, and PPI medication were significantly lower in dCRT group. Furthermore, patients in dCRT group had significantly less weight loss than that of surgery group. These results suggested that the patient suffering caused by dCRT could be less than that of surgery. The preservation of the esophagus is another benefit. A phase II trial (JCOG9708) revealed good survival outcomes in terms of the 4-year OS and RFS rates (80.5% and 68.1%, respectively) [9]. Several retrospective trials comparing dCRT with esophagectomy were reported. Motoori et al. reported that no significant difference was found between dCRT and esophagectomy in OS, whereas the esophagectomy group displayed significantly better PFS than that of dCRT group in patients with clinical T1N0M0 ESCC [25]. Semenkovich et al. reported that, although a trend toward better survival for patients receiving esophagectomy was observed, no statistical significance was found in the survival of patients, whether receiving esophagectomy, endoscopic resection, chemoradiation, or no treatment in clinical T1bN0 esophageal cancer from the National Cancer Database [26]. The results of this study were

consistent with those studies and suggested that dCRT may become a promising alternative treatment with clinical T1bN0M0 ESCC. Recently, a parallel-group controlled trial for Stage IA ESCC (JCOG0502) reported no significant difference for OS between surgery and dCRT for clinical T1bN0M0 ESCC (5-year OS; 86.5% versus 85.5%, 5-year RFS; 81.7% versus 71.6%) [27].

In this study, salvage therapy for local recurrence led to the 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% [28]. Regarding PDT, a multicenter phase II study reported that salvage PDT using talaporfin and a diode laser showed an excellently high local CR rate (88.5%) for local failure after dCRT [29]. 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.

ESCC has a malignant potential with a high incidence of LN metastasis [30]. From the result of JCOG0502, the sites of LN metastasis were the upper- or middle-mediastinal region in the upper thoracic ESCC and the lower-mediastinal or abdominal region in the lower thoracic ESCC, although LN metastasis from middle thoracic ESCC was observed in all 3

regions [30]. However, in this study, patients with upper-thoracic ESCC showed no recurrence at middle-mediastinal LN. In upper-thoracic ESCC, the radiation area included thoracic paratracheal LN, and radiation to this region could contribute to the prevention of LN recurrence. This result also suggested that elective nodal irradiation should be performed even for clinical T1bN0M0 cases. Treatment outcomes for LN recurrence after dCRT are still wrong. Moreover, late toxicities after dCRT, which potentially lead to a decline in survival rate, could be another concern [9, 31, 32]. Interestingly, 1 patient experienced LN recurrence > 5 years after dCRT in this study. These results advocated long-term follow-up after dCRT was necessary even with a superficial lesion.

The regimen of dCRT was controversial. In a parallel-group controlled trial (JCOG0502), the regimen was consisted of 70 mg/m^2 of cisplatin, 700 mg/m^2 of 5-FU and irradiation of 60Gy, which showed excellent outcomes [27].

This study has some limitations. First, selection bias regarding patient background existed because the study was a retrospective study at a single institution. Furthermore, although the selection of treatment was determined by the patient's preference, patients in better condition tended to undergo surgery. However, this study included consecutive patients to minimize selection bias. Second, the accuracy of preoperative T and N staging were inadequate. The rate

of LN metastasis with tumor in muscularis mucosa is equivalent to that of tumor in submucosa (> 200 μ m) [5, 6]. Previous reports suggested that EUS is useful for the accurate T staging [33]. Furthermore, the NCCN guidelines state that endoscopic resections of small nodular lesions can provide more accurate T staging than EUS [7]. For N staging, smoking impairs LN assessment. Most patients enrolled in this study were smokers, complicating the diagnosis of swollen LN. Fine-needle aspiration biopsy under EUS was reported more accurate than CT [7, 33]. Third, this study was inconclusive in indicating the equivalences between surgery and dCRT because of the small number of enrolled patients. Moreover, the study design was nonrandomized. However, to enforce a randomised study comparing therapeutic interventions is difficult due to patient denial. The results of this study could have a certain clinical significance. At last, some patients stopped follow-up (self-suspended) in both groups.

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

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Figure legends

Fig. 1 Flow diagram of the study inclusion and exclusion criteria

Fig. 2 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 $p < 0.05$

Fig 1

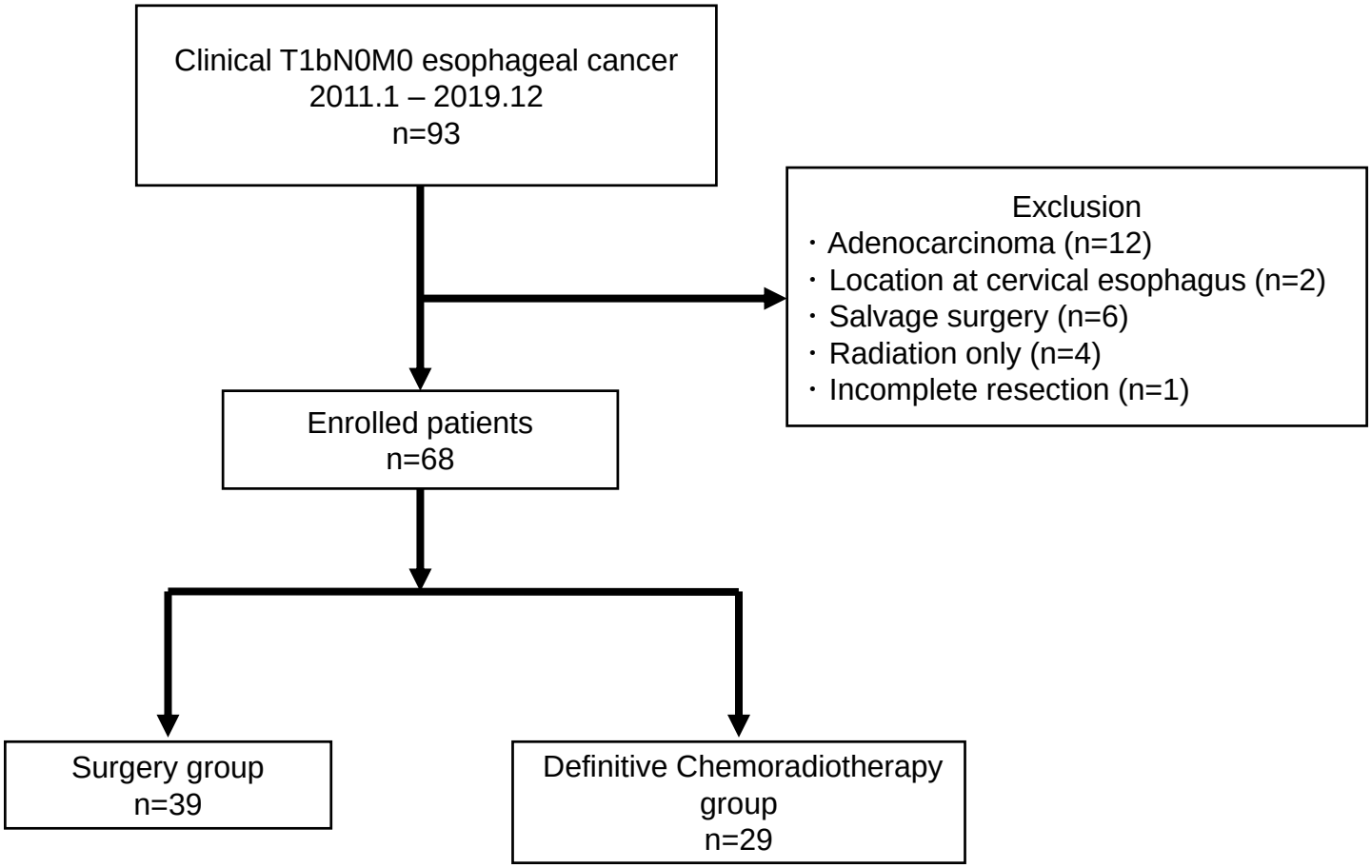
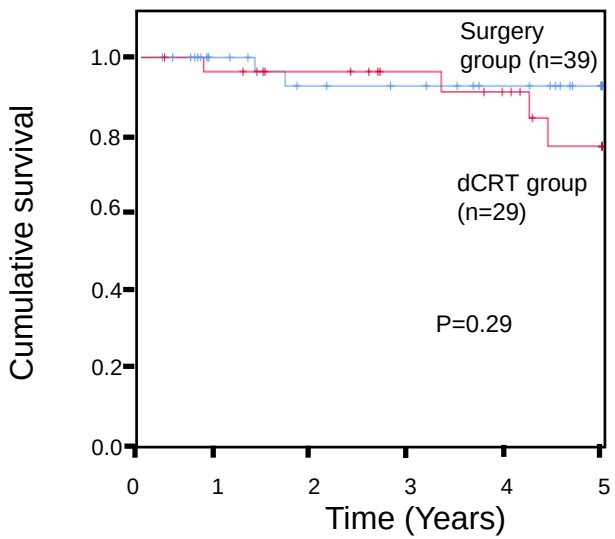

Clinical T1bN0M0 esophageal cancer
2011.1 – 2019.12
n=93
Exclusion
・Adenocarcinoma (n=12)
・Location at cervical esophagus (n=2)
・Salvage surgery (n=6)
・Radiation only (n=4)
・Incomplete resection (n=1)
Enrolled patients
n=68
Surgery group
n=39
Definitive Chemoradiotherapy group
n=29

Fig 2

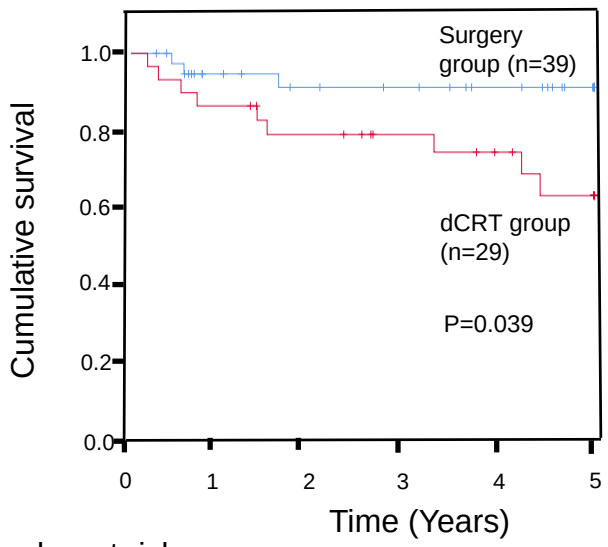
a Overall survival



Number at risk

Surgery Group	39	30	25	23	19	11
dCRT Group	29	27	23	19	16	11

b Recurrence free survival

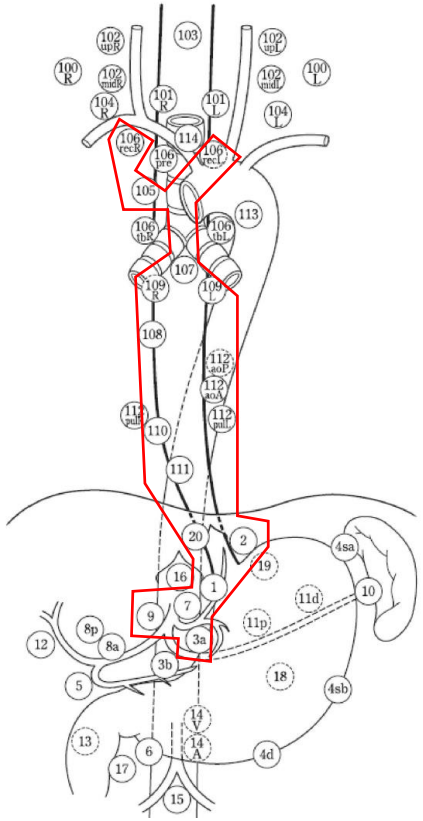


Number at risk

Surgery Group	39	29	25	23	19	11
dCRT group	29	25	21	17	14	11

Online Resource 1

a



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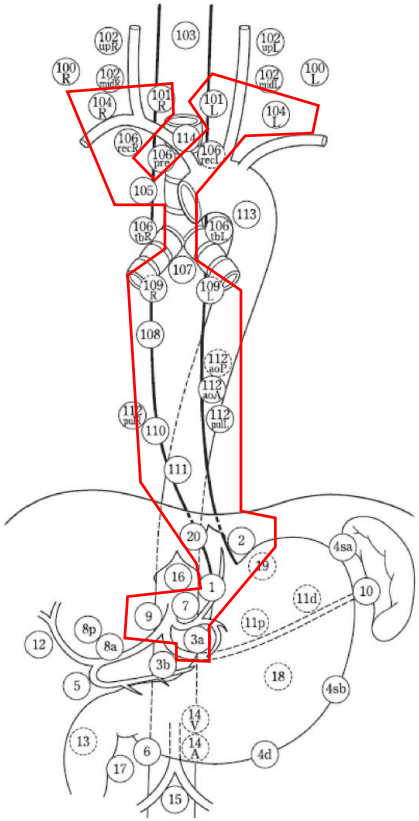

c

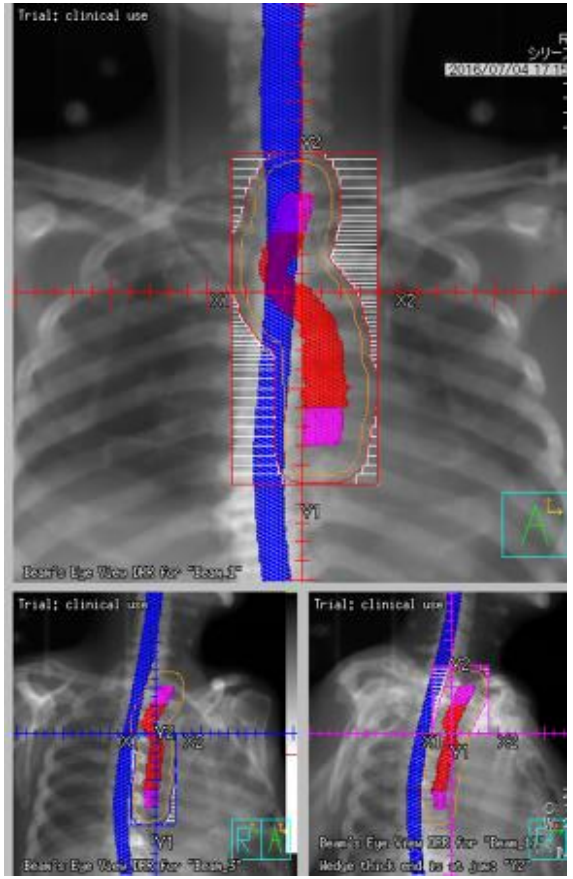

Table 1 Patient characteristics

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 (92.3%)	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
FEV1.0, L	2.37 (1.09-3.35)	2.45 (1.39-3.25)	2.28 (1.09-3.35)	0.19
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 length*	4 (1.3-10)	4 (1.5-9)	4 (1.3-10)	0.091
Tumor invasion				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%)	

EUS (%)	28 (41.2%)	15 (38.5%)	13 (44.8%)	0.63

*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 (from superior margin of the sternum to tracheal bifurcation); Mt, middle thoracic esophagus (superior half between tracheal bifurcation and esophagogastric junction); Lt, lower thoracic esophagus (thoracic esophagus from inferior half between tracheal bifurcation and esophagogastric junction); sm, submucosa; EUS, endoscopic ultrasound

Table 2 Surgical and pathological 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-MM (%)	5 (12.8%)
T1b (%)	32 (82.1%)
T2 (%)	2 (5.1%)
LNs metastasis (UICC TNM 8th)	
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%)
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 ≥ 2 (%)	11 (28.2%)
Anastomotic leakage, CD ≥ 2 (%)	6 (15.4%)
Surgical site infection, CD ≥ 2 (%)	7 (17.9%)
RLNP, CD ≥ 1 (%)	4 (10.3%)
Postoperative hospital stays, days*	14 (11–59)
90-day 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; MM, muscularis mucosa; CD, Clavien–Dindo classification; RLNP, recurrent laryngeal nerve palsy

Table 3 Clinical features of definitive chemoradiotherapy group

Characteristics	dCRT group (n = 29)
Chemotherapy regimen	
CDDP+5-FU (%)	25 (86.2%)
CDGP+5-FU (%)	4 (13.8%)
Clinical response (RECIST guideline v1.1)	
CR (%)	27 (93.1%)
SD (%)	2 (6.9%)
TRG (Mandard's grade)	
TRG1. Complete regression	27 (93.1%)
TRG5. Tissue of tumor without changes of regression	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%)
90-day treatment related mortality	0

dCRT, definitive chemoradiation therapy; CDDP, cisplatin; 5-FU, 5-fluorouracil; CDGP, nedaplatin; RECIST, Response Evaluation Criteria in Solid Tumor; TRG, Tumor regression grade; CR, Complete response; SD, Stable disease

Table 4 The invasiveness of each treatment

Characteristics	all patients (n=68)	surgery group (n=39)	dCRT group (n=29)	p-value
Rehospitalization	10 (14.7%)	3 (7.7%)	7 (24.1%)	0.085
GERD (LA classification Grade≥A)	20 (29.4%)	16 (41.0%)	4 (13.8%)	0.016
Stenosis	23 (33.8%)	22 (56.4%)	1 (3.4%)	<0.001
PPI medication ≥6 months	43 (63.2%)	39 (100%)	4 (13.8%)	<0.001

dCRT, definitive chemoradiotherapy; GERD, gastroesophageal reflex disease; LA classification, Los Angeles classification; PPI, proton-pump inhibitor

Table 5 Distribution of recurrence site and strategies of subsequent therapy

No	Group	age	site	Clinical tumor invasion	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 (3.6Gy/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