



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

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

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4 Ryoma Haneda, MD^{1,2}; Eisuke Booka, MD, PhD¹; Kenjiro Ishii, MD, PhD¹; Hirotohi Kikuchi,
5 MD, PhD²; Yoshihiro Hiramatsu, MD, PhD²; Kinji Kamiya, MD, PhD²; Hirofumi Ogawa,
6 MD³; Hirofumi Yasui, MD⁴; Hiroya Takeuchi, MD, PhD² and Yasuhiro Tsubosa, MD, PhD¹

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8 1. Division of Esophageal Surgery, Shizuoka Cancer Center, Shizuoka, Japan

9 2. Department of Surgery, Hamamatsu University School of Medicine, Shizuoka, Japan

10 3. Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, Japan

11 4. Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

12

13 Corresponding author: Eisuke Booka, MD, PhD

14 Division of Esophageal Surgery, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo,
15 Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan

16 E-mail: e.booka@scchr.jp

1 Tel: +81-55-989-5222

2 Fax: +81-55-989-5783

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4 **Running head**

5 Chemoradiotherapy versus esophagectomy for early esophageal cancer

6

7 **Keywords**

8 esophageal squamous cell carcinoma, esophagectomy, chemoradiotherapy

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10 **Ethics approval and consent to participate**

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

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15 **Conflict of interests**

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

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1 **Informed consent**

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

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1 **Abstract**

2 **Background:** The standard treatment for patients with clinical T1bN0M0 esophageal
3 squamous cell carcinoma is radical esophagectomy. Definitive chemoradiotherapy is regarded
4 as a treatment option, and recently, good clinical outcomes of this treatment have been reported.
5 This study compared prognosis after definitive chemoradiotherapy with radical esophagectomy.

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

11 **Results:** Among 68 patients, 39 patients underwent surgery and 29 patients received definitive
12 chemoradiotherapy. No significant difference was noted in overall survival between the two
13 groups. However, the rate of 5-year recurrence free survival was significantly lower in
14 definitive chemoradiotherapy group than that of surgery group (91.1% vs. 62.7%, Hazard ratio
15 3.976, 95% Confidence interval 1.076–14.696, $p = 0.039$). Patients who had local recurrence
16 after definitive chemoradiotherapy received endoscopic submucosal dissection or
17 photodynamic therapy as salvage therapies, and resulted in no disease progression and a good

1 prognosis.

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

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1 **Introduction**

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

8 According to the 2017 esophageal cancer practice guidelines in Japan and the National
9 Comprehensive Cancer Network (NCCN) guidelines, radical esophagectomy with regional
10 lymph node (LN) dissection is a standard treatment for patients with clinical T1bN0M0 ESCC
11 [5, 6, 7]. However, esophagectomy is a highly invasive procedure with a high risk of
12 postoperative complications [8]. Definitive chemoradiotherapy (dCRT) is a treatment option
13 when esophagectomy is contraindicated. Good clinical outcomes of dCRT for patients with
14 clinical stage I ESCC have been reported [9].

15 We hypothesized the efficacy of dCRT is equivalent to that of esophagectomy in patients
16 with clinical T1bN0M0 ESCC, and therefore, dCRT may become a promising alternative
17 treatment. In this study, the recurrence free survival (RFS) and overall survival (OS) after

1 dCRT were compared to those of esophagectomy.

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1 **Material and Methods**

2 **Patients**

3 From January 2011 to December 2019, 93 consecutive patients with clinical T1bN0M0
4 esophageal cancer were retrospectively investigated at Shizuoka Cancer Center. Smokers
5 included both current smokers and former smokers. Patients who regularly drink more than 14
6 grams of alcohol were defined as drinkers from National Institutes on Alcohol Abuse and
7 Alcoholism. All patients underwent esophagoduodenogastroscopy (EGD), computed
8 tomography (CT) from the neck to the pelvis, ultrasound evaluation of the neck and the
9 abdomen, and positron emission tomography (PET). Endoscopic ultrasound (EUS) was
10 performed to support the diagnosis of tumor invasion. Pathological findings were cited from
11 pathological report. Diagnosis of clinical and pathological stage was determined based on the
12 Union for International Cancer Control TNM classification of malignant tumors 8th edition
13 [10]. All procedures were conducted in accordance with institutional and national standards on
14 human experimentation, as confirmed by the Ethics Committee of Shizuoka Cancer Center,
15 and with the Declaration of Helsinki of 1964 and its subsequent versions. Informed consent
16 was obtained from all individual participants included in the study.

17 Patient eligibility for study enrolment was based on the following inclusion criteria: (1)

1 histologic diagnosis of ESCC by endoscopic biopsy; (2) Eastern Cooperative Oncology Group
2 (ECOG) performance status (PS) of 0 to 1; (3) primary lesion site in the thoracic esophagus;
3 (4) no prior chemotherapy or radiotherapy; (5) curative resection.

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

11

12 **Surgical procedure**

13 Surgical treatment consisted of subtotal esophagectomy with 2- or 3-field LN dissection
14 and reconstruction using gastric tube or pedicled jejunum with microvascular anastomosis. The
15 standard LN dissection comprised removal of mediastinal LNs with bilateral recurrent nerve
16 LNs and abdominal LNs, including the pericardial LNs and LNs along the lesser curvature and
17 left gastric artery in 2-field LN dissection (Supplementary Fig 1a, Online Resource 1). In

1 addition, bilateral supraclavicular LNs were also dissected in 3-field LN dissection
2 (Supplementary Fig 1b, Online Resource 1). In transthoracic approach, video-assisted
3 thoracoscopic surgery in the left decubitus position was generally performed. The abdominal
4 approach was typically laparotomy. Postoperative complications were categorized using the
5 Clavien–Dindo classification [11, 12].

6

7 **Definitive Chemoradiotherapy**

8 Chemoradiotherapy consisted of 70 mg/m² of cisplatin, 700 mg/m² of 5-FU, and
9 irradiation of 60Gy [9]. If cisplatin was not suitable because of insufficient renal function,
10 nedaplatin was used. Radiation was planned to deliver a total of 60 Gy / 30 Fr using a linear
11 accelerator with a 6-, 10-, or 18-MV photon beam. Before planning CT, metallic clips were
12 placed as markings on the cranial and the caudal margin of the lesion (Supplementary Fig 1c,
13 Online Resource 1). Tumor response was defined according to the Response Evaluation
14 Criteria in Solid Tumor guidelines v1.1 radiologically [13, 14]. Tumor regression grade was
15 classified by the Mandard's classification histologically [15]. Adverse events were evaluated
16 by Common Terminology Criteria for Adverse Events v5.0 [16].

17

1 **Follow-up**

2 Post-treatment follow-up was EGD and CT every 6 months for 5 years after
3 esophagectomy in surgery group. In dCRT group, post-treatment follow-up was EGD and CT
4 every 3 months for 1 year and every 4 months in the next 1 year. After 2 years, both EGD and
5 CT were performed every 6 months. According to the Japanese classification of esophageal
6 cancer, to confirm histologically, biopsy was performed another 2 times when clinical response
7 reached complete response (CR) by EGD [17]. Selective investigations such as cervical
8 ultrasound evaluation, magnetic resonance imaging, and PET were performed when recurrence
9 was suspected.

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

14 OS was calculated from initial treatment to death or until the end of study (May 31,
15 2020). RFS was defined as the date from initial treatment to the detection of recurrence by PET
16 or the end of study (May 31, 2020).

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1 **Statistical analysis**

2 All statistical analyses were conducted using SPSS software version 26.0 (IBM Corp.,
3 Armonk, NY, USA). Categorical data were analyzed using Fisher's exact test or the chi-squared
4 test as appropriate. Means and standard deviations were calculated, and differences were
5 identified using the *t* test. The Mann–Whitney U test was used in nonparametric analysis.
6 Survival outcomes were analyzed using the Kaplan–Meier method and log–rank tests.
7 Hazard ratio (HR) was calculated using Cox proportional hazards regression models. The
8 threshold for significance was $p < 0.05$.

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1 **Results**

2 **Patient characteristics**

3 Sixty-eight patients who enrolled in this study were stratified into 2 groups—39 patients
4 underwent surgery and 29 patients received dCRT—and compared (Fig. 1). In dCRT group, 4
5 patients did not tolerate surgery due to comorbidity; 2 patients had alcoholic-related liver
6 cirrhosis; 1 patient had a history of coronary artery bypass grafting; and 1 patient had low
7 pulmonary function. The median follow-up period was 49.6 (3.9–112.2) months in all patients,
8 44.9 (3.9–112.2) months in surgery group, and 50.2 (4.2–109.1) months in dCRT group.
9 Clinical characteristics such as age, gender, the population of smoker and drinker, ECOG PS,
10 comorbidities of diabetes mellitus, prior myocardial infarction, arrhythmia and chronic hepatitis,
11 history of gastrectomy and lung resection, renal and respiratory function were similar between
12 the two groups. Patients with chronic hepatitis tended to be more in dCRT group. Furthermore,
13 patients with alcoholic liver disorder also tended to be more in dCRT group (2.6% in surgery
14 group vs 17.6% in dCRT group, $p=0.076$), however, no patient had cirrhosis. There was also
15 no significant difference in tumor location, length, and invasion (Table 1).

16

17 **Treatment outcomes**

1 Clinical outcomes of surgery group were shown in Table 2. Subtotal esophagectomy
2 with 2-field LN dissection was performed for 12 patients (30.8%) and 27 patients (69.2%)
3 underwent 3-field LN dissection. At the point of the reconstruction, the gastric tube via the
4 retrosternal route was adopted in 36 patients (92.3%). Pedicled jejunum with microvascular
5 anastomosis via anterior sternal route was performed in 2 patients; 1 patient had a history of
6 distal gastrectomy due to gastric ulcer and another patient underwent composite resection of
7 the stomach. The other patient with immunosuppressive therapy for rheumatoid arthritis used
8 gastric conduit via anterior sternal route, considering a risk of anastomotic leakage.
9 Postoperative complications such as pneumonia, anastomotic leakage, and surgical site
10 infection of Clavien–Dindo grade II or higher and recurrent laryngeal nerve palsy of Clavien–
11 Dindo grade I or higher were observed in 17 (43.6%), 6 (15.4%), 7 (17.9%) and 4 patients
12 (10.3%), respectively. Median postoperative hospital stay was 14 (11–59) days. No instances
13 of 90-day mortality were observed. Pathologic findings showed 5 patients (12.8%) were T1a
14 (muscularis mucosa), 32 (82.1%) were T1b and 2 (5.1%) were T2. LN metastasis was found in
15 8 patients (20.5%). Of these patients, 7 received postoperative adjuvant chemotherapy by
16 intravenous infusion of 80 mg/m² of cisplatin and 800 mg/m² of 5-FU [18]. The other 1 patient
17 with LN metastasis at the left supraclavicular region received chemoradiotherapy consisted of

1 70 mg/m² of cisplatin, 700 mg/m² of 5-FU, and irradiation of 50.4Gy.

2 Clinical outcomes in dCRT group were shown in Table 3. Twenty-eight (96.6%)
3 patients completed two courses of chemotherapy and irradiation until 60 Gy. Only 1 patient
4 stopped receiving radiation by 58 Gy due to pneumonia. Adverse events were as follows:
5 leukopenia in 5 (17.2%), neutropenia in 5 (17.2%), thrombocytopenia in 2 (6.9%), esophagitis
6 in 5 (17.2%), and febrile neutropenia in 1 (3.4%). Twenty-seven patients (93.1%) achieved CR
7 after dCRT and 2 (6.9%) was stable disease. According to the Mandard's classification, 27
8 (93.1%) patients was classified as TRG1 (complete regression), and 2 (6.9%) was TRG 5
9 (tissue of tumor without changes of regression). The median duration until achieve CR was
10 121 days (42–485). No treatment related mortality of 90-day after initial treatment had occurred.

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

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

4

5 **Patient survival and disease recurrence**

6 There was no significant difference in OS between the two groups (Fig. 2a). The rate of
7 3-year OS was 92.9% in surgery group and 96.4% in dCRT group (HR 0.571, 95% Confidence
8 interval (CI) 0.052–6.299, $p = 0.65$) and the rate of 5-year OS was 92.9% in surgery group and
9 77.8% in dCRT group (HR 2.471, 95% CI 0.451–13.522, $p = 0.29$). The rate of 3-year RFS
10 was similar between the groups with 91.1% in surgery group and 78.7% in dCRT group (HR
11 2.59, 95% CI 0.647–10.363, $p = 0.18$). However, the rate of 5-year RFS was significantly lower
12 in dCRT group at 62.7% than that of surgery group at 91.1% (HR 3.976, 95% CI 1.076–14.696,
13 $p = 0.039$) (Fig. 2b). The causes of mortality were as follows; 1 patient had recurrence of the
14 primary tumor and 2 patients had pneumonia in surgery group. In dCRT group, the causes of
15 mortality were recurrence of the primary tumor in 1 patient and other malignancies in 3 patients.

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

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

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1 Discussion

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

8 The standard treatment for clinical T1bN0M0 ESCC is radical esophagectomy in Japan
9 [5, 6]. However, esophagectomy is associated with higher rates of postoperative complications,
10 such as pneumonia, anastomotic leakage and recurrent laryngeal nerve palsy [19]. We
11 previously reported the correlation between postoperative complications and poor long-term
12 survival [20]. However, minimal invasive esophagectomy is expected to reduce the degree of
13 surgical invasiveness and postoperative complications [21]. In addition, the progress of
14 perioperative care is reported as another cause of reduced mortality [22-24]. Therefore,
15 esophagectomy has become less invasive and the postoperative mortality rate at 90 days
16 decreased from 3.2% to 1.9% from 2011 to 2018 [8]. In this study, surgery provided excellent
17 OS, and this result confirmed the substantial status of radical esophagectomy as a standard

1 treatment for clinical T1bN0M0 ESCC.

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

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

6 In this study, salvage therapy for local recurrence led to the improvement of clinical
7 outcomes after dCRT. Makazu et al. reported no recurrence was detected after salvage
8 endoscopic resection for 54% of patients and the 5-year survival rate was 41.6% [28].
9 Regarding PDT, a multicenter phase II study reported that salvage PDT using talaporfin and a
10 diode laser showed an excellently high local CR rate (88.5%) for local failure after dCRT [29].
11 The results of this study suggested early detection of local recurrences by frequent follow-up
12 after dCRT enabled successful treatment by ESD or PDT, and ultimately, OS after dCRT could
13 be prolonged to be comparable to that achieved after esophagectomy.

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

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

10 The regimen of dCRT was controversial. In a parallel-group controlled trial (JCOG0502),
11 the regimen was consisted of 70 mg/m² of cisplatin, 700 mg/m² of 5-FU and irradiation of
12 60Gy, which showed excellent outcomes [27].

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

1 of LN metastasis with tumor in muscularis mucosa is equivalent to that of tumor in submucosa
2 ($> 200 \mu\text{m}$) [5, 6]. Previous reports suggested that EUS is useful for the accurate T staging
3 [33]. Furthermore, the NCCN guidelines state that endoscopic resections of small nodular
4 lesions can provide more accurate T staging than EUS [7]. For N staging, smoking impairs LN
5 assessment. Most patients enrolled in this study were smokers, complicating the diagnosis of
6 swollen LN. Fine-needle aspiration biopsy under EUS was reported more accurate than CT [7,
7 33]. Third, this study was inconclusive in indicating the equivalences between surgery and
8 dCRT because of the small number of enrolled patients. Moreover, the study design was
9 nonrandomized. However, to enforce a randomised study comparing therapeutic interventions
10 is difficult due to patient denial. The results of this study could have a certain clinical
11 significance. At last, some patients stopped follow-up (self-suspended) in both groups.

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

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1 **Figure legends**

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

3

4 Fig. 2 Kaplan–Meier curves of overall survival between surgery group and definitive
5 chemoradiotherapy (dCRT) group (a) and recurrence free survival between surgery group and
6 dCRT group (b). The threshold for significance was $p < 0.05$

7

8

Fig 1

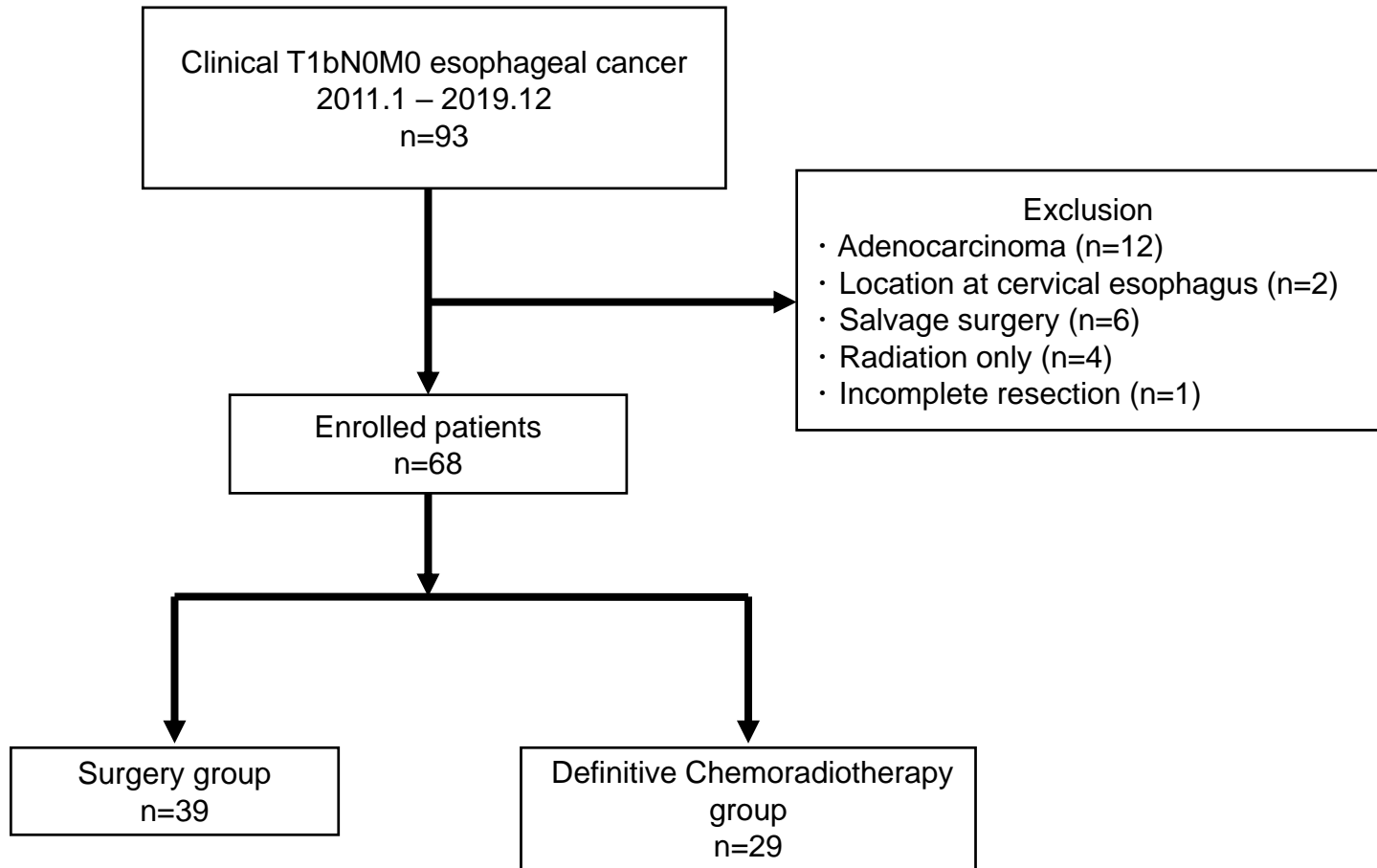
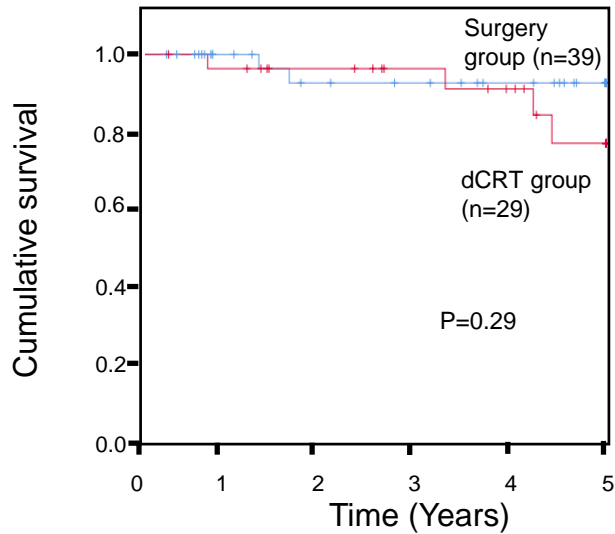


Fig 2

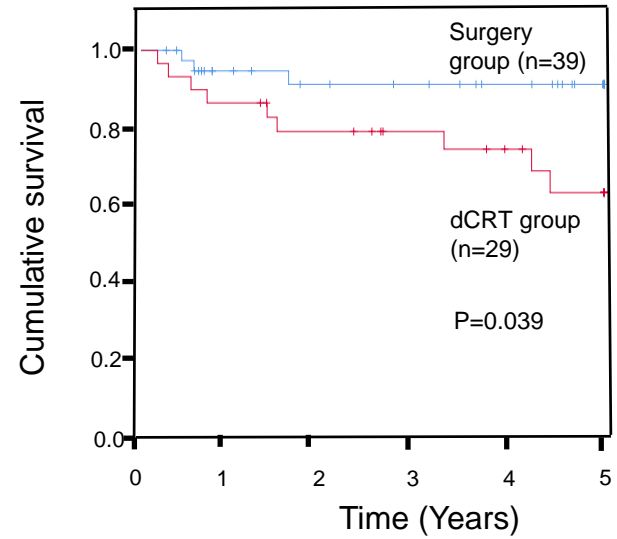
a Overall survival



Number at risk

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

b Recurrence free survival

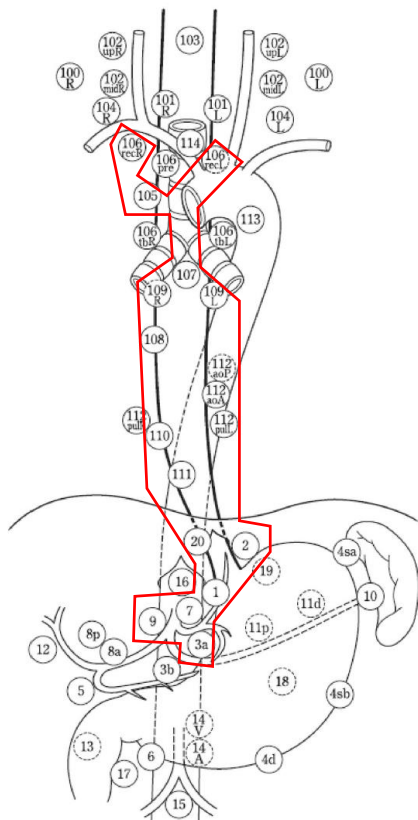


Number at risk

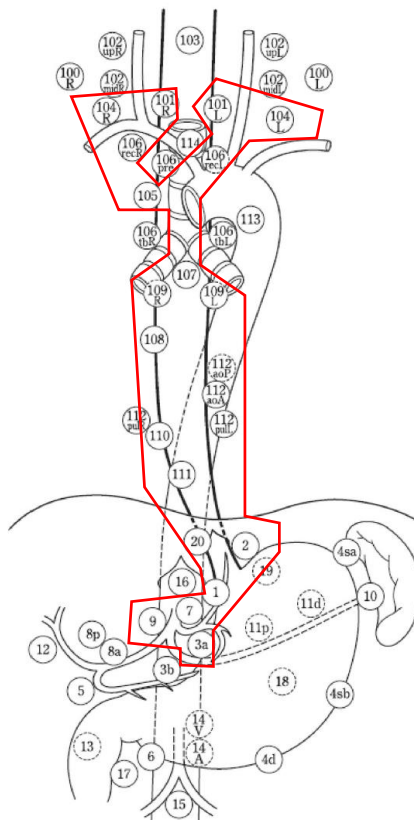
| | | | | | | |
|---------------|----|----|----|----|----|----|
| Surgery Group | 39 | 29 | 25 | 23 | 19 | 11 |
| dCRT group | 29 | 25 | 21 | 17 | 14 | 11 |

Online Resource 1

a



b



c

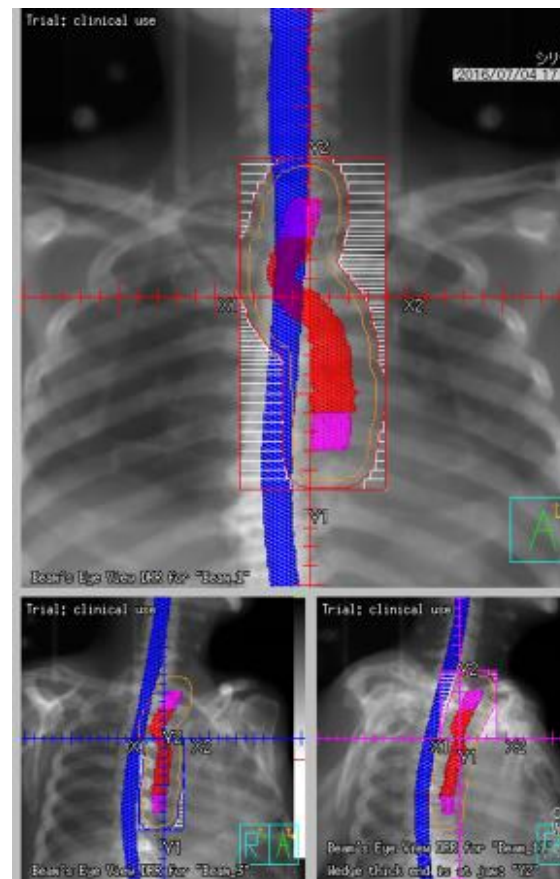


Table 1 Patient characteristics

| 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) |
| LN 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%) |
| LN 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 \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) |
| 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 \geq 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 \geq 6 months | 43 (63.2%) | 39 (100%) | 4 (13.8%) | <0.001 |

dCRT, definitive chemoradiotherapy; GERD, gastroesophageal reflux 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