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

Ryoma Haneda1,2 · Eisuke Booka1 · Kenjiro Ishii1 · Hirotoshi Kikuchi2 · Yoshihiro Hiramatsu2 · Kinji Kamiya2 · Hirofumi Ogawa3 · Hirofumi Yasui4 · Hiroya Takeuchi2 · Yasuhiro Tsubosa1

Accepted: 7 February 2021 / Published online: 23 February 2021
© Société Internationale de Chirurgie 2021

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, which 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.

Supplementary Information The online version of this article contains supplementary material available at https://doi.org/10.1007/s00268-021-06016-4

Eisuke Booka e.booka@scchr.jp

1 Division of Esophageal Surgery, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
2 Department of Surgery, Hamamatsu University School of Medicine, Shizuoka, Japan
3 Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, Japan
4 Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan
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 [5–7]. 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.

Materials 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 g 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 0–1; (3) primary lesion site in the thoracic esophagus; (4) no prior chemotherapy or radiotherapy; and (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 (two patients); incomplete resection (one patient); salvage surgery (six patients); and radiation therapy alone (four 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 two- or three-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 three-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/m² of cisplatin, 700 mg/m² of 5-FU, and irradiation of 60 Gy [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

Posttreatment follow-up was EGD and CT every 6 months for 5 years after esophagectomy in surgery group. In dCRT group, posttreatment 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 two 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 two groups—39 patients underwent surgery and 29 patients received dCRT—and compared (Fig. 1). In dCRT group, four patients did not tolerate surgery due to comorbidity; two patients had alcoholic-related liver cirrhosis; one patient had a history of coronary artery bypass grafting; and one 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 are shown in Table 2. Subtotal esophagectomy with two-field LN dissection was performed for 12 patients (30.8%), and 27 patients (69.2%) underwent three-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

| 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%)              | 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 Forced expiratory volume in 1 s; 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
performed in two patients; one 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%), seven (17.9%) and four patients (10.3%), respectively. Median postoperative hospital stay was 14 (11–59) days. No instances of 90-day mortality were observed. Pathologic findings showed five patients (12.8%) were T1a (muscularis mucosa), 32 (82.1%) were T1b and two (5.1%) were T2. LN metastasis was found in eight patients (20.5%). Of these patients, seven received postoperative adjuvant chemotherapy by intravenous infusion of 80 mg/m² of cisplatin and 800 mg/m² of 5-FU [18]. The other one patient with LN metastasis at the left supraclavicular region

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%)              |
| **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                   |
received chemoradiotherapy consisting of 70 mg/m² of cisplatin, 700 mg/m² of 5-FU and irradiation of 50.4 Gy.

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

Table 4 shows 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) (+ 0.5 vs. − 6.1 kg, 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: one patient had recurrence of the primary tumor and two patients had pneumonia in surgery group. In dCRT group, the causes of mortality were recurrence of the primary tumor in one patient and other malignancies in three patients.

Table 5 shows clinical strategies for patients with recurrence. In surgery group, one patient received chemotherapy consisting 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 two, four and three patients, respectively. Two patients with local recurrences underwent salvage therapies; one 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, one received six 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 four patients (Patient Nos. 5, 6, 8 and 9). The LN recurrences were outside the radiation field in all four patients. The recurrence of distal organ was found in middle- and lower-thoracic ESCC. The LN recurrence for one patient occurred > 5 years after the initial therapy at the left paracardial region (Patient No. 8).

**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.
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 are 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...
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 [5–7]. 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 vs. 85.5%, 5-year RFS; 81.7 vs. 71.6%) [27].

In this study, salvage therapy for local recurrence led to the improvement in 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 multi-center 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 three regions [30]. However, in this study, patients with upper-thoracic ESCC showed no recurrence at middle mediastinal LN. In upper-thoracic ESCC, the irradiation 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, one 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 consisted of 70 mg/m² of cisplatin, 700 mg/m² of 5-FU and irradiation of 60 Gy, 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 was inadequate. The rate of LN metastasis with tumor in muscularis mucosa is equivalent to that of tumor in submucosa (> 200 μm) [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 randomized 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.

Acknowledgements The authors thank Kohei Takizawa and Yohei Yabuuchi of Division of Endoscopy, Shizuoka Cancer Center, with respect to endoscopic diagnosis. And the authors also thank Keita Mori, Takanori Kawabata and Akifumi Nozu of Division of Clinical Research Support Center, Shizuoka Cancer Center, for assisting in statistical analysis.

Declarations

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

Ethical approval 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 the Declaration of Helsinki of 1964 and its subsequent versions.

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

References

1. Torre LA, Bray F, Siegel RL et al (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108
2. Matsuda S, Takeuchi H, Kawakubo H et al (2016) Current advancement in multidisciplinary treatment for resectable cStage II/III esophageal squamous cell carcinoma in Japan. Ann Thorac Cariovasc Surg 22:275–283
3. Shapiro J, van Lanschot JJB, Hulshof MCCM et al (2015) Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 16:1090–1098
4. Ando N, Ozawa S, Kitagawa Y et al (2000) Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg 232:225–232
5. Kitagawa Y, Uno T, Oyama T et al (2019) Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 1. Esophagus 16:1–24
6. Kitagawa Y, Uno T, Oyama T et al (2019) Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus 16:25–43
7. Farjahl F, Gerdes H, Gibson M, et al (2018) NCCN guidelines version 2. Esophageal and esophagogastric junction cancers NCCN evidence block/EM. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal_blocks.pdf.
8. Kakeji Y, Takahashi A, Hasegawa H et al (2020) Surgical outcomes in gastroenterological surgery in Japan: report of the National clinical database 2011–2018. Ann Gastroenterol Surg 4:250–274
9. Kato H, Sato A, Fukuda H et al (2009) A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan clinical oncology group study (JCOG9708). Jpn J Clin Oncol 39:638–643
10. Brierley JD, Gospodorowicz MK, Witterkind C (2017) TNM classification of malignant tumors, 8th edn. Wiley, Oxford, UK, pp 59–62
11. Clavien PA, Barkun J, de Oliveira ML et al (2009) The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 250:187–196
12. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
13. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Nat Cancer Inst 92:205–216
14. Eisenhauer E, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
15. Mandard AM, Dalibard F, Mandard JC et al (1994) Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Cancer 73:2680–2686
16. National Cancer Institute. Cancer therapy evaluation program, common toxicity criteria. Version 5.0 National Cancer Institute; 2017. Last updated 27 March, 2020. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
17. The Japan Esophageal Society (2015) Japanese classification of esophageal cancer, 11th edn. Kanehara, Japan, pp 114–123
18. Ando N, Kato H, Igaki H et al (2012) A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 19:68–74
19. Takeuchi H, Miyata H, Gotoh M et al (2014) A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg 260:259–266
20. Booka E, Takeuchi H, Suda K et al (2018) Meta-analysis of the impact of postoperative complications on survival after oesophagectomy for cancer. BJNS Open 2:276–284
21. Takeuchi H, Miyata H, Ozawa S et al (2017) Comparison of short-term outcomes between open and minimally invasive esophagectomy for esophageal cancer using a nationwide database in Japan. Ann Surg Oncol 24:1821–1827
22. Watanabe M, Okamura A, Tihata T et al (2018) Recent progress in perioperative management of patients undergoing esophagectomy for esophageal cancer. Esophagus 15:160–164
23. Steenhagen E, van Vulpen JK, van Hillegersberg R et al (2017) Nutrition in peri-operative esophageal cancer treatment. Expert Rev Gastroenterol Hepatol 11:663–672
24. Bolger JC, Loughney L, Tully R et al (2019) Perioperative preparation and rehabilitation in esophageogastric malignancies: a systematic review. Dis Esophagus 32:1–11
25. Motoori M, Yano M, Ishihara R et al (2012) Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. Ann Surg Oncol 19:2135–2141
26. Semenkovich TR, Hudson JL, Subramanian M et al (2019) Trends in treatment of T1N0 esophageal cancer. Ann Surg 270:434–443
27. Kato K, Igaki H, Nozaki I et al (2019) Parallel-group controlled trial of esophagectomy versus chemoradiotherapy in patients with clinical stage I esophageal carcinoma (JCOG0502). J Clin Oncol 37:7–7
28. Makazu M, Kato K, Takisawa H et al (2014) Feasibility of salvage photodynamic therapy using talaporfin sodium (ME2906) and diode laser (PNL6405EPG) for local failure after...
chemoradiotherapy or radiotherapy for esophageal cancer. Oncotarget 8:22135–22144
30. Akutsu Y, Kato K, Igaki H et al (2016) The prevalence of overall and initial lymph node metastasis in clinical T1N0 thoracic esophageal cancer: From the results of JCOG0502, a prospective multicenter study. Ann Surg 264:1009–1015
31. Lavin VJ, Mehta S, Sumra P et al (2018) Experience of definitive chemoradiation for oesophageal cancer within a large regional cancer treatment centre: improving outcomes and tolerability. Clin Oncol 30:650–657
32. Smit JK, Muijs CT, Burgerhof JG et al (2013) Survival after definitive (chemo) radiotherapy in esophageal cancer patients: a population-based study in the north-east Netherlands. Ann Surg Oncol 20:1985–1992
33. Choi J, Kim SG, Kim JS et al (2010) Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc 24:1380–1386

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.