Long-term outcomes of an esophagus-preserving chemoradiotherapy strategy for patients with endoscopically unresectable stage I thoracic esophageal squamous cell carcinoma

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ABSTRACT

Background and purpose: To assess the long-term outcomes of a multimodal approach for maximum esophagus preservation in operable patients with endoscopically unresectable stage I thoracic esophageal squamous cell carcinoma (ESCC).

Materials and methods: The medical records of patients with stage I thoracic ESCC treated with our protocol between 1992 and 2005 were retrospectively reviewed. Our protocol consisted of neoadjuvant concurrent chemoradiotherapy, followed by either additional definitive chemoradiotherapy for good responders (CRT group) or surgery for moderate or poor responders (CRT-S group) after an interim appraisal.

Results: A total of 51 patients were analysed. The median age of the patients was 67 years. The median follow-up period was 124.8 months. After the interim assessment, 49 and 2 cases were assigned to the CRT and CRT-S groups, respectively. In the intent-to-treat analyses, overall survival (OS), disease-free survival (DFS), cumulative incidence for death from esophageal cancer, and that for loss of esophageal function were 78.9%, 53.5%, 10.5%, and 20.4% at 5 years, and 55.2%, 27.8%, 18.2%, and 22.9% at 10 years, respectively. Grade 3 late toxicities occurred with the following incidences: esophageal stenosis in 1 case, esophageal ulcer in 1 case, and pericardial effusion in 2 cases. No grade 4 or higher toxicities were observed.

Conclusion: Long-term survival and esophagus preservation outcomes were favorable, with acceptable toxicities. Our results suggest that CCRT is an alternative treatment for majority of operable patients with endoscopically unresectable stage I thoracic ESCC in combination with salvage therapy.

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Introduction

Recently, the detection rates for early stage esophageal cancer have increased as endoscopic technologies for cancer screening have improved [1,2]. Superficial esophageal cancer is potentially curable by endoscopic resection (ER) unless it reaches the muscularis mucosae (m3) and submucosa (sm) because subsequent lymph node recurrence occurs in 18% and 50% of patients with m3 and sm diseases, respectively [3]. Therefore, surgery has been the mainstay of curative management for endoscopically unresectable early stage esophageal cancer.

Patients with early stage esophageal squamous cell carcinoma (ESCC) are generally treated with esophagectomy and prophylactic two- or three-field lymphadenectomy [4–6]. Recently, some studies have reported that survival outcomes of concurrent chemoradiotherapy (CCRT) for stages I–II ESCC do not appear to differ significantly from those of surgery [7,8]. Therefore, CCRT has been considered an alternative treatment for early stage ESCC to maintain quality of life.

In 1991, we initiated a multimodal approach aimed at maximum esophagus preservation in operable patients with endoscopically unresectable thoracic ESCC. We previously reported early results of our approach, indicating that most patients with early stage ESCC could maintain esophageal integrity with our protocol with favorable overall survival (OS) rates [9–11]. However, long-term follow-up is necessary to assess the outcomes of definitive CCRT because recurrences or late toxicities may arise even after 5 years. There have been few reports on the long-term outcomes of early stage ESCC patients treated with CCRT based on a uniform treatment policy, although there have been several reports on patients with advanced-stage ESCC or those treated with esophagectomy [5,12–16]. Therefore, this study assessed the long-term outcomes of the proposed approach.

Methods

Informed consent and ethical approval

Prior to treatment initiation, surgeons and radiation oncologists explained to each patient the purpose, procedure, risks of our protocol, and the alternative treatment such as surgery without neoadjuvant therapy and definitive CCRT. The patients provided signed informed consent. This retrospective analysis was approved in August 2017 by the Institutional Ethical Review Board of Tenri Hospital (No:848).

Patients

We retrospectively reviewed the medical records of all patients treated with our protocol for newly diagnosed stage I thoracic ESCC between January 1992 and December 2005 at our institution. The eligibility criteria were as follows: histologically proven thoracic ESCC, clinical stage I (cT1N0M0) classified by the 6th edition of the Union for International Cancer Control, Eastern Cooperative Oncology Group performance status score of 0–2, sufficient renal (i.e., serum creatinine ≤1.5 mg/dL, and creatinine clearance ≥60 mL/min), and liver (total bilirubin ≤1.5 mg/dL, glutamate oxaloacetate transaminase and glutamate pyruvate transaminase ≤2 times the upper limit of normal) functions allowing definitive CCRT or surgery, and no synchronous or metachronous cancers within the previous five years other than non-melanoma skin cancer. Patients with previous malignancies were eligible if there was no evidence of recurrence for >5 years from diagnosis. Patients with multiple esophageal carcinomas were included. The staging procedures were conducted based on the findings of a barium study, esophagoscopy with Lugol staining, endoscopic ultrasonography (US), cervical US, computed tomography (CT) scans, and radionuclide bone scanning.

Overview of the Tenri protocol

A schematic of our protocol is shown in Fig. 1. The details of the protocol have been described previously [9–11]. Operable patients with stage I ESCC were initially treated with neoadjuvant CCRT followed by interim appraisal. Based on the assessment, good responders (CRT group) were treated with additional definitive CCRT, followed by high-dose-rate intraluminal brachytherapy (HDRIBT), in consideration of the aggressiveness of the disease. On the other hand, moderate or poor responders (CRT-S group) were treated with surgery in combination with intraoperative radiotherapy for abdominal nodes and postoperative radiotherapy to the supraclavicular fossa if patients did not receive initial radiotherapy.

NA-CCRT

External-beam radiation therapy (EBRT) consisted of a dose of 44 Gy, at 1.1 Gy per twice-daily fraction. The initial field included both the Lugol-unstained area near the primary tumor and the regional lymph node areas. The field generally included the supraclavicular fossa for upper thoracic tumors. Concurrent chemotherapy consisted of cisplatin 60 mg/m^2 as a bolus injection on day 1, and 5-fluorouracil 400 mg/m^2 as a continuous infusion on days 1–4, which was repeated every 3 weeks.

Interim appraisal

Immediately after completion of NA-CCRT, an interim response assessment was conducted based on the following examinations: appearance of any new lesions or metastasis evaluated based on barium study, esophagoscopy, cervical US, and CT scans. The tumor regression rate was calculated using the two greatest perpendicular diameters evident on endoscopic US and a barium swallow. Patients were assigned to good responders (CRT group) or moderate or poor responders (CRT-S group) according to whether evidence of a 75% superior Regression rate was identified or not.

CRT group

In the CRT group, EBRT was restarted within an approximate 2-week rest period and continued with an additional course of chemotherapy. HDRIBT was added after EBRT, although its indication was determined by the physician's judgment in consideration of the aggressiveness of the disease in each case. The HDRIBT was performed with a dose of 3.5–5.5 Gy per fraction, 5 mm below the surface of the esophageal mucosa, and repeated weekly up to 2–3 times.

CRT-S group

In the CRT-S group, surgery was performed 2–3 weeks after the completion of NA-CCRT. It comprised a standard right thoracic esophagectomy, three-field node dissection (including supraclavicular, mediastinal, and abdominal node areas), and reconstruction via the presternal route through the stomach or colon. Intraoperative radiotherapy for abdominal node areas with a single dose of 20–23 Gy, prescribed to the 90% isodose, was planned to prevent regional recurrence. Postoperative radiotherapy to the supraclavicular fossa up to a total dose of 45–50 Gy in conventional fractions was basically delivered if the region was not irradiated in the initial treatment.

Follow-up and assessment

Symptoms and toxicities were assessed at least once per week during treatment. Response assessment was conducted every 3–4 months based on chest X-rays, esophagoscopy, and a barium study. CT scans, as well as cervical and abdominal US, were performed every 6 months or when recurrence was suspected. If recurrence was detected in the CRT group,
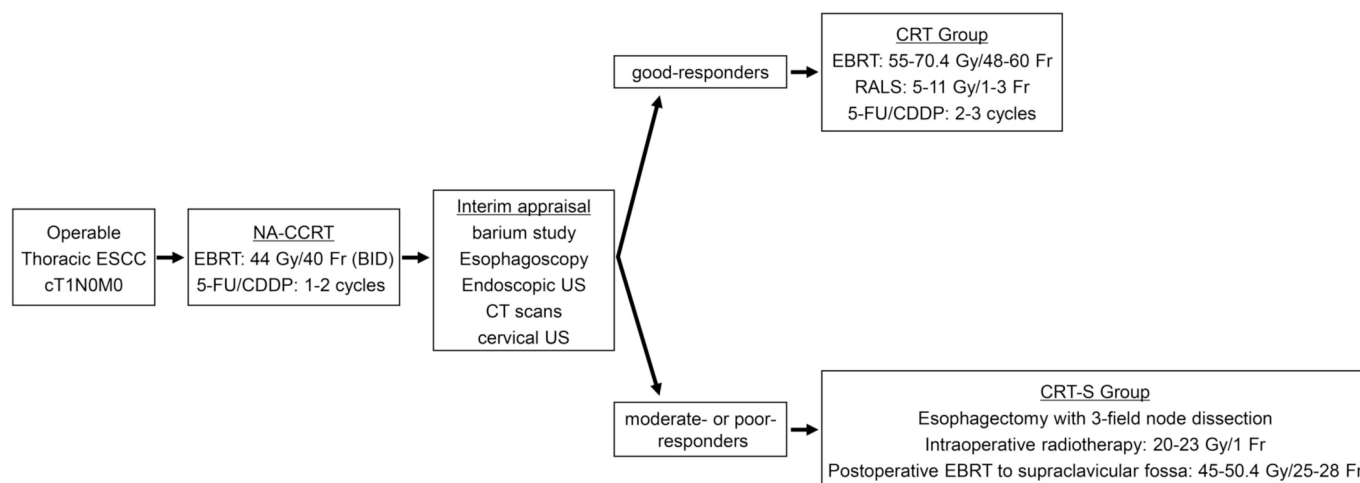
Fig. 1. Details of the Tenri protocol *abbreviations*: BID: twice a day.

salvage treatments such as ER or esophagectomy were planned after restaging.

Statistical analyses

Data were analysed using an intent-to-treat approach, not per-protocol approach, regardless of eligibility for treatment. The Kaplan–Meier method was used to estimate the follow-up period, OS rate and disease-free survival (DFS) rate. Competing risk analysis was used to estimate the cumulative incidence for death from esophageal cancer and that for loss of esophageal function. Local recurrence was defined as any detectable local disease at follow-up in the initial irradiation field (in-field local recurrence). Metachronous esophageal cancer was defined as histologically proven ESCC outside the field. The occurrence of each event was calculated from the initiation of EBRT to the date of onset of the clinical event or the last follow-up. The clinical event for OS was death from any cause. The clinical event for DFS was the earliest recurrence or death from any cause. As for the cumulative incidence of death from esophageal cancer, death from other diseases was set as a competing event, and patients lost to follow-up or survival were censored. For the cumulative incidence of loss of esophageal function, esophageal resection or loss of esophageal function (i.e., due to locoregional recurrence or late toxicity) was counted as the event, death from other causes with preserved esophageal functions was set as a competing event, and patients lost to follow-up or survival without the event were censored.

We evaluated acute and late toxicities due to CCRT based on the Common Terminology Criteria for Adverse Events version 4.0. Acute toxicity was defined as events within 3 months after completion of the protocol treatments, and late toxicity was defined as events occurring at any point thereafter.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.5–1) (The R Foundation for Statistical Computing, Vienna, Austria) [17].

Results

Patient characteristics

Medical records of 85 patients with endoscopically unresectable stage I thoracic ESCC were retrospectively reviewed. Of those, 16 medically inoperable patients and 3 patients who refused our protocol were excluded. Of 66 patients treated using our protocol, 15 patients with a history of other synchronous or metachronous cancers within the

previous five years were excluded from the analyses. The remaining 51 patients were enrolled in this study. Patients' flow diagram and the characteristics of the 51 eligible patients are shown in Fig. 2 and Table 1.

Among them, we identified 46 patients as good responders and 5 patients as moderate or poor responders based on interim appraisal. Three patients of the moderate or poor responder group underwent definitive CCRT in compliance with each patient's wishes. Subsequently, 49 and 2 cases were assigned to the CRT and CRT-S groups, respectively (Fig. 3).

Treatments

All patients received NA-CCRT, which consisted of EBRT with a dose of 44 Gy and at least one cycle of concurrent chemotherapy. In the CRT group, the median EBRT dose was 59.4 Gy (range, 55–66 Gy). HDRIBT was performed in 40 patients, up to a median dose of 10.5 Gy (range, 5–11 Gy in 1–3 fractions). In the CRT-S group, all patients were scheduled to undergo curative surgery and intraoperative radiotherapy, although one patient avoided intraoperative radiotherapy because of intraoperative bleeding. They did not receive postoperative irradiation for the following reasons. One with upper thoracic esophageal cancer had already received preoperative irradiation to the supraclavicular fossa. The other patient developed an anastomotic leakage.

Functional and oncological outcomes

The median follow-up period was 124.8 months (95% CI, 94.8–133.2). Twenty-one patients died during the follow-up period. The causes of death were esophageal cancer, secondary malignancies, heart disease, pneumonia, and unknown reason in 9, 8, 2, 1, and 1, respectively. Among the remaining 30 surviving patients, 6 patients were lost to follow-up within 5 years. In the intent-to-treat analyses, the 5- and 10-year the OS rates were 78.9% (95% confidence interval [CI], 64.4–88.1) and 55.2% (95% CI, 38.6–69.0), respectively (Fig. 4A). The cumulative incidence of death from esophageal cancer was 10.5% (95% CI, 3.8–21.2) and 18.2% (95% CI, 8.3–31.0) at 5 and 10 years, respectively (Fig. 4B). The patterns of the first failures are listed in Table 2. Among 26 recurrences, in-field local recurrences were observed in 19 cases, and the time to these recurrences is listed in Table 3. No metachronous esophageal cancer was observed. The 5- and 10-year DFS rates were 53.5% (95% CI, 38.7–66.2) and 27.8% (95% CI, 14.7–42.7), respectively (Fig. 4C). Loss of esophageal function was observed in 12 cases; 2 cases of planned esophagectomy (CRT-S group); 9 cases of salvage esophagectomy for endoscopically unresectable in-field local recurrence (T1, in 6 cases; T3, in 1 case; unknown size, in 2 cases); and 1 case of loss of
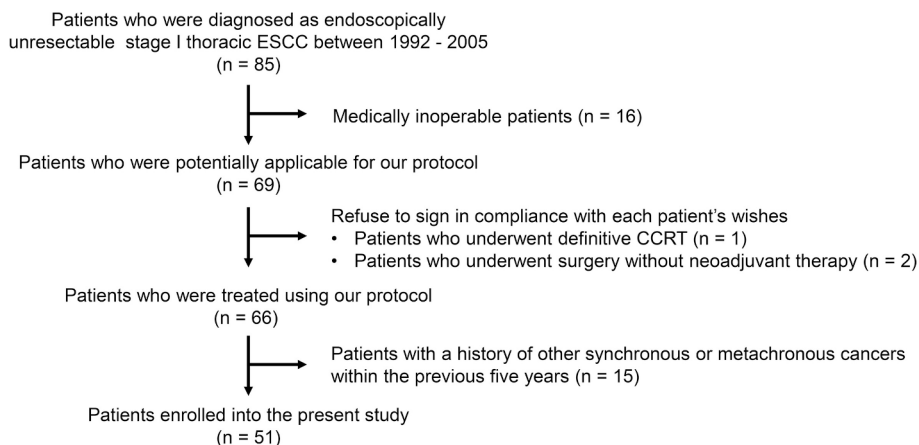
Patients who were diagnosed as endoscopically
unresectable stage I thoracic ESCC between 1992 - 2005
(n = 85)

→ Medically inoperable patients (n = 16)

Patients who were potentially applicable for our protocol
(n = 69)

→ Refuse to sign in compliance with each patient's wishes
• Patients who underwent definitive CCRT (n = 1)
• Patients who underwent surgery without neoadjuvant therapy (n = 2)

Patients who were treated using our protocol
(n = 66)

→ Patients with a history of other synchronous or metachronous cancers
within the previous five years (n = 15)

Patients enrolled into the present study
(n = 51)

Fig. 2. Patients' flow diagram.

Table 1
Patient characteristics (N = 51).

Age (years)	
Median	67
Range	48–81
Gender	
Male	41
Female	10
ECOG performance status	
0	45
1	4
2	2
Tumor location	
Upper	5
Middle	28
Lower	18
T factor	
T1a	16
T1b	35
Multiple lesions	
Yes	2
No	49
Date of enrollment	
1992–1996	10
1997–2001	16
2002–2005	25

Data are presented as number of patients (%). *Abbreviations*:
ECOG, Eastern Cooperative Oncology Group.

esophageal function caused by pharyngeal cancer, not by late toxicity, which was observed more than 10 years after treatment initiation. The cumulative incidence for loss of esophageal function was 20.4% (95% CI, 10.4–32.8) and 22.9% (95% CI, 12.1–35.8) at 5 and 10 years, respectively (Fig. 4D).

Toxicity and feasibility

The incidence of grade 3 or higher adverse events is listed in Table 4. The most common acute toxicity was leukopenia, which was observed in 13 patients. Late toxicities such as esophageal stenosis, esophageal ulcer, and pericardial effusion were observed in 1, 1, and 2 patient, respectively. No grade 4 or higher toxicities were observed. No severe adverse events were observed in patients who received a second round of EBRT for recurrence disease. One patient in the CRT-S group required reconstruction due to anastomotic leakage during the perioperative period. Of the 9 patients who received salvage surgery for locoregional recurrence, 2 required reconstruction surgery due to anastomotic stenosis, although the details of the postoperative complication in one patient remains unknown as it took place at another hospital. No fatal complications related to surgery were observed.

Discussion

In the present study, we demonstrated favorable survival outcomes, with adequate esophagus preservation and acceptable late toxicity, of
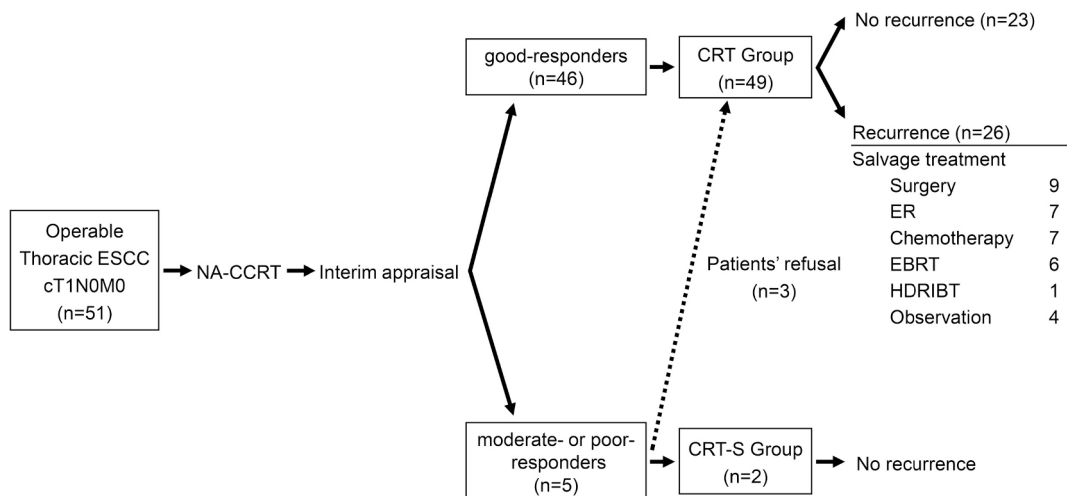
good-responders
(n=46)

CRT Group
(n=49)

→ No recurrence (n=23)

Recurrence (n=26)
Salvage treatment
Surgery	9
ER	7
Chemotherapy	7
EBRT	6
HDRIBT	1
Observation	4

Operable
Thoracic ESCC
cT1N0M0
(n=51)

→ NA-CCRT → Interim appraisal

Patients' refusal
(n=3)

moderate- or poor-
responders
(n=5)

→ CRT-S Group
(n=2)

→ No recurrence

Fig. 3. Information about patients treated according to the Tenri protocol.
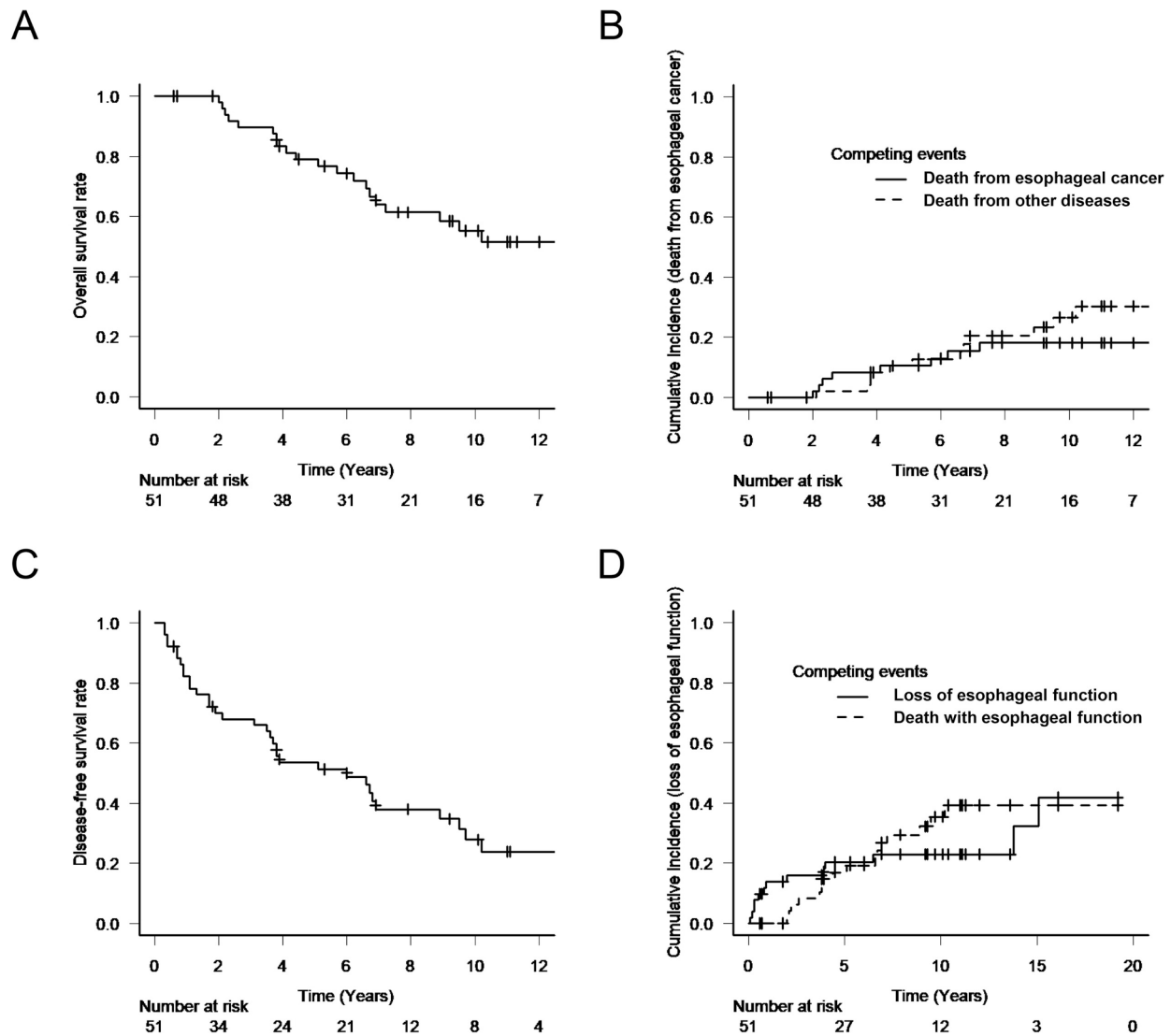
A

B

C

D

Fig. 4. (A) Overall survival rate, (B) cumulative incidence for death from esophageal cancer and from other diseases, (C) disease-free survival rate, and (D) cumulative incidence for loss of esophageal function for endoscopically unresectable stage I ESCC.

Table 2
Patterns of first failure (*N* = 26).

Site	n (%)
Local	19 (73)
Regional	2 (8)
Distant	3 (12)
Local/Regional	1 (4)
Local/Distant	1 (4)

Data are presented as number of patients (%).

Table 3
Time to in-field local recurrence after treatment initiation (N = 19).

Time	
~2 year	9
2–5 year	4
5–year	6

Table 4
Acute and late toxicities of Grade 3 or higher.

Toxicity	G3	G4
Acute		
Leukopenia	13	0
Anemia	2	0
Thrombocytopenia	0	0
Dysphagia	2	0
Late		
Esophageal stenosis	1	0
Esophageal ulcer	1	0
Pericardial effusion	2	0
Pleural effusion	0	0
Radiation pneumonitis	0	0

our multimodal approach for operable patients with stage I ESCC. Majority of the patients were treated with definitive CCRT based on the interim appraisal, and to the best of our knowledge, this is the first report of CCRT for operable stage I ESCC with a long-term follow-up period (median: 10–years).

In our study, the 5- and 10-year OS rates for patients with a median age of 67 years were 78.9% and 55.2%, respectively. A recent study reported that the 10-year OS rate of radiotherapy plus daily-low-dose

chemotherapy for stage I ESCC was around 60% [18]. This result appeared to be comparable to our study. It has been reported that the 5- and 10-year OS rates of esophagectomy for stage I esophageal cancer were 77–78%, and 62–70%, respectively [5,6,14–16]. Tanaka *et al.* reported that the 5- and 10-year OS rates of esophagectomy for stage I ESCC patients with a median age of 63 years were 77% and 62%, respectively [16]. Overall, the OS rates of CCRT do not appear to be markedly inferior to those of surgery, although direct comparisons are difficult.

Late recurrence after definitive CCRT for ESCC is an important issue to be resolved [7,12,19,20]. In our study, half of the patients developed recurrent disease during the follow-up period, and more than 70% of the recurrences were in-field local recurrences. Previous studies reported that the recurrence rate after esophagectomy for stage I ESCC was 18–28% during a median follow-up period of 79–108 months for survivors [5,16]. Our recurrence rate was higher than that of esophagectomy; however, "the local recurrence" rate may be overestimated because our definition of in-field local recurrence potentially included in-field metachronous esophageal cancer. Although two patients with synchronous multiple esophageal cancers were included in our study, it was difficult to evaluate the impacts of the multiple lesions on the treatment outcomes. Therefore, this issue needs to be addressed in the future. Nevertheless, we achieved satisfactorily high OS and esophagus preservation rates regardless of unfavorable DFS rates. This was presumably due to our continuous and careful observation after CCRT, which allowed appropriate intervention of salvage treatment for recurrent cases. In fact, nearly half of the in-field local recurrences were minor recurrences that were successfully salvaged without esophagectomy. Recently, photodynamic therapy has been shown to be a novel local treatment that can be applied to deeper residues after CCRT with an acceptable safety margin. In a phase II study, Yano *et al.* reported that patients with T1b or T2 residue after CCRT could be successfully salvaged by photodynamic therapy with a local complete response rate of 88.5% [21]. In our study, at least 6 patients experienced superficial recurrence. Provided that they had been salvaged by photodynamic therapy, the esophagus preservation rate in our study would have been higher.

Accelerated repopulation is commonly recognized as the main reason for poor local control when the overall treatment time is prolonged [22,23]. In our study, the accelerated repopulation of tumor cells during 1–2 weeks of treatment interruption for interim appraisal may cause local recurrence after radiotherapy. Hence, we had better reconsider the criteria of interim appraisal and shortened the treatment interruption to overcome accelerated repopulation. Recent reports have shown that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is useful for response assessment after neoadjuvant therapy for ESCC patients [24,25]. We expect FDG-PET to be validated for response assessment in addition to anatomic approaches such as endoscopic US and CT scans.

Although definitive CCRT is superior to surgery in terms of esophageal preservation, late toxicities should be considered [26–28]. According to the clinical trials investigating the effect of radiation dose escalation, such as the Radiation Therapy Oncology Group (RTOG) trial 94-05 and the ARTDECO Study, a higher irradiation dose of 61.6–64.8 Gy was not advantageous for survival outcomes, probably because of the low tolerability against the toxicities [4,29]. RTOG 9207 reported a high incidence of esophageal fistulas after brachytherapy combined with CCRT [30]. These studies suggested that the esophagus is a major dose-limiting organ. However, in our study, grade 3 or higher esophageal stenosis and ulcer were observed only in one case, and other toxicities were also acceptable compared with other CCRT studies for esophageal carcinoma [7,31]. The low incidence of severe toxicities in our study might be due to the use of the hyperfractionation technique to reduce the damage to the heart and mediastinum, and a lower dose of chemotherapy than that in recent studies.

This study had several limitations. First, as it was a single-institutional retrospective study with a small number of patients, our experience cannot be directly compared to prospective studies. Second, as diagnostic modalities such as FDG-PET were not performed for staging, the clinical outcomes may have been underestimated due to the potential metastases. Third, since the approach of our protocol was different from the modern standard treatment (*e.g.*, HDRIBT and the lower dose of chemotherapy in our protocol), it may impact on the outcomes of our study [32]. Owing to these limitations, our findings cannot provide definitive conclusions. Nevertheless, our results were based on long-term follow-up data under a predetermined uniform treatment protocol. Therefore, we believe that our results provide baseline data for CCRT in combination with salvage therapy for endoscopically unresectable but operable stage I thoracic ESCC, which indicates the usefulness of CCRT as an alternative treatment to surgical resection. Recently, a phase II trial of combined treatment of ER and CCRT for stage I ESCC [Japan Clinical Oncology Group (JCOG) trial 0508] has been completed [33]. In 2019 Gastrointestinal Cancers Symposium, JCOG 0502 provided early reports that the 5-year OS rates of CCRT for endoscopically unresectable cT1bN0M0 ESCC were noninferior to those of esophagectomy [85.5% (95% CI, 78.9–90.1) in CRT arm vs 86.5% (95% CI, 81.0–90.5) in surgery arm] [34]. We hope that these studies will clarify the therapeutic uses of CCRT for esophagus preservation in patients with stage I ESCC and confirm our findings.

Conclusions

Our long-term survival and esophagus preservation outcomes were considered favorable, with acceptable toxicities. Our results suggest that CCRT is an alternative treatment for the majority of operable patients with endoscopically unresectable stage I thoracic ESCC in combination with salvage therapy.

Sources of support

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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