



# Treatment outcomes of extended-field radiation therapy for thoracic superficial esophageal cancer

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**Purpose:** To evaluate the efficacy and safety of extended-field radiation therapy for patients with thoracic superficial esophageal cancer (SEC).

**Materials and Methods:** From May 2007 to October 2016, a total of 24 patients with thoracic SEC (T1a and T1b) who underwent definitive radiotherapy and were analyzed retrospectively. The median total radiotherapy dose was 64 Gy (range, 54 to 66 Gy) in conventional fractionation. All 24 patients received radiotherapy to whole thoracic esophagus and 23 patients received elective nodal irradiation. The supraclavicular lymph nodes, the celiac lymph nodes, and both of those nodal areas were included in 11, 3, and 9 patients, respectively.

**Results:** The median follow-up duration was 28.7 months (range 7.9 to 108.0 months). The 3-year overall survival, local control, and progression-free survival rates were 95.2%, 89.7%, and 78.7%, respectively. There were 5 patients (20.8%) with progression of disease, 2 local failures (8.3%) and 3 (12.5%) regional failures. Three patients also experienced distant metastasis and had died of disease progression. There were no treatment-related toxicities of grade 3 or higher.

**Conclusion:** Definitive extended-field radiotherapy for thoracic SEC showed durable disease control rates in medically inoperable and endoscopically unfit patients. Even extended-field radiotherapy with elective nodal irradiation was safe without grade 3 or 4 toxicities.

**Keywords:** Esophageal neoplasms, Radiotherapy, Endoscopic mucosal resection

## Introduction

Esophageal cancer is the 8th most common cancer worldwide and the 6th most common cause of cancer-related death worldwide [1]. The detection rate of superficial esophageal cancer (SEC), which is defined as a tumor limited to the mucosa or submucosa, has been increasing by the widespread endoscopic screening and the development of new endoscopic

techniques [2-4]. Recently, endoscopic resection is recognized as a possible curative option for SEC confined within the mucosal epithelium or the lamina propria mucosa (T1a) [5,6], however, submucosal tumors (T1b) or large mucosal tumors are considered to be not suitable for endoscopic resection. In addition, pT1 esophageal cancer is frequently accompanied with a lymph node metastasis with 5-year metastasis rate of 5.7% (0.4%–8.7% for T1a and 25.7% for T1b) [7]. As a

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result, esophagectomy with lymph node dissection has been considered as the standard treatment for SEC, however, esophagectomy is highly invasive and accompanied with increased morbidity and mortality rates [8,9].

Instead of surgery, concurrent chemoradiotherapy (CCRT) or radiotherapy alone can be an alternative option. Several studies have reported favorable outcomes of CCRT or radiotherapy alone for SEC patients with the local control (LC) rates of 70% to 80% [10-13]. However, the use of concurrent chemotherapy, radiation field, and radiation dose remain unclear.

In the present study, we investigated the treatment outcomes of radiotherapy alone with extended-field radiation for patients with SEC.

## Materials and Methods

### 1. Patients

Between May 2007 and October 2016, a total of 24 patients with SEC who underwent radiotherapy with or without endoscopic resection at our institution were included in this study (Table 1). Pretreatment evaluation included a medical history and physical examination. Laboratory studies included complete blood cell count and blood chemistries. For stage work-up, esophagogastroduodenoscopy (EGD) with Lugol staining, chest computerized tomography (CT) and endoscopic ultrasonography (EUS) were performed. To evaluate the distant metastasis, patients were evaluated by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), bone scans, and abdomen CT. Clinical stage was based on the 7th edition of the American Joint Committee on Cancer (AJCC) TNM classification.

### 2. Radiotherapy

Radiotherapy was delivered using megavoltage photon beam or proton beam. A conventional fractionation schedule with a fraction size of 2 Gy was used in all patients. Three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and proton beam therapy (PBT) was used in 17, 4, and 3 patients, respectively. The gross tumor volume (GTV) was defined by the tumor visualized on CT, FDG-PET or the area where were marked within 1 cm proximal and distal to the primary tumor site using endoscopic clips marked by an endoscopy specialist before taking a planning CT. For all 24 patients, the initial clinical target volume (CTV) included the whole thoracic esophagus (from the upper esophageal sphincter to the esophagogastric junction). Elective nodal areas were included in the initial CTV except in 1 patient. The

**Table 1.** Patients' characteristics (n = 24)

Characteristic	Value
Age (yr)	71.5 (39-81)
≥70	13 (54.2)
<70	11 (45.8)
Gender	
Male	21 (87.5)
Female	3 (12.5)
ECOG performance status	
0-1	22 (91.7)
2	2 (8.3)
Tumor location	
Middle thoracic	18 (75.0)
Lower thoracic	6 (25.0)
T stage	
T1a	4 (16.7)
T1b	20 (83.3)
Tumor size (cm)	2.5 (0.6-6.2)
≥2.5	13 (54.2)
<2.5	11 (45.8)
ESD	
No	10 (41.7)
Yes	14 (58.3)

Values are presented as median (range) or number (%).

ECOG, Eastern Cooperative Oncology Group; ESD, endoscopic submucosal dissection.

supraclavicular lymph nodes (SCN), the celiac lymph nodes, and both of those nodal areas were included in 20, 12, and 9 patients, respectively. In patients with middle thoracic SEC, SCN and celiac lymph nodes were irradiated in 88.9% and 61.2% of cases, respectively. In the patients with lower thoracic SEC, SCN and celiac lymph nodes were included in the radiation field for 66.7% and 83.3% of cases, respectively. A shrinking field technique was used in 23 patients except the patient treated with a total radiation dose of 54 Gy. The boost CTV encompassed the primary tumor with a margin of at least 1 cm for all directions. The planning treatment volume (PTV) was created by adding 0.5-1 cm of margin to the CTV. The initial PTV was treated with 40-54 Gy (median dose, 44 Gy). To reduce lung irradiation, anterior-posterior parallel opposite fields were used in the initial phase. To restrict the spinal cord dose, anterior and posterior oblique fields were used for the boost phase. For the patients underwent endoscopic submucosal dissection (ESD), total radiation doses of 54-66 Gy were administered, whereas total radiation doses of 60-66 Gy were administered for the patients received radiotherapy alone. As a result, the total radiation dose ranged between 54 and 66 Gy (median dose, 64 Gy). Variables related to radiotherapy are

**Table 2.** Radiation therapy

Characteristic	Value
Total radiation dose (Gy)	64 (54–66)
Radiation dose for initial PTV (Gy)	44 (40–54)
SCN irradiation	
No	4 (16.7)
Yes	20 (83.3)
Celiac LN irradiation	
No	12 (50.0)
Yes	12 (50.0)
RT field	
Whole esophagus	1 (4.2)
Whole esophagus + SCN	11 (45.8)
Whole esophagus + celiac	3 (12.5)
Whole esophagus + SCN + celiac	9 (37.5)
RT modality	
3D-CRT	17 (70.8)
IMRT	4 (16.7)
Proton beam therapy	3 (12.5)

Values are presented as median (range) or number (%).

PTV, planning target volume; SCN, supraclavicular lymph nodes; LN, lymph nodes; RT, radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

summarized in Table 2.

### 3. Follow-up and statistical analysis

During radiotherapy, patients were examined weekly to check treatment-related toxicities. Patients were followed up with EGD or chest CT every 3 months in the first 2 years, and every 6 months thereafter. Treatment related toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment responses were evaluated according to the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1. Survival duration was calculated from the date of initiation of radiotherapy to the last follow-up or the considered events (local failure, regional failure, distant failure, or death). Survival rates were calculated using the Kaplan-Meier method. The log-rank test was used to assess the statistical differences in Kaplan-Meier estimates. Differences in clinical features between patients treated with ESD followed by radiotherapy and radiotherapy alone were analyzed using the Pearson chi-square or independent samples t-tests. Statistical analyses were conducted using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

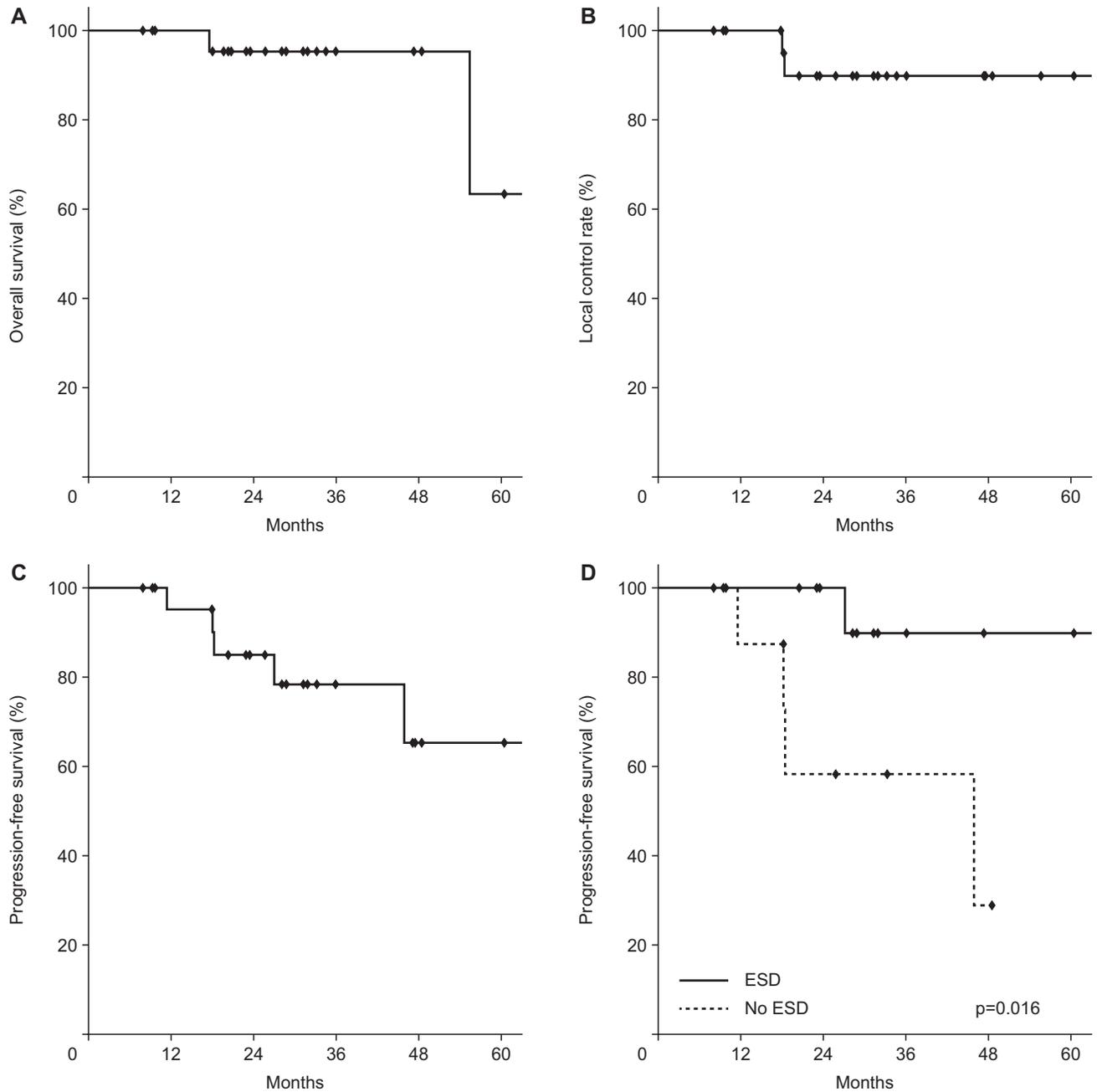
## Results

### 1. Patient characteristics and clinical profile

Pretreatment patients and tumor characteristics are listed on Table 1. Median age was 71.5 years (range, 39 to 81 years), with 21 males (87.5%) and 3 females (12.5%). The tumor location of 18 patients (75%) was mid-thoracic esophagus and the other 6 patients (25%) had tumor in lower thoracic esophagus. Of the 24 patients, 10 patients (41.7%) received radiotherapy for the first-line treatment, because they were not candidate for endoscopic resection due to submucosal invasion seen in EUS. Eight patients were medically unfit to undergo esophagectomy due to old age, heart diseases, cerebrovascular disease, and poor lung function, while 2 patients strongly refused to take surgery. The remaining 14 patients (58.3%), who initially presented with T1a diseases in EUS, underwent radiotherapy after ESD because of their pathologic features including the invasion of tumors into muscularis mucosae (M3 according to the Japanese subclassification [14,15]) or submucosa (T1b).

### 2. Treatment outcomes

The median follow-up period was 28.7 months (range, 7.9 to 108.0 months). The 3-year overall survival (OS), LC, and progression-free survival (PFS) rates were 95.2%, 89.7%, and 78.7%, respectively (Fig. 1A–1C). Among the 24 patients, 5 patients (20.8%) experienced disease progression, and 2 patients (8.3%) had died at the time of analysis. These 2 patients died from disease progression. Local failure and regional failure developed in 2 patients (8.3%) and 3 patients (12.5%), respectively. Among the 3 patients experienced regional recurrence, 2 patients also presented with distant metastasis. Of the 5 patients presenting with disease progression, salvage surgery, radiotherapy, CCRT, and chemotherapy were performed in 1, 1, 1, and 2 patients, respectively. Among them, 2 patients who treated with surgery and CCRT, respectively, remained without evidence of disease. The details of patients who experienced recurrences is summarized in Table 3. The patients treated with radiotherapy following ESD showed better PFS compared with the patients treated with radiotherapy alone (3-year PFS rate: 90.0% vs. 58.3%;  $p = 0.016$ ). This result is shown in Fig. 1D. The proportion of initial clinical T1a disease was higher in the patients treated with ESD followed by radiotherapy than the patients treated with radiotherapy alone (100% vs. 10%;  $p = 0.001$ ). However, the proportion of T1a disease at final stage (16.7% vs. 10%;  $p = 0.459$ ) and median tumor size (2.1 cm vs. 3 cm;  $p = 0.601$ ) did not show significant differences between



**Fig. 1.** Kaplan-Meier plot of (A) overall survival, (B) local control, (C) progression-free survival of all patients, and (D) progression-free survival according to the endoscopic submucosal dissection (ESD).

the patients treated with ESD followed by radiotherapy and radiotherapy alone. The 4 patients with T1a disease did not present with recurrence.

**3. Toxicities**

No grade 3 or higher toxicities were observed during the acute and chronic phases. Acute grade 2 esophagitis was

developed in 6 patients (25%) during treatment. Four patients (16.7%) experienced stenosis of esophagus after treatment, 2 for grade 1 and 2 for grade 2. These 2 patients with grade 2 esophageal stenosis underwent radiotherapy following ESD and had received intervention with balloon dilatation. After the treatment, grade 1 radiation pneumonitis was observed in 12 patients (50%) and there was no grade 2 or

Table 3. Summary of patients with recurrence

No.	Age (yr)/sex	T stage	Location	Size (cm)	Total radiation dose (Gy)	Elective nodal irradiation	Failure site	PFS (mo)	Salvage treatment	Mortality	OS (mo)
1	74/M	T1b	Lower	6	63	SCN	Local (primary site)	18.2	Chemotherapy	No	20.7
2	67/M	T1b	Middle	2.5	66	SCN	Local (primary site)	18.0	Esophagectomy	No	19.6
3	51/F	T1b	Middle	5	64	SCN	Regional (celiac axis)	45.8	Chemotherapy	Yes	55.5
4	72/M	T1b	Middle	3	66	SCN + celiac	Distant (para-aortic nodes)	11.4	Radiotherapy	Yes	17.6
5	81/M	T1	Middle	1.2	60	SCN	Regional (celiac axis) Regional (SCN) Distant (neck nodes)	27.1	CCRT	No	34.5

PFS, progression-free survival; OS, overall survival; SCN, supraclavicular lymph nodes; CCRT, concurrent chemoradiotherapy.

higher radiation pneumonitis. Among the patients, who experienced radiation pneumonitis, 11 patients received the total radiation dose of 60 Gy or more.

### Discussion and Conclusion

The number of patients with SEC is increasing particularly in Asia due to screening for upper gastrointestinal tract cancers [16,17]. Esophagectomy has been considered as the standard treatment for localized esophageal cancer as well as SEC. Recently, to avoid treatment-related morbidity and mortality of esophagectomy, endoscopic approach is increasingly used for SEC. However, due to high rate of lymphatic metastasis in esophageal cancer even in T1 lesions, the application of endoscopic resection is highly limited to small T1 lesions without evidence of lymphovascular invasion [18,19]. Therefore, esophagectomy is still the standard treatment for patients with SEC invading the submucosa. However, definitive radiotherapy with or without concurrent chemotherapy can be considered for unfit patients for surgery, because esophagectomy can result in long-term complications including dysphagia, reflux, and deterioration of quality of life [20,21].

Oh et al. [13] reported the treatment outcomes of hypofractionated definitive radiotherapy of 60 Gy with a daily dose of 3 Gy per fraction without chemotherapy for patients with esophageal cancer. In their study, 25 patients had SEC among the total of 70 patients, and the 2-year OS and LC rates were 80.0% and 81.6%, respectively for patients with SEC. Koide et al reported the treatment outcomes of CCRT for 123 patients with SEC. In their study, the 5-year OS, PFS, and LC rates were 77%, 47%, and 63%, respectively [22]. In these studies, radiotherapy was delivered to involved-field around gross tumors without elective nodal irradiation. Esophageal cancer frequently presents as a multicentric disease or submucosal skip spread due to the rich submucosal lymphatics in the esophagus. Therefore, in RTOG 85-01, extended-radiation field encompassing from the supraclavicular region to the gastroesophageal junction was used [23]. However, the results of RTOG 85-01 were not superior than RTOG 94-05, which adopted involved-field radiation field with 5-cm longitudinal margins and a 2-cm radial margin [24]. One prospective randomized clinical trial that compared extended- and involved-field for cervical and upper thoracic esophageal cancer demonstrated there was no significant difference in median survival between involved-

and extended-field radiation [25]. Generally, extended-field radiation has been considered that potential for treatment-related morbidity is higher than involved-field radiation. As a result, recently, majority of institutions adopted involved-field radiation with concurrent chemotherapy for SEC.

The treatment outcomes of patients with thoracic esophageal cancer remains poor due to the high incidence of lymph node metastasis [26]. Therefore, our policy is to include whole esophagus, SCN, and celiac lymph nodes for all cases in the setting of radiotherapy alone for esophageal cancer. However, we did not include SCN or celiac lymph nodes in the radiation field, when the risk of radiation-induced toxicities due to wide radiation fields was expected to be higher than clinical benefits of wide radiation fields. A previous study demonstrated the pattern of lymph node metastasis in patients with thoracic esophageal squamous cell carcinoma [27]. According to this study, the risk for SCN metastasis in middle and lower thoracic esophageal cancer and the risk for celiac lymph node metastasis in upper thoracic esophageal cancer were relatively low less than 5%. As a result, it may be possible to omit irradiation for SCN or celiac lymph nodes according to the site and extent of disease.

In the present study, we used extended-field radiation, which includes whole esophagus and para-esophageal lymph nodes with or without SCN and celiac axis, without chemotherapy. The concurrent use of chemotherapy during radiotherapy can result in increased toxicities. In RTOG 85-01 study, 10% of patients treated with CCRT experienced acute life-threatening toxicities or treatment-related mortality (TRM), while 2% of patients treated with radiotherapy alone experienced acute life-threatening toxicities without TRM. In addition, in the previous study, which tested hypofractionated radiotherapy with a total radiation dose of 60 Gy, no patients with clinical T1-2 disease presented with grade 3 or higher toxicities, while 10% of all patients experienced those [13]. This finding suggests that the patients with more advanced stages can experience more severe radiation-induced toxicities. In our study, extended-field radiotherapy without chemotherapy produced durable outcomes with a 3-year PFS rate of 78.7% without excessive toxicities. There was no grade 3 adverse event, and acute and chronic radiation pneumonitis and esophagitis were acceptable. Consequently, we suggest that extended-field radiotherapy can be a good treatment option for SEC, especially in medically unfit patients for surgery or chemotherapy. Moreover, the use of advanced radiotherapy techniques such as IMRT or PBT has been continuously increasing. IMRT and PBT provide better radiation dose

distribution to the target and reduced radiation doses to normal tissues including lungs, heart, and trachea. Therefore, adverse events of extended-field irradiation can be reduced by the use of IMRT and PBT. Consequently, the therapeutic benefit of the extended-field radiotherapy and omission of chemotherapy may be greater than the potential risk of adverse events by extended-field radiotherapy.

In our study, the treatment outcomes were superior in patients who received radiotherapy following ESD than patients who received radiotherapy alone. The patients treated with ESD followed by radiotherapy presented with higher proportion of T1a disease and smaller tumor size, however these differences were not statistically significant. The reason why the patients treated with ESD followed by radiotherapy showed better PFS than the patients treated with radiotherapy alone may be due to the earlier clinical stage and exact T stage in patients who underwent ESD. In addition, grade 2 esophageal stenosis to require endoscopic treatments is occurred in two patients received ESD, while there was no grade 2 or higher esophageal stenosis in patients received radiation without ESD.

Our study has a limitation of non-randomized, retrospective analysis, and small number of patients. However, given that esophagectomy is the standard treatment for SEC, our number of patients is reasonable. In addition, we cannot analyze the prognostic value of T stage, because the number of patients with T1a was small. To investigate the benefits of extended-field radiation without chemotherapy, further randomized trials comparing the extended-field radiotherapy and the involved-field radiotherapy with concurrent chemotherapy will be needed.

In conclusion, our study showed that the extended-field radiation therapy without chemotherapy for medically inoperable and endoscopically unfit SEC patients produced reasonable treatment outcomes without significant toxicities of grade 3 or higher. We will continue to investigate, apply, and monitor the extended-field radiotherapy using advanced radiation technology such as IMRT or PBT for patients with SEC.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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