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Clinical outcome of definitive radiation therapy for superficial esophageal cancer

Yutaro Koide[1,*], Takeshi Kodaira[1], Hiroyuki Tachibana[1], Natsuo Tomita[1], Chiyoko Makita[1], Makoto Itoh[1], Tetsuya Abe[2], Kei Muro[3], Masahiro Tajika[4], Yasumasa Niwa[4], Yoshiyuki Itoh[5], and Shinji Naganawa[5]

[1]Department of Radiation Oncology, Aichi Cancer Center Hospital, Chikusa-ku, Nagoya, [2]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Chikusa-ku, Nagoya, [3]Department of Clinical Oncology, Aichi Cancer Center Hospital, Chikusa-ku, Nagoya, [4]Department of Endoscopy, Aichi Cancer Center Hospital, Chikusa-ku, Nagoya, and [5]Department of Radiology, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Japan

*For reprints and all correspondence: Yutaro Koide, Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. E-mail: ykoide@aichi-cc.jp

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Abstract

Objective: To analyze the clinical outcome of concurrent chemoradiotherapy in superficial esophageal cancer patients.
Methods: We retrospectively analyzed data for 123 patients with superficial esophageal cancer who received external beam radiotherapy without intracavitary brachytherapy plus systemic chemotherapy during 1998–2015. Elective nodal irradiation was not performed. The dosage to planning treatment volume was 60 Gy in 30 fractions. The main outcome measure was overall survival.
Results: Patient characteristics were as follows: median age, 66 (41–83) years; male/female ratio, 106/17; squamous cell carcinoma/other, 122/1; cT1a/cT1b, 27/96; cervical esophagus/upper thoracic esophagus/middle thoracic esophagus/lower thoracic esophagus, 7/9/66/41 and concurrent chemoradiotherapy/radiotherapy alone, 100/23. Cisplatin and 5-fluorouracil were the most commonly used agents (85%). At the last follow-up (median 60.5 months), 91 (74%) patients were alive. Complete response was achieved in 116 (94.4%) patients. The 5-year overall survival, progression-free survival and local control rates were 77.0, 46.9 and 62.7%, respectively, similar to that in the elderly patients ($P = 0.878$, 0.754 and 0.648, respectively). There were 55 failures: 42 local, 10 regional and 3 distant failures. Nine local and seven regional failures developed out-of-field. Thirty-eight local failures (90%) were successfully salvaged, of which 30 (71%) were salvaged via endoscopic removal; only 2 regional failures (20%) were salvaged. Fifteen G3 acute toxicities occurred. One pneumonitis (G3), one pneumothorax (G3) and two pericardial effusion (G2) were the late toxicities observed. There were no G4 toxicities or treatment-related deaths.
Conclusions: Concurrent chemoradiotherapy without intracavitary brachytherapy was effective and safe for superficial esophageal cancer, even in elderly patients.

Key words: aged, chemoradiotherapy, elderly, esophageal neoplasms, lymphatic irradiation, toxicity

Introduction

Recently, improved multimodal endoscopy, computed tomography (CT) and positron emission tomography (PET)/CT approaches have allowed the detection of esophageal cancer at earlier stages. According to the Comprehensive Registry of Esophageal Cancer in Japan, clinical stage (cStage) 0/1 increased from 23.1 to 30.8% of all cases from 1999 to 2009 (1,2). Contrary to the tendency in western countries, where 50% of patients have adenocarcinoma, the majority of Japanese patients have squamous cell carcinoma, and only 5% have adenocarcinoma.

Esophageal cancer is often accompanied with lymph node metastasis (LNM), even at early stages. Yamashina et al. reported that the cumulative 5-year metastasis rate was 5.2% in pT1 patients (0.4–8.7% in pT1a and 25.7% in pT1b) (3). Patients with epithelium/lamina propria (EP/LPM) are candidates for endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), and muscularis mucosa or cT1b patients are candidates for surgery with D2 or greater lymph node (LN) dissection as first-line therapy. If the patient had EP/LPM cancer, multiple lesions or large circumference lesion was thought not to be a candidate for EMR/ESD because of technical difficulty. Difficult cases or patients who refuse to undergo EMR/ESD or surgery may choose to undergo external beam radiotherapy (EBRT) or chemoradiotherapy (CRT). Although there are no randomized clinical trials comparing definitive CRT and surgery for resectable esophageal cancer, some clinical reports of CRT demonstrated promising results. In these trials, elective nodal irradiation (ENI) was not performed, and overall survival (OS) of CRT was comparable to that of surgery (4,5).

The number of reports regarding the results of radiotherapy for superficial esophageal cancer (SEC) is limited, and the necessity of ENI for SEC is still unclear. We previously reported that adding intracavitary brachytherapy (ICBT) to CRT increases the risk of significant ulceration (6). Since then, we started treating SEC without ICBT at our unit. In this study, we analyzed the clinical outcome of definitive radiation therapy without ICBT in SEC patients, including elderly patients. This paper describes the recurrence pattern (local/regional/distant), site (inside irradiation field/outside irradiation field) and salvage therapy for these patients.

Patients and methods

Patient selection

This study included 123 patients with SEC who received EBRT or CRT at Aichi Cancer Center Hospital between June 1998 and March 2015. Patients treated with ICBT or adjuvant radiotherapy after EMR/ESD, and patients who did not receive definitive radiotherapy (at least 50 Gy in total) were excluded. Before starting the treatment, all patients were evaluated through anamnesis, physical examination, laboratory test (complete blood count, serum chemistry and tumor markers), esophagoscopy with iodine staining, CT from neck to abdomen, and PET/CT to evaluate tumor location, length, circumference, depth of invasion and regional node or distant metastasis. The disease stage was based on the 7th edition of TNM classification (International Union against Cancer TNM classification; UICC 2009), and treatment management was decided after discussion among a group of surgeons, endoscopists, medical oncologists and radiation oncologists.

The Institutional Review Board of our hospital approved this study. All patients gave written informed consent.

Radiotherapy

Radiotherapy with megavoltage photon beam was started concurrently with systemic chemotherapy. The gross tumor volume was defined based on the primary tumor marked with a clip before taking a simulator film or planning CT. The clinical target volume was defined as a gross tumor volume with 2 cm of cranio-caudal margin. Elective nodal areas were not included in the clinical target volume. The planning treatment volume was defined as a clinical target volume with 0.5–1.5 cm of margin in consideration of respiratory movements. The irradiation field was set a leaf margin of 0.5 cm on the planning treatment volume. The routine dosage to planning treatment volume was 60 Gy in 30 fractions, and all patients were treated using three-dimensional conformal radiotherapy (3D-CRT). The spinal cord did not receive more than 45 Gy. Lung and heart doses were minimized in each patient. Parallel-opposed fields method (2 F) was used initially, but since 2007, 4 fields method (4 F) was used to reduce heart toxicity.

Chemotherapy

The most common regimens of chemotherapy were 5-fluorouracil (5-FU) and cisplatin (FP). A total of 73 patients received two cycles of 5-FU (700 mg/m^2 intravenously at D1–4) and cisplatin (70 mg/m^2 intravenously at D1) every 4 weeks (standard-dose FP) (7). Between 2001 and 2007, some elderly patients with medical illness received low-dose FP (5-FU [200 mg/m^2] and cisplatin [4 mg/m^2] every weekday for 6 weeks) or middle-dose FP (two cycles of 5-FU [400 mg/m^2 on days 1–5 and 8–12] and cisplatin [40 mg/m^2 on days 1 and 8] every 5 weeks) (8,9). Ten patients with simultaneously diagnosed head and neck squamous cell carcinoma received intravenous 5-FU and nedaplatin with an alternating setting (6).

Follow-up

Treatment response was evaluated with esophagoscopy and CT at 1 month after the completion of radiation therapy. Patients with complete remission (CR) were followed up at 2–3 months intervals for the first 2 years and at 4–6 months intervals thereafter (6). Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Local failure (LF) was defined as recurrent or new lesions of esophagus regardless of the irradiation field. Regional failure was defined as regional LNM. Distant failure was defined the other recurrent lesions of LF or regional failure (RF). Distant recurrent lesions with LF and/or RF were only counted for distant failure (DF). When they were found a mucosal residual lesion or local recurrences, EMR/ESD were intended to salvage esophageal lesion. Surgery was considered for the local lesion inaccessible to EMR/ESD, or regional recurrences. If neither ESD nor surgery was possible, CRT was performed for local or regional recurrences located out-of-field, and chemotherapy was performed for other recurrences.

Statistical analysis

OS was measured from the date of starting treatment to the last follow-up or death from any cause. Progression-free survival (PFS) was measured from the date of starting treatment to the date of disease progression or death from any cause. Local control (LC) was defined as local progression as an event. All esophageal lesions including those located out of radiation field were counted as local progression. The OS, PFS and LC rate were calculated using Kaplan–Meier estimates (10). In a univariate analysis, factors of gender, age (≥70 years vs. <70 years), ECOG performance status (PS; 0 vs. 1–2), tumor length (>3 cm vs. ≤3 cm), tumor depth (T1a vs. T1b), tumor circumference (≥1/2 vs. <1/2), multicentric lesions (MCL; yes vs. no), multiple Lugol-voiding lesions (MLV; yes vs. no), double cancer (DCa; yes vs. no), CRT (yes vs. no) and treatment duration (≥45 days vs. <45 days) were evaluated using the log-rank test. Cox's proportional hazards model was used in a multivariate analysis to evaluate independent prognostic factors for each endpoint. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). More precisely, it is a modified version of R commander (version 1.6–3) that was designed to add statistical functions frequently used in biostatistics (11).

Results

Patient and treatment characteristics

Table 1 presents the characteristics of the patients. At the last follow-up (5 November 2015), 91 patients (74.0%) were alive (57 were without recurrence and 34 were with recurrence) and 32 (26.0%) had died. Fourteen patients died of the disease and 18 patients died of other cause (12 of other cancer, 2 of pneumonia, 1 of cholecystitis, 1 of stroke and 1 of traumatic subdural hemorrhage). One patient could not be evaluated for this treatment because he died early of other cancer.

The median follow-up period was 60.5 months (range, 4.7–167.2 months). Forty-three patients (35.0%) were aged over 70 years. A total of 100 patients (81.3%) received systemic chemotherapy, and FP regimen was used in 85 of them. One T1a patient and 9 T1b patients received adjuvant FP [two cycles of 5-FU (800 mg/m^2 intravenously at D1–4) and cisplatin (80 mg/m^2 intravenously at D1)]. The rest of 15 patients were treated as follows; 10 were 5-FU and nedaplatin, 1 was only 5-FU, 1 taxotere, 1 S-1 and 1 unknown. Twenty-three patients did not receive any chemotherapy, and some of them were irradiated over 60 Gy (8 were 66 Gy and 1 was 70 Gy). A total of 96 patients were T1b and 27 patients were T1a. Thirty-seven patients (30.1%) had MCL and 81 patients (65.9%) had MLV. Sixty patients (48.8%) were treated with 4 F, 61 (49.6%) with 2 F, 1 (0.81%) with three fields and 1 (0.81%) with conformation radiotherapy.

Table 1. Patient characteristics

Gender	
Male	106
Female	17
Age (years)	
Median (range)	66 (41–83)
≥70	43
PS	
0	59
1	63
2	1
Primary tumor site	
Cervical esophagus	7
Upper thoracic esophagus	9
Middle thoracic esophagus	66
Lower thoracic esophagus	41
Length (cm)	
>3	54
≤3	69
Depth of invasion	
T1a	27
T1b	96
Circumference	
≤1/2	69
>1/2	53
Unknown	1
MCL	
Yes	37
No	86
MLV	
Yes	81
No	41
Unknown	1
DCa	
Yes	57
No	66
CRT	
Yes	100
No	23
Treatment duration, days	
≥45	56
<45	67

MCL, multicentric lesions; MLV, multiple Lugol-voiding lesions; DCa, double cancer; CRT, chemoradiotherapy.

Treatment outcomes

Of all patients treated with chemotherapy, 93 (93.0%; 95% confidence interval [CI] 86.1–97.1%) completed the chemotherapy treatment. A total of 120 patients (97.6%; 95% CI 93.0–99.5%) completed radiotherapy. Nineteen patients prolonged radiotherapy for more than 50 days. Among these patients, 11 were conformed to 1-week rest by planned schedule (7), 4 delayed the treatment because of acute Grade 3 esophagitis and 5 postponed the treatment to after the New Year's holiday. One patient received 70.2 Gy in 39 fractions because he was treated simultaneously for hypopharyngeal cancer close to his cervical esophageal cancer.

A total of 116 patients (94.3%; 95% CI 88.6–97.7%) achieved CR, while 4 and 2 patients achieved partial response and stable disease, respectively. The 5-year rates of OS, PFS and LC were 76.8% (95% CI 67.2–83.8%), 46.9% (95% CI 37.4–55.9%) and 64.1% (95% CI 53.9–72.7%), respectively (Fig. 1A–C). There were no significant differences for OS, PFS and LC between 4 F and 2 F patients.

Failure site and salvage treatment

A total of 55 patients (44.7%) relapsed (Table 2): 42 (76.3%) developed LF, 10 (18.1%) developed RF and 3 (5.5%) developed DF. One of the DF patients had relapse at the para-aortic LN, and the remaining 2 developed lung metastases. Nine of LF (7.3%) and seven of RF (5.7%) developed out-of-field failures (three supraclavicular LN [SCLN], two mediastinum LN [MLN], one SCLN + MLN and one abdominal LN).

Among the patients with LF, 30 (71.4%) received successful EMR/ESD, 6 (14.3%) salvage surgery, 4 (9.5%) salvage CRT, 1 (2.4%) chemotherapy and 1 (2.4%) BSC. Among the patients with RF, one received surgery, five CRT and four chemotherapy. Among the patients with DF, two received chemotherapy and one BSC. Thirty-eight (90.5%) of LF, two (20.0%) of RF and one (33.3%) of DF patients could be successfully salvaged (Fig 2).

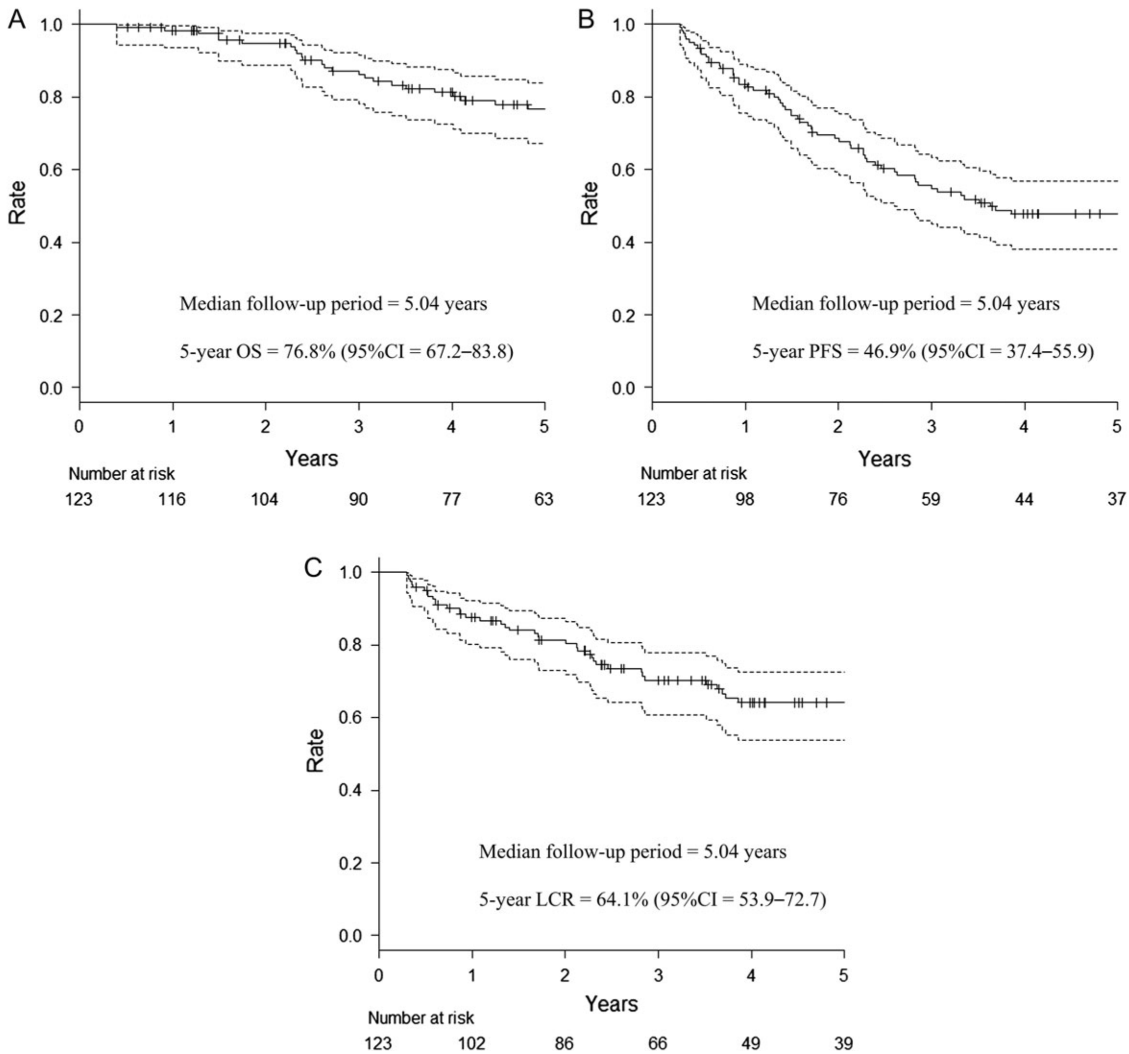

Figure 1. (A) Overall survival curve of all patients. (B) Progression-free survival curve of all patients. (C) Local control curve of all patients.

Table 2. Failure site and salvage treatment

Failure site	No.	Salvage treatment	No.
Local	42	EMR/ESD	30
		Surgery	6
		CRT	4
		CHT	1
		BSC	1
Regional	10	Surgery	1
		CRT	5
		CHT	4
Distant	3	CHT	2
		BSC	1

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; CHT, chemotherapy; BSC, best supportive care.

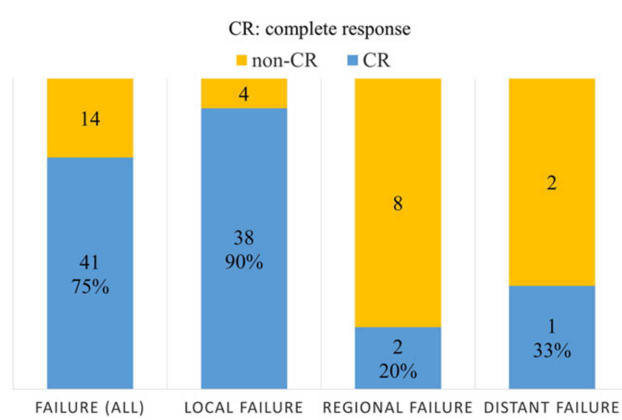

Figure 2. Salvage treatment and efficacy.

Univariate analyses

Table 3 presents the results of the univariate analysis for OS, PFS and LC. Tumor length (>3 cm vs. ≤3 cm, 68.6% vs. 83.9%, $P < 0.01$), MLV (yes vs. no, 73.0% vs. 88.9%, $P = 0.03$), DCa (yes vs. no, 63.4% vs. 88.9%, $P < 0.01$) and CRT (yes vs. no, 79.6% vs. 62.9%, $P < 0.01$) were significant prognostic factors for 5-year OS. Tumor length (36.4% vs. 56.8%, $P = 0.01$), circumference (≥50% vs. <50%, 32.8% vs. 59.8%, $P = 0.02$), MLV (42.1% vs.

Table 3. Univariate analysis of survival and tumor control according to prognostic factors

Variable	*n*	5-Year OS (95% CI)	*P* value	5-Year PFS (95% CI)	*P* value	5-Year LCR (95% CI)	*P* value
Gender							
Male	106	0.772 (0.671–0.846)	0.857	0.456 (0.355–0.552)	0.274	0.593 (0.483–0.687)	0.0222*
Female	17	0.729 (0.368–0.905)		0.641 (0.337–0.834)		1.000 (1.000–1.000)	
Age (years)							
≥70	43	0.766 (0.583–0.876)	0.878	0.481 (0.310–0.634)	0.864	0.685 (0.496–0.815)	0.648
<70	80	0.769 (0.650–0.853)		0.477 (0.361–0.584)		0.623 (0.498–0.726)	
PS							
0	59	0.795 (0.652–0.885)	0.918	0.452 (0.313–0.581)	0.949	0.661 (0.508–0.777)	0.436
1–2	64	0.742 (0.601–0.839)		0.498 (0.364–0.618)		0.624 (0.479–0.739)	
Length (cm)							
>3	54	0.686 (0.532–0.798)	<0.01*	0.364 (0.233–0.496)	0.0219*	0.508 (0.354–0.643)	<0.01*
≤3	69	0.839 (0.713–0.913)		0.568 (0.434–0.681)		0.740 (0.601–0.837)	
Depth							
T1a	27	0.714 (0.488–0.854)	0.119	0.324 (0.158–0.503)	0.12	0.414 (0.204–0.613)	0.0364*
T1b	96	0.785 (0.675–0.861)		0.526 (0.414–0.626)		0.707 (0.592–0.794)	
Circumference							
≤1/2	69	0.828 (0.701–0.904)	0.0668	0.598 (0.467–0.707)	0.0392*	0.748 (0.614–0.842)	0.0118*
>1/2	53	0.702 (0.542–0.816)		0.328 (0.197–0.464)		0.499 (0.343–0.637)	
MCL							
Yes	37	0.801 (0.628–0.900)	0.754	0.526 (0.352–0.674)	0.917	0.648 (0.460–0.785)	0.386
No	86	0.750 (0.626–0.838)		0.453 (0.337–0.562)		0.636 (0.509–0.738)	
MLV							
Yes	81	0.730 (0.613–0.817)	0.0255*	0.421 (0.310–0.529)	0.0441*	0.598 (0.473–0.703)	0.101
No	41	0.889 (0.687–0.964)		0.622 (0.436–0.763)		0.727 (0.534–0.851)	
DCa							
Yes	57	0.634 (0.481–0.753)	<0.01*	0.389 (0.258–0.517)	0.0159*	0.618 (0.470–0.736)	0.257
No	66	0.889 (0.769–0.948)		0.556 (0.419–0.674)		0.674 (0.531–0.782)	
CRT							
Yes	100	0.796 (0.692–0.869)	<0.01*	0.520 (0.413–0.617)	0.0416*	0.670 (0.559–0.759)	0.363
No	23	0.629 (0.369–0.806)		0.272 (0.098–0.483)		0.449 (0.169–0.698)	
Duration (days)							
≥45	55	0.784 (0.634–0.878)	0.893	0.544 (0.391–0.674)	0.142	0.713 (0.551–0.825)	0.129
<45	68	0.757 (0.622–0.849)		0.427 (0.304–0.544)		0.582 (0.443–0.698)	

n, number of patients; CI, confidence interval; OS, overall survival; PFS, progression-free survival; LCR, local control rate.
*Significantly different ($P < 0.05$).

62.2%, $P = 0.04$) and DCa (38.9% vs. 55.6%, $P = 0.02$) were significant prognostic factors for 5-year PFS. Tumor length (48.5% vs. 72.7%, $P < 0.01$), gender (male vs. female, 57.8% vs. 100%, $P = 0.02$), circumference (47.5% vs. 73.8%, $P = 0.01$) and the depth of invasion (T1a vs. T1b, 40.2% vs. 69.0%, $P = 0.04$) were significant prognostic factors for LC. OS, PFS and LC rates of elderly patients did not show any significant differences compared to those of others.

Multivariate analyses

Table 4 presents the results of the multivariate analysis for OS, PFS and LC. MLV (hazard ratio [HR] 3.92; $P = 0.02$), DCa (HR 3.60; $P < 0.01$) and radiotherapy alone (HR 2.54; $P = 0.02$) were independent unfavorable factors for OS. Extended circumference (HR 1.878; $P = 0.01$) and DCa (HR 1.847; $P = 0.01$) were independent unfavorable factors for PFS. Only extended circumference (≥50%: HR 2.17; $P = 0.01$) proved to be an unfavorable factor of LC.

Toxicity

A total of 15 acute Grade 3 toxicities (7 esophagitis, 2 anorexia, 4 neutropenia and 1 liver dysfunction cases) and 3 late toxicities developed. All of the acute toxicities recovered within a few weeks after the completion of treatment. There were no cases of esophageal ulcer, stenosis, treatment-related death or development of Grade 4 toxicities. Two patients developed Grade 2 pericardial effusion without any symptom. Both patients were treated by 2 F, not 4 F. Another patient irradiated with standard-dose FP by 4 F had an onset of dyspnea 11 weeks after the treatment. He was diagnosed radiation pneumonitis needed hospitalization and treated with systemic corticosteroids. He recovered and was discharged in a week, but he suffered from secondary pneumothorax during tapering of steroids, for which he performed tube placement with autologous blood pleurodesis. At the last follow-up, his symptoms had subsided. His pneumonitis and pneumothorax were regarded as Grade 3 toxicities.

Discussion

Although the number of SEC patients has increased in Japan (1,2), the role of CRT for SEC remains unclear. The JCOG9708 trial reported favorable results (7), which have been widely applied in Japanese institutions. However, there are still few reports of SEC treated with definitive radiotherapy. In this study, concurrent CRT with definitive radiotherapy was effective and safe for SEC, even in elderly patients. Clinical trials often fail to include elderly patients. Therefore, our results are applicable to our clinical practice.

Table 4. Multivariate analysis of survival and tumor control according to selected factors

Variable	OS		PFS		LCR	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender						
Male vs. female	NA	NA	NA	NA	7.231 (0.993–52.65)	0.051
Length (cm)						
>3 vs. ≤3	1.072 (0.925–1.242)	0.357	1.007 (0.904–1.122)	0.896	1.039 (0.916–1.179)	0.548
Depth						
T1a vs. T1b	NA	NA	NA	NA	1.607 (0.831–3.108)	0.159
Circumference						
≤1/2 vs. >1/2	1.967 (0.935–4.136)	0.0747	1.641 (0.978–2.752)	0.0606	2.168 (1.170–4.016)	0.0139*
MLV						
T1a vs. T1b	3.919 (1.244–12.34)	0.0196*	2.085 (1.147–3.791)	0.0160*	1.57 (0.739–3.337)	0.241
DCa						
Yes vs. no	3.596 (1.504–8.595)	<0.01*	1.573 (0.955–2.591)	0.0755	NA	NA
CRT						
Yes vs. no	2.544 (1.149–5.631)	0.0213*	2.17 (1.206–3.905)	<0.01*	NA	NA

NA, not available.
*Significantly different ($P < 0.05$).

In this study, 5-year OS and PFS were 76.8% (95% CI 67.2–83.8%) and 46.9% (95% CI 37.4–55.9%), respectively. Our previous study showed similar findings for survival [63.0% (95% CI 51.0–75.0%)] and disease control [48.1% (95% CI 36.5–59.7%)]. Although there were several biases due to retrospective basis in our study, we believe that acquired results would be comparable to that of JCOG9708 or the surgical series (6,7,12). We stopped using ICBT because of the increased risk of severe ulceration (6). However, the PFS did not worsen compared to our previous report. Motoori et al. reported 60.6% of 5-year PFS, and the JCOG9708 study achieved 68.1% of 4-year PFS, but these results require careful interpretation of the definition of LF (7,12). In those studies, local recurrence cases, which could be salvaged with EMR/ESD, were excluded. Our study accounted for 42 (76.4%) LF in total, and 30 (54.5%) of them were successfully manageable by EMR/ESD. If these recurrences were excluded, the survival rate (severe recurrence-free survival; SRFS) would be 79.9% (71.0–86.4%), which is close to that of the surgical series (73.8%) (12). Indeed, CRT for SEC might have higher risk of LF than surgery, and adequate use of salvage EMR/ESD would produce OS and SRFS rates comparable to those of the surgical series.

Unfavorable factors of OS were MLV, DCa, larger tumor (>3 cm) and RT. All these factors, with the exception of larger tumor ($P = 0.0543$) were independent unfavorable factors in multivariate analysis. Some investigators reported that esophageal cancer patients with MLV often develop a second primary cancer in the gastrointestinal or head and neck area (13–15). Our cohort showed similar tendency for higher rate of DCa (51.8% vs. 34.1% in MLV vs. others; $P = 0.0638$). This might contribute to decreased OS of MLV patients.

Whether addition of chemotherapy to EBRT for SEC improves survival remains unclear. Cooper et al. proved the benefit of chemotherapy plus EBRT compared to EBRT alone, but the majority of patients had locally advanced tumors, and patients with adenocarcinoma histopathology were also included (16). Nemoto et al. reported the 3-year OS of CRT for SEC was 90% while that of EBRT alone was 70% in 104 SEC patients, which was not statistically different but possibly clinically meaningful (17). In our study, 23 patients could not receive chemotherapy due to several reasons such as poor general condition and/or existed comorbidity or others. Although these factors might have affected poor outcome, our results supported their studies.

Larger tumor and EC (>1/2) were unfavorable factors of PFS. EC was also an unfavorable factor of PFS in multivariate analysis. Larger and/or extended tumor was difficult to treat with endoscopy even if the tumor depth was limited to EP/LPM, and surgery or CRT was considered. Our results showed these patients developed LF more frequently than the others did. However, about two-thirds (over 65%) could be salvaged with EMR/ESD.

Our study included 43 (35%) elderly patients (≥70 years old). As far as we know, there have been few reports of CRT for SEC in elderly patients. Xu et al. showed effectiveness of CRT for esophageal squamous cell cancers; however, it contained a variety stage while only 1 SEC patient (18). Our analysis did not show any significant difference in the OS, PFS and LC rates between elderly patients and others. Since elderly patients could not sometimes be candidate for surgical treatment because of their comorbidity, CRT without ENI was believed to be reasonable options especially for elderly patients.

At the last follow-up, there were only three patients (2.44%) who experienced G2 or G3 late adverse events. In the JCOG9708 study, which used the 2 F method, cardiac ischemia (G2: 1, G3: 1) and pericarditis (G1 asymptomatic: 12, G2 symptomatic: 2) developed. Since 2007, we changed from 2 F to 4 F in order to minimize cardiac radiation damage. As a result, two (3.28%) patients treated with 2 F experienced G2 (asymptomatic) pericardial effusion, whereas no patients treated with 4 F experienced cardiac adverse events. There are few reports about the difference in clinical cardiac effects between 2 F and 4 F. Our cohort also had 1 (0.81%) G3 radiation pneumonitis and pneumothorax (the same patient), but the remaining 120 patients did not experience G3 or more late adverse events. Since only one patient had G3 late events, we believe that our treatment was sufficiently safe.

It is controversial whether ENI is necessary or not for SEC. Onozawa et al. reported that ENI is effective for preserving LNM (19), but their study sample comprised various stages of esophageal cancer. We believe that ENI is not necessary for SEC, because the risk of LNM in SEC patients is not so high, and chemotherapy may contribute to decreased LNM ratio. As Yamashina et al. reported, 25.7% or T1b patients treated with EMR/ESD developed LNM, but only 10 out of 96 T1b patients (10.4%) developed LNM in the present series. Seven LNM (7.29% in T1b) developed outside radiation field, and three (3.13% in T1b) were inside radiation field. Motoori et al. reported relatively higher rate of outside-field LNM (13 of 71 patients) (12) compared to that of our series. We thought that there was not significant difference between both analyses, because there were considerable biases due to retrospective basis. But the reason of lower rate of LNM in our series might be explained by relatively higher compliance of concurrent chemoradiotherapy (93%) with adjuvant FP (9.4%) in selected patients. In addition, our cohort included patients who could take some advantage in diagnostic accuracy by modern technique of both endoscopy and PET or PET/CT. Indeed, once LNM occurred, salvage treatment would be difficult. In our study, only two patients (20%) of LNM could be successfully salvaged. One of them (outside-field recurrence) was salvaged with CRT and the other (inside-field recurrence) was salvaged with surgery (Fig 2). Despite the small number of cases, surgery for LNM could be an effective salvage treatment. Akutsu et al. reported in their prospective study (the JCOG0502 surgery group) that 27.0% of cT1N0 cases receiving esophagectomy had pathologic LNM, and reported a high prevalence of LNM. Indeed, 36.7% of those cases also had skip metastases in broad area, which required more extended prophylaxis (20). In our study, LNM also developed in broad area (three SCLN, two MLN, one SCLN + MLN and one abdominal LN). However, few reports have shown a survival advantage of CRT with ENI (compared to CRT without ENI) in SEC patients. Uchinami et al. retrospectively analyzed 90 SEC patients (39 with ENI and 51 without ENI) and reported that ENI was not independent prognostic factor for disease-specific survival or disease-free survival (21). The extended radiation field may increase the rate of severe adverse events (22). Therefore, one must choose the radiation field carefully to balance efficacy and toxicity. JCOG0502, a prospective study comparing CRT (4 F without ENI) to surgery with D2 or more LN dissection, is currently underway. The results are expected to help determine the combination of adoptive radiotherapy with concurrent chemotherapy.

One limitation of our study is that it was a non-randomized, retrospective analysis of data from a single institution. We did not compare surgery and CRT directly, which might obscure the actual efficacy and safety of our treatment. There are few prospective trials about long-term cardiac toxicity in patients treated with the 4 F method. A prospective, randomized controlled study such as the JCOG0502 trial is necessary to select the appropriate treatment option.

In conclusion, our study showed that definitive CRT without ENI for SEC has an OS rate comparable to that of surgery. The efficacy and safety of CRT without ENI was considerably high, even in elderly patients. MLV, DCa, larger tumor and EC were significantly unfavorable factors. Larger tumor and EC were also associated with significantly poorer LF. EMR/ESD plays an important role in successful salvage for LF.

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Conflict of interest statement

None declared.

References

1. Registration Committee for Esophageal Cancer. *Comprehensive Registry of Esophageal Cancer in Japan*. 3rd edn. Tokyo: The Japan Society for Esophageal Diseases, 2002.
2. Tachimori Y, Ozawa S, Numasaki H, et al. Comprehensive registry of esophageal cancer in Japan, 2009. *Esophagus* 2016;13:110–37.
3. Yamashina T, Ishihara R, Nagai K, et al. Long-term outcome and metastatic risk after endoscopic resection of superficial esophageal squamous cell carcinoma. *Am J Gastroenterol* 2013;108:544–51.
4. Yamamoto S, Ishihara R, Motoori M, et al. Comparison between definitive chemoradiotherapy and esophagectomy in patients with clinical stage I esophageal squamous cell carcinoma. *Am J Gastroenterol* 2011;106:1048–54.
5. Motoori M, Yano M, Ishihara R, et al. Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. *Ann Surg Oncol* 2012;19:2135–41.
6. Kodaira T, Fuwa N, Tachibana H, et al. Retrospective analysis of definitive radiotherapy for patients with superficial esophageal carcinoma: consideration of the optimal treatment method with a focus on late morbidity. *Radiother Oncol* 2010;95:234–9.
7. Kato H, Sato A, Fukuda H, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). *Jpn J Clin Oncol* 2009;39:638–43.
8. Shinoda M, Ando N, Kato K, et al. Randomized study of low-dose versus standard-dose chemoradiotherapy for unresectable esophageal squamous cell carcinoma (JCOG0303). *Cancer Sci* 2015;106:407–12.
9. Kato K, Muro K, Minashi K, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). *Int J Radiat Oncol Biol Phys* 2011;81:684–90.
10. Kaplan E, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457–81.
11. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.
12. Motoori M, Yano M, Ishihara R, et al. Comparison between radical esophagectomy and definitive chemoradiotherapy in patients with clinical T1bN0M0 esophageal cancer. *Ann Surg Oncol* 2012;19:2135–41.
13. Muto M, Hironaka S, Nakane M, et al. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. *Gastrointest Endosc* 2002;56:517–21.
14. Hori K, Okada H, Kawahara Y, et al. Lugol-voiding lesions are an important risk factor for a second primary squamous cell carcinoma in patients with esosphageal cancer or head and neck cancer. *Am J Gastroenterol* 2011;106:858–66.
15. Katada C, Yokoyama T, Yano T, et al. Alcohol consumption and multiple dysplastic lesions increase risk of squamous cell carcinoma in the esophagus, head, and neck. *Gastroenterology* 2016;151:860–9.
16. Cooper J, Guo M, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG85-01). *JAMA* 1999;281:1623–7.
17. Nemoto K, Yamada S, Nishio M, et al. Results of radiation therapy for superficial esophageal cancer using the standard radiotherapy method recommended by the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) study group. *Anticancer Res* 2006;26:1507–12.
18. Xu HY, Du ZD, Zhou L, et al. Safety and efficacy of radiation and chemoradiation in patients over 70 years old with inoperable esophageal squamous cell carcinoma. *Oncol Lett* 2014;7:260–6.

19. Onozawa M, Nihei K, Ishikura S, et al. Elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for squamous cell carcinoma of the thoracic esophagus. *Radiother Oncol* 2009;92:266–9.
20. Akutsu Y, Kato K, Igaki H, et al. The prevalence of overall and initial lymph node metastases in clinical T1N0 thoracic esophageal cancer. *Ann Surg Epub* 2016;264:1009–1015.
21. Uchinami Y, Myojin M, Takahashi H, et al. Prognostic factors in clinical T1N0M0 thoracic esophageal squamous cell carcinoma invading the muscularis mucosa or submucosa. *Radiat Oncol* 2016;11:84.
22. Ishikura S, Nihei K, Ohtsu A, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–702.