Original Article

Clinical outcomes of definitive radiotherapy for patients with cT1aN0M0 esophageal cancer unsuitable for endoscopic resection and surgery

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Background: Studies on the clinical outcomes of radiotherapy for clinical (c)T1aN0M0 (*UICC-TNM Classification, Eighth Edition*) esophageal cancer (EC) are limited. Therefore, this retrospective study aimed to clarify the clinical outcomes of definitive radiotherapy (RT) or chemoradiotherapy (CRT) for cT1aN0M0 EC unsuitable for endoscopic resection and surgery.

Methods: Patients with cT1aN0M0 esophageal squamous cell carcinoma who underwent definitive RT or CRT between January 2009 and December 2020 were retrospectively reviewed. The initial response, toxicities, survival rates, recurrence patterns, and salvage treatments of the patients were evaluated. Initial response was measured using the Response Evaluation Criteria in Solid Tumors guideline. Toxicity was assessed and documented following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Survival rates from the date of initiation of treatment were measured using the Kaplan–Meier method.

Results: Twenty patients treated with definitive RT or CRT were included in the study. The median follow-up duration was 55 months (range, 13–131 months). All patients achieved complete response to the initial treatment. Grade 3 acute toxicities observed esophagitis (10%), pneumonitis (5%), and leukopenia (5%). Late toxicities higher than grade 3 were not observed. The 1-, 3-, and 5-year overall and disease-specific survival rates were 100% and 100%, 83% and 100%, and 67% and 100%, respectively. No treatment-related deaths occurred. Among the 20 patients, 6 showed local recurrence and 2 showed metachronous recurrence. Seven patients underwent salvage endoscopic submucosal dissection (ESD), and one underwent argon plasma coagulation treatment. After the endoscopic treatment, no recurrences were observed.

Conclusions: Definitive RT or CRT was considered an alternative initial treatment for patients with cT1aN0M0 EC who were unsuitable for endoscopic resection and surgery.

Keywords: Superficial esophageal cancer; radiotherapy; chemoradiotherapy (CRT); comorbidity; endoscopic treatment

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Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide and the sixth leading cause of death (1). Due to improvements in diagnostic procedures, the number of patients with superficial EC has been increasing. According to the Comprehensive Registry of Esophageal Cancer in Japan, the incidence rate of clinical stage I cancer among all patients with cancer increased from 23.1% in 1999 to 38.6% in 2013 (2).

Endoscopic resection is generally indicated for patients with tumors invading the lamina propria mucosa (LPM). Endoscopic resection or esophagectomy is the main treatment for patients with tumors invading the muscularis mucosa (MM) (3,4). However, in clinical practice, radiotherapy (RT) is often an alternative treatment for patients depending on their comorbidities, tumor localization, and extensive extension. Recently, results of some RT cases for clinical (c)T1bN0M0 EC have been reported (5,6). The outcomes of chemoradiotherapy (CRT) showed a trend toward non-inferiority in comparison with surgery in terms of overall survival (OS) in patients with cT1bN0M0 EC (6).

In Japan, several retrospective studies have shown promising clinical outcomes of definitive RT or CRT for stage I, including cT1aN0M0 EC (7-10). However, a few detailed reports discussed the recurrence patterns and subsequent salvage treatments, and efficacy from the point of view of organ preservation focused on cT1aN0M0. Therefore, this study aimed to clarify the clinical outcomes of definitive RT for cT1aN0M0 EC unsuitable for endoscopic resection and surgery. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-773/rc).

Methods

Study population

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The retrospective study protocol was reviewed and approved by the Juntendo Hospital ethics review board (No. H20-0391). Informed consent was obtained in the form of opt-out on the Juntendo University website. Those who did not provide consent were excluded. We reviewed the medical records, RT treatment plans, and diagnostic images of patients with EC who underwent definitive RT or CRT in the Juntendo Hospital between January 2009 and December 2020. Eligibility criteria were as follows: (I) a pathologically proven esophageal squamous cell carcinoma; (II) Eastern Cooperative Oncology Group performance status (11) scores of 0–2; (III) cT1aN0M0 cancer based on the *UICC-TNM Classification*, *Eighth Edition* (12); and (IV) medically unsuitable for endoscopic resection and surgery. Patients who previously underwent endoscopic resection, surgery, RT, or chemotherapy for EC were excluded. EC was comprehensively diagnosed using physical findings, upper gastrointestinal endoscopy, and computed tomography. Magnifying endoscopy and endoscopic ultrasonography were used for the clinical diagnostic differentiation among T1a-epithelium (EP)/LPM, T1a-MM, and T1b-submucosa diseases in patients with EC (3). Comorbidities were estimated with the Charlson comorbidity index on the basis of 12 disease comorbidity categories (from 1 to 6 accordant with the relative risk of 1-year mortality) (13,14).

Treatment

External irradiation with 6 MV or 10 MV X-rays was performed with a linear accelerator; the daily dose of RT was 2.0 Gy based on the International Commission on Radiation Units of Measurement points, administered 5 days a week, for a total dose of 60 to 66 Gy. Either elective nodal irradiation (ENI), covering the bilateral supraclavicular and mediastinal lymph node regions, or involved-field irradiation (IFI) including the primary tumor with a margin of 2–4 cm was used. Three-dimensional conformal RT was performed for all patients. We used 2–4 fields to avoid the spinal cord. In patients who underwent two-field irradiation, the beam direction was changed after irradiation with 40 Gy. ENI was used in patients with normal respiratory and cardiac functions.

Chemotherapy was combined with RT in all patients, with the exception of those with poor general conditions. The chemotherapeutic regimen consisted of either 5-fluorouracil (5-FU; 700 mg/m^2 on days 1–4 every 4 weeks) plus cisplatin (CDDP; 70 mg/m^2 on day 1 every 4 weeks) or docetaxel (DOC; 10 mg/m^2 on day 1 per week). The 5-FU plus CDDP regimen was used in patients with normal renal function, and the DOC therapy was used in elderly patients and patients with a declining renal function. After treatment completion, patients were followed up at 1- to 3-month intervals for the first 2 years and at 4- to 6-month intervals thereafter. Follow-up assessments included history taking and physical examination, blood test, upper gastrointestinal

endoscopy, and computed tomography. A single radiation oncologist with expertise in esophageal cancer assessed the outcomes of this evaluation.

Outcomes

The initial response was measured based on the Response Evaluation Criteria in Solid Tumors guideline (version 1.1) (15) and using endoscopy findings for the primary tumor following the modified criteria of the 10th edition of the Japanese Classification of Esophageal Cancer established by the Japanese Society for Esophageal Disease. Complete response (CR) was defined as the disappearance of the primary tumor and irregular erosive lesions, ulcerative lesions, or apparently elevated lesions as observed during endoscopy and/or the absence of malignant cells in biopsy specimens (16). Conformation about patients who achieved CR was mandatorily obtained at least 1 month after CR was noted. Radiological imaging studies, upper gastrointestinal endoscopy, and medical records of physical examinations were used to identify the sites of recurrence. Metachronous recurrence was defined as the presence of recurrent lesions outside the primary site, and local recurrence was defined as the presence of recurrent lesions at the primary site. Salvage treatments conducted following recurrence were also assessed. Toxicity was assessed and documented following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (17). Toxicities were defined as acute if they occurred within 3 months and as late if they occurred after 3 months post-treatment, respectively.

Statistical analyses

The OS and disease-specific survival (DSS) rates from the date of initiation of treatment were measured using the Kaplan–Meier method. Death from any cause was defined as an event to calculate the OS rate, and esophageal cancer-related death was defined as an event to calculate the DSS. Statistical analyses were performed with EZR version 1.54 (18).

Results

Patients' characteristics

Between January 2009 and December 2020, 32 patients with cT1aN0M0 EC underwent definitive RT or CRT. Among these 32 patients, 12 had previously undergone endoscopic resection and the remaining 20 underwent definitive RT or CRT. *Table 1* shows the patients' characteristics. The patients who were unsuitable for endoscopic resection displayed spread of cancer along the entire tumor circumference (15 patients) and widespread tumor progression (6 patients) (including duplicates). The patients who were unsuitable for surgery displayed comorbidities (12 patients), double cancer (5 patients), and desire for esophageal conservation (7 patients) (including duplicates). Comorbidities included atrial fibrillation requiring anticoagulation in six patients, renal failure requiring dialysis in four patients, unstable angina requiring antiplatelet therapy in two patients, severe chronic obstructive pulmonary disease in two patients, and severe Parkinson's disease in one patient (including duplicates). The median follow-up period was 50 months (range, 13–131 months) for the entire cohort and 55 months (range, 13–131 months) for 14 survivors. Among the 14 survivors, 3 patients were lost to follow-up.

Initial response and survival

All patients achieved CR at initial treatment. The 1-, 3-, and 5-year OS and DSS rates were 100% and 100%, 83% and 100%, and 67% and 100%, respectively (*Figure 1*). Among the six patients, three died of other cancers and the remaining three died of other causes, including chronic obstructive pulmonary disease (one patient) and aspiration pneumonia from cerebral infarction (two patients).

Toxicity

Table 2 shows toxicities associated with RT or CRT. Grade 3 acute esophagitis was noted in two patients (10%); grade 3 acute pneumonia in one patient (5%); grade 3 leukocytopenia in one patient (5%); grade 3 or worse late toxicities in none; and grade 4 or 5 toxicities in none.

Patterns of recurrence and salvage treatments

Table 3 shows a summary of patients with recurrence. Recurrence was observed in eight patients (local recurrence in six and metachronous recurrence in two). In two patients with metachronous recurrence, distances from the initial tumor to the metachronous recurrence were 50 and 60 mm, respectively.

No lymph node and distant metastases were observed.

Table 1 Patients' characteristics

Characteristics	Data
Age, years, median [range]	70 [41–82]
Sex, n [%]	
Male	13 [65]
Female	7 [35]
ECOG PS score, n [%]	
0	6 [30]
1	13 [65]
2	1 [5]
Location of the primary tumor, n [%]	
Cervix	1 [5]
Upper thorax	0
Middle thorax	15 [75]
Lower thorax	3 [15]
Abdomen	1 [5]
Invasion depth, n [%]	
EP	0
LPM	11 [55]
MM	9 [45]
Tumor craniocaudal length, mm, median [range]	60 [20–160]
Tumor circumference, n [%]	
Entire	15 [75]
≥3/4 and < entire	4 [20]
≥1/2 and <3/4	1 [5]
Charlson comorbidity index, n [%]	
2	8 [40]
3	5 [25]
4	4 [20]
5	2 [10]
6	1 [5]
Concurrent chemotherapy, n [%]	
None	8 [40]
DOC	11 [55]
FP	1 [5]
Total radiation dose, n [%]	
60 Gy	18 [90]
66 Gy	2 [10]
Radiation field, n [%]	
ENI	10 [50]
IFI	10 [50]

DOC, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; ENI, elective nodal irradiation; EP, epithelium; FP, 5-fluorouracil and cisplatin; IFI, involved-field irradiation; LPM, lamina propria mucosa; MM, muscularis mucosa.

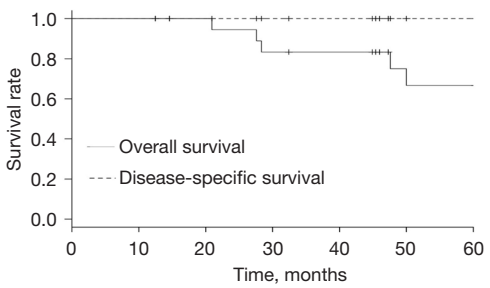

Figure 1 Kaplan–Meier estimates of survival.

Table 2 Treatment toxicities

CTCAE v5.0	Grade 1 or 2	Grade 3
Acute toxicity, n [%]		
Malaise	5 [25]	–
Esophagitis	17 [85]	2 [10]
Dermatitis	1 [5]	–
Pneumonitis	–	1 [5]
White blood cell decreased	9 [45]	1 [5]
Anemia	4 [20]	–
Decreased platelet count decreased	4 [20]	–
Late toxicity, n [%]		
Dysphasia	2 [10]	–
Pleural effusion	4 [20]	–
Pericardial effusion	7 [35]	–
Pneumonitis	3 [15]	–
Hypothyroidism	3 [15]	–

CTCAE, Common Terminology Criteria for Adverse Events.

Table 3 Summary of recurrent cases

Age, years	Sex	ECOG PS	Primary tumor location	Invasion depth	Tumor craniocaudal length (mm)	Tumor circumference	RT field	RT dose (Gy)	CRT	Months to disease recurrence	Recurrence lesions	Salvage therapy	Resected invasion depth	Resected tumor length (mm)	Resected Tumor circumference	Status at last follow-up from salvage therapy (months)
70	Male	1	Mt	MM	20	Entire	IFI	66	No	7	Metachronous	APC	–	–	–	DID 22
61	Male	1	Lt	LPM	100	Entire	IFI	60	Yes	15	Local	ESD	EP	14	<1/2	ANED 104
65	Male	1	Ae	LPM	50	Entire	ENI	60	No	17	Local	ESD	EP	30	<1/2	ANED 16
62	Male	0	Mt	MM	30	Entire	ENI	60	Yes	17	Local	ESD	EP	5	<1/2	ANED 73
41	Male	0	Mt	MM	160	Entire	ENI	60	Yes	43	Local	ESD	EP	18	<1/2	ANED 44
73	Male	1	Mt	LPM	40	Entire	IFI	60	Yes	50	Metachronous	ESD	LPM	31	<1/2	ANED 32
72	Male	1	Mt	MM	100	Entire	ENI	60	Yes	55	Local	ESD	EP	12	<1/2	DID 7
49	Female	0	Mt	MM	150	Entire	ENI	66	Yes	80	Local	ESD	EP	8	<1/2	ANED 45

ANED, alive with no evidence of disease; APC, argon plasma coagulation; CRT, chemoradiotherapy; DID, died of intercurrent disease; ECOG PS, Eastern Cooperative Oncology Group performance status; ENI, elective nodal irradiation; EP, epithelium; ESD, endoscopic submucosal dissection; IFI, involved-field irradiation; LPM, lamina propria mucosa; MM, muscularis mucosa; RT, radiotherapy.

After identifying recurrence, seven patients underwent salvage ESD and one underwent argon plasma coagulation (APC). Following endoscopic treatment, recurrence was not observed in any of the patients.

Discussion

The present study was designed to understand the clinical outcomes of definitive RT or CRT for patients with cT1aN0M0 EC unsuitable for endoscopic resection and surgery. In this study, the 5-year DSS rates were 100%. None of the patients died of treatment-related causes. All patients with recurrence were treated with salvage ESD or APC.

Table 4 enlists in detail the few previous studies that included patients with cT1aN0M0 EC. The CR rates in our study and in those conducted previously were favorable. Nemoto *et al.* and Ishikawa *et al.* reported that RT alone using IFI with or without intracavitary brachytherapy (ICBT) achieved 100% CR and demonstrated no regional lymph node recurrence (7,8). In our hospital, ENI was administered to patients with normal respiratory and cardiac functions a nd CRT with DOC was administered to older patients and patients with declining renal function owing to its radiosensitizing properties (19,20). However, CRT may cause severe hematologic toxicities (9). Previous studies reported fetal esophageal fistula with RT plus ICBT, whereas our study did not include any patient with severe esophageal fistula with RT or CRT (9,10). For stage II/III EC, the survival rate with CRT plus ICBT was not different from that of CRT alone (21). At present, ICBT, including palliative-intent treatment, is rarely performed for EC in Japan (3,22). The local recurrence rate in this study was slightly high as compared with those in previous studies (7-10). This might be associated with the longer tumor craniocaudal length in our study than in previous studies that reported that long tumor craniocaudal length was a prognostic factor for local recurrence of superficial EC, consistent with the findings of this study (8,23). All the patients who were unsuitable for endoscopic resection as the initial treatment because they displayed spread along the entire circumference or widespread tumor progression were treated with salvage ESD or APC. This can be attributed to the effect of regular follow-up with endoscopy. A previous study reported that patients with cT1–2 and N0 at baseline treated with salvage endoscopic resection showed significantly good prognosis in terms of OS (24). Regular follow-up with endoscopy and multidisciplinary treatment are considered important to manage cT1aN0M0

Table 4 Literature review of studies that included radiotherapy cases for cT1 aN0 M0 esophageal cancer

Author	Year	No.	Age, years, median [range]	Sex (male/female) (%)	PS (0/1–2) (%)	Tumor craniocaudal length, mm, median [range]	Median prescribed dose, Gy	ICBT (yes/no) (%)	CRT (yes/no) (%)	Field ENI/IFI (%)	CR rate (%)	5-year OS (%)	5-year DSS (%)	Local recurrence (%)	Regional lymph node recurrence rate (%)	Distant metastasis (%)	Grade 3 esophagitis (%)	Grade 3–5 esophageal fistula (%)	Grade 3 leukopenia (%)
Nemoto (7)	2001	52	68 [43–89]*	85/15*	NS	NS	65	63/37*	3/97*	0/100	100	62	81	12	0	0	NS	NS	NS
Ishikawa (8)	2006	18	70 [50–86]*	89/11	39/61	Almost <50	60–70 (range)	33/67	0/100	0/100	100	NA	100	0	0	0	15*	3*	NS
Yamada (9)	2006	23	67 [48–83]*	89/11	NS	36 [10–140]*	59.8*	100/0	100/0	0/100	NS	NA	85.2	17	0	0	3*	3*	21*
Murakami (10)	2011	44	70 [43–89]*	92/8*	79/21*	Almost <30*	54	61/39	0/100	100/0	98	84	97	29	2	0	2	3*	1
Our report	2021	20	70 [41–82]	65/35	30/70	60 [20–160]	60	0/100	60/40	64/36	100	67	100	30	0	0	2	0	1

*, including submucosal cancer. CR, complete response; DSS, disease-specific survival; ECOG PS, Eastern Cooperative Oncology Group performance status; ENI, elective nodal irradiation; EP, epithelium; ICBT, intracavitary brachytherapy; IFI, involved-field irradiation; LPM, lamina propria mucosa; MM, muscularis mucosa; NS, not stated; OS, overall survival.

EC. Accordingly, CRT, ENI, and ICBT might be overtreatments for toxicities, and RT alone and regular follow-up with endoscopy for salvage endoscopic treatments might be an appropriate treatment for cT1aN0M0 EC.

The current study has limitations associated with its retrospective design. First, the sample size was small; thus, statistical analysis was insufficient. Second, the external validity might be low. Some institutions performed subtotal-to-total circumferential resection with prophylactic steroids for more than 75% of the EC circumference (25,26). A phase III study aimed at prospectively evaluating the stenosis-preventive effect of submucosal triamcinolone injection and oral prednisolone treatment is ongoing (27). However, RT may be necessary for patients at high risk of esophageal stricture despite being treated with prophylactic steroids. Third, we could not demonstrate a difference in the appropriate treatment strategy between LPM and MM EC. Assessing the risk factors associated with metachronous lymph node or distant metastasis in patients treated with endoscopic resection revealed that the incidence of metastasis increased progressively with advancing depth of invasion. In a multivariate analysis, the depth of invasion was identified as the only significant risk factor, with a hazard ratio of 13.1 for pathological T1a-MM in comparison with pathological T1a-EP/LPM EC (28). CRT using ENI may be considered a definitive treatment for preventing regional lymph node recurrence in patients diagnosed with cT1a-MM EC. Therefore, a multicenter prospective study with a uniform strategy, such as EP/LPM EC for RT alone using IFI, is warranted.

In conclusion, definitive RT or CRT was considered an alternative initial treatment for patients with cT1aN0M0 EC who are contraindicated for endoscopic resection and surgery because no EC- and treatment-related deaths have been reported using salvage treatments. RT alone and regular follow-up with endoscopy for salvage endoscopic treatments might be appropriate treatment strategies for cT1aN0M0 EC.

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Footnote

Reporting Checklist: The authors have completed the

STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-773/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-773/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-773/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Juntendo Hospital review board (No. H20-0391), and informed consent was obtained in the form of an opt-out option displayed on the Juntendo University website. Those who did not provide consent were excluded.

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