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ORIGINAL ARTICLE

Long-term results of chemoradiotherapy with elective nodal irradiation for resectable locally advanced esophageal cancer in three-dimensional planning system

Shota Miyoshi[1] · Ikuno Nishibuchi[1] · Yuji Murakami[1] · Tsuyoshi Katsuta[1] · Nobuki Imano[1] · Junichi Hirokawa[1] · Yoichi Hamai[2] · Manabu Emi[2] · Morihito Okada[2] · Yasushi Nagata[1]

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Abstract

Background We evaluated the long-term results of definitive chemoradiotherapy (CRT) with elective nodal irradiation (ENI) using a three-dimensional (3D) planning system for resectable, locally advanced esophageal squamous cell carcinoma (LA-ESCC).

Methods This retrospective study included 65 patients with LA-ESCC who started CRT between 2006 and 2017. Patients with Stage I–IV LA-ESCC according to the Union for International Cancer Control TNM classification (eighth edition) were included. In stage IV, only supraclavicular lymph node (LN) metastasis was included. All patients received radiotherapy with ENI and concurrent chemotherapy with platinum and 5-fluorouracil.

Results The median age of the patients was 70 years (range 52–83 years). Stage I, II, III, and IV diseases were observed in 3 (5%), 28 (43%), 22 (34%), and 12 patients (18%), respectively. The median prescription dose was 66 Gy (range 50.4–66 Gy). The median follow-up period for the survivors was 71 months (range 8–175 months). The 5-year overall survival (OS) and progression-free survival rates were 54 and 43%, respectively. The 5-year OS rates for stages I–II and III–IV were 67 and 42%, respectively. Recurrence occurred in 29 patients (45%), and recurrence of regional LNs only occurred in 2 patients (3%). Grade 3 or higher late adverse events were observed in 8 patients (12%). Grade 5 heart failure occurred in two patients (3%); both had cardiovascular disease before treatment.

Conclusion The long-term results of definitive CRT with ENI for resectable LA-ESCC were favorable. ENI with a 3D planning system may reduce regional LN recurrence and late adverse events.

Keywords Resectable locally advanced esophageal cancer · Chemoradiotherapy · Elective nodal irradiation · Three-dimensional planning system · Onco-cardiology

Introduction

Esophageal cancer is difficult to detect in its early stages and is often diagnosed as advanced cancer. Locally advanced esophageal cancer has a high mortality rate, and various studies have been conducted on the treatment strategies [1–5]. Neoadjuvant therapy, such as chemotherapy or chemoradiotherapy (CRT) followed by esophagectomy, is currently the standard of care for resectable locally advanced esophageal squamous cell carcinoma (LA-ESCC) [6]. On the other hand, definitive CRT is a treatment option for patients who are unsuitable for surgery or refuse it, but there are no clinical trials directly comparing it to the current standard of care [7, 8]. Recently, there have been reports of good results with definitive CRT, which may be further improved by optimization of irradiation methods and advances in treatment techniques.

One of the most frequently discussed irradiation methods for esophageal cancer is elective nodal irradiation (ENI). ENI is a tradeoff between regional control and toxicities, especially late cardiopulmonary toxicities [9–13]. However,

✉ Ikuno Nishibuchi
ikuno@hiroshima-u.ac.jp

[1] Department of Radiation Oncology, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

[2] Department of Surgical Oncology, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

esophageal cancer has a high rate of lymph node (LN) metastasis, so three-field LN dissection is the standard technique in surgery [14–18]. Furthermore, even with definitive CRT with ENI, most adverse events (AEs) have been reported using two-dimensional (2D) planning systems, and there are few reports on ENI using three-dimensional (3D) planning systems [5, 19]. Therefore, in this study, we retrospectively assessed the efficacy and tolerability of definitive CRT with ENI using a 3D planning system for resectable LA-ESCC.

Materials and methods

Patients

From 2006 to 2017, all patients underwent CRT for resectable LA-ESCC at Hiroshima University Hospital, and 65 patients met the following criteria:

1. Patients with histologically proven squamous cell carcinoma by upper gastrointestinal endoscopy.
2. Clinical stage I–IV disease according to the Union for International Cancer Control TNM classification (eighth edition). In stage I, only patients with T1N1 disease were included. In stage IVB, only patients with supraclavicular LN metastasis were included. Patients with T4a disease were excluded from the study. For staging, all patients underwent contrast-enhanced computed tomography (CT), and positron emission tomography-CT (PET-CT) were also performed after 2009.
3. The patients were treated with curative intent radiotherapy (RT) with ENI using a 3D planning system.
4. Patients who received concurrent chemotherapy with platinum plus 5-fluorouracil (5-FU).

Radiotherapy

RT planning was performed with 6–10 MV X-rays, using 3D-conformal RT or intensity-modulated radiation therapy (IMRT).

The gross tumor volumes of the primary lesion and metastatic LNs were contoured as GTVp and GTVn, respectively. The GTVp was defined as the entire circumference of the esophagus at the level of the tumor. The GTVn was defined as LNs with a short diameter of ≥ 5 mm on CT, and FDG-PET findings were also used as references. The clinical target volumes of the primary lesion, metastatic LN, and subclinical LN areas for ENI were contoured as CTVp, CTVn, and CTVsub, respectively. The CTVp was GTVp with a margin of 15–20 mm vertically and 5 mm horizontally. The CTVn was GTVn with a 5 mm margin. The CTVsub according to the primary tumor sites included cervical, supraclavicular, and upper mediastinal LNs for cervical esophagus (Ce); supraclavicular, upper mediastinal, and subcarinal LNs for upper thoracic esophagus (Ut); upper to lower mediastinal and perigastric LNs for middle thoracic esophagus (Mt) or lower thoracic esophagus (Lt); and middle to lower mediastinal, perigastric, and celiac artery LNs for esophagogastric junction tumors. CTVp, CTVn, and CTVsub were combined into CTVinitial. The planning target volumes for the initial and boost irradiations were contoured as PTVinitial and PTVboost, respectively. The PTVinitial was CTVinitial with a margin of 5–10 mm horizontally and 8–15 mm vertically. The PTVboost was defined as CTVp and CTVn with the same margin as PTVinitial.

Regarding the irradiation method, only 3D-conformal RT was used in all cases of thoracic esophageal cancer, but IMRT was used in some cases of cervical esophageal cancer. In cases in which treatment was initiated with 3D-conformal RT, PTVinitial was irradiated with a dose of 40 Gy in 20 fractions and PTVboost was irradiated with a dose of 20–26 Gy in 10–13 fractions. 3D-conformal RT was performed using multiple beams whenever possible. Some patients were irradiated with IMRT only for PTVboost. In cases where treatment was initiated with IMRT, the dose of PTVboost was 60–66 Gy in 30–33 fractions, and the dose of ENI (a region of PTVinitial minus PTVboost) was 48–52.8 Gy in 30–33 fractions.

Chemotherapy

The standard chemotherapy regimen consists of a combination of cisplatin and 5-FU. Two cycles of cisplatin (70 mg/m^2) on day 1 and 5-FU (700 mg/m^2) on days 1–4 were administered at an interval of 4 weeks. For maintenance chemotherapy, from approximately 4 weeks after CRT, two cycles of cisplatin (80 mg/m^2) on day 1 and 5-FU (800 mg/m^2) on days 1–5 were administered at an interval of 4 weeks. Changes in the chemotherapy regimen from cisplatin to nedaplatin, or reduction of chemotherapeutic dosages, were ultimately determined by clinicians based on renal function, cardiac function, age, and general condition.

Follow-up

The initial tumor response was assessed by endoscopic biopsy and enhanced CT, according to the Response Evaluation Criteria in Solid Tumors, approximately 1–2 months after treatment was completed. For the post-treatment evaluation, we performed a physical examination, enhanced CT, and upper gastrointestinal endoscopy every 3–4 months in the first year and at least every 6 months thereafter.

Statistical analysis

Clinical data were updated on September 21, 2021. Overall survival (OS) was defined as the time from the initiation of RT to death from any cause. Progression-free survival (PFS) was defined as the time from the initiation of RT to the first documentation of disease progression or death from any cause. The Kaplan–Meier method was used to calculate survival rates. For univariate analysis (UVA), the log-rank test was used to compare the survival rates. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using JMP Pro 16 software (SAS Institute Inc., Cary, NC, USA). We used the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to assess toxicities. This study was approved by the Human Ethics Review Committee of our institution (E-2411).

Results

Patients

The characteristics of the 65 patients are summarized in Table 1. The median age of the patients was 70 years (range 52–83 years). The most common tumor location was the Mt in 27 patients (42%). Stage I, II, III, and IV diseases were observed in 3 (5%), 28 (43%), 22 (34%), and 12 (18%) patients, respectively. In terms of underlying medical conditions before treatment, cardiovascular disease, including hypertension, was found in 30 patients, and diabetes mellitus was found in 10 patients.

Treatment

The treatment-related characteristics are summarized in Table 1. The median total dose was 66 Gy/33 fractions (range 50.4–66 Gy). Fifty-two patients (80%) received 3D-conformal RT using multi-portal irradiation (three or more beams) or IMRT from the start of treatment.

The chemotherapeutic regimens of cisplatin plus 5-FU and nedaplatin plus 5-FU were used in 49 patients (75%) and 16 patients (25%) at the start of treatment, respectively.

Survival and failure patterns

The median follow-up times for survivors and all patients were 71 months (range 8–176) and 42 months (range 5–176), respectively. Forty-seven patients (72%) had complete clinical tumor responses. The 2- and 5-year OS rates were 69 and 54%, respectively (Fig. 1). The 2- and 5-year PFS rates were 53 and 43%, respectively (Fig. 1). The 5-year OS rates of stages I–II and III–IV were 67 and 42%, respectively (Fig. 2A) ($P = 0.0550$). The 5-year

Table 1 Patient characteristics

	$N = 65$	100 (%)
Age, years, median (range)	70 (52–83)	–
Sex		
Male	56	86.2
Female	9	13.8
Performance status		
0	52	80.0
1	12	18.5
2	1	1.5
Tumor location		
Cervical esophagus	21	32.3
Upper thoracic esophagus	6	9.2
Middle thoracic esophagus	27	41.5
Lower thoracic esophagus	11	16.9
Histological type		
Squamous cell carcinoma	65	100
T category		
T1b	40	61.5
T2	19	29.2
T3	6	9.2
N category		
N0	30	46.2
N1	26	40.0
N2	8	12.3
N3	1	1.5
Clinical stage		
I	3	4.6
II	28	43.1
III	22	33.8
IV	12	18.5
Multiple cancer		
Yes	15	23.1
No	50	76.9
Reasons for receiving the CRT		
Request	49	75.4
Not suitable for surgery	16	24.6
Cardiovascular diseases (including hypertension)		
Yes	30	46.2
No	35	53.8
Diabetes mellitus		
Yes	10	15.4
No	55	84.6
Clinical tumor responses		
Complete responses	47	72.3
Partial responses	16	24.6
No changes	1	1.5
Unknown	1	1.5
Total prescription dose		
Median	66 Gy	
Range	50.4–66 Gy	

Table 1 (continued)

	N = 65	100 (%)
Number of beams at the start of treatment		
Cervical esophagus		
Three or more beams or IMRT	15	71.4
Two	5	23.8
Unknown	1	4.8
Thoracic esophagus		
Three or more beams or IMRT	37	84.1
Two	4	9.1
Unknown	3	6.8
Concurrent chemotherapy		
Cisplatin + 5-fluorouracil	49	75.4
Nedaplatin + 5-fluorouracil	16	24.6

PFS rates of stages I–II and III–IV were 57 and 30%, respectively (Fig. 2B) ($P = 0.0584$). The 5-year OS rates of the Ce and Ut–Lt groups were 71 and 46%, respectively (Fig. 3A) ($P = 0.0405$). The 5-year PFS rates of the Ce and Ut–Lt groups were 50 and 39%, respectively (Fig. 3B) ($P = 0.2749$). Recurrence occurred in 29 (45%) patients. The initial recurrence sites were local in 16 patients (25%), regional LNs in 8 (12%), distant in 10 (15%), and metachronous esophageal cancer in 6 (9%). Recurrence only within the irradiated area occurred in 14 patients (22%), and recurrence of regional LNs only occurred in 2 patients (3%). All local recurrences and 4 regional LN recurrences occurred within the PTVboost, and 4 regional LN recurrences occurred within the ENI. In the 2 cases of regional LN recurrence only, one was within PTVboost, and one was within ENI. The results of the UVA for OS and PFS are summarized in Table 2. On UVA, the performance status (PS) score, T category, and clinical tumor responses were significantly associated with OS and PFS.

Toxicity

Table 3 shows the acute and late AEs. Grade 3 or higher acute AEs occurred in 46 (70%) patients. The most common acute AE was leukopenia (37 patients, 57%). A grade 4 acute AE of hyponatremia occurred in only one patient, and no grade 5 acute AEs occurred. There were 12 events of grade 3 or higher late AEs in eight patients (12%). All grade 3 or higher late AEs were observed in patients with thoracic esophageal cancer (18%, shown in Table 4). Grade 5 late AEs were observed in two patients (3%), both of which were grade 5 heart failure in patients who had cardiovascular disease before treatment. One of the two patients had a history of chronic atrial fibrillation and ventricular tachycardia. The patient died 37 months after the start of treatment because of acute exacerbation of chronic heart failure. Grade 4 pleural effusion, pericardial effusion, and hypothyroidism were observed in this patient. Another patient had a history of hypertension and was determined to be intolerant to surgery due to his general condition. He had only grade 2 pleural and pericardial effusions, with no severe late AEs, and died of heart failure 49 months after the start of treatment, which was judged to be a possible late AE due to RT, since there was no other apparent cause.

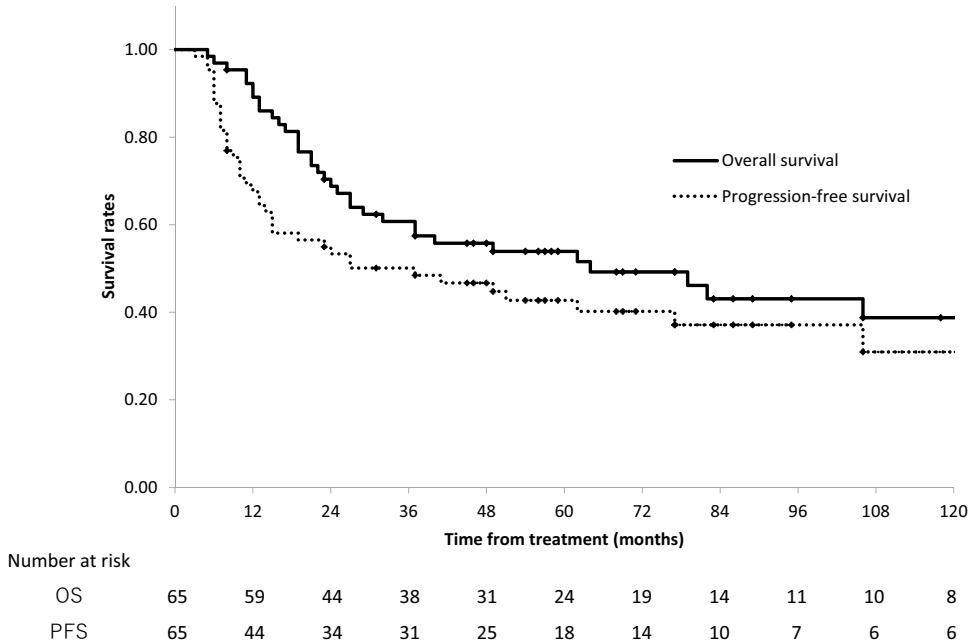
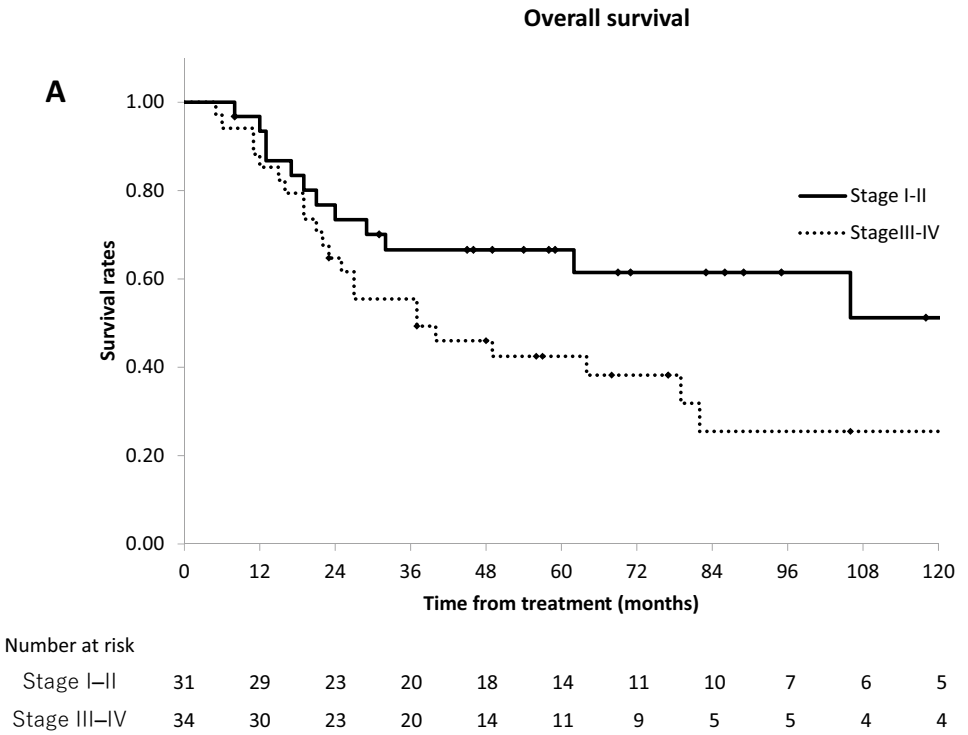


Fig. 1 OS and PFS rates for all patients. The 5-year OS and PFS rates of all patients were 54 and 43%, respectively. *OS* overall survival, *PFS* progression-free survival



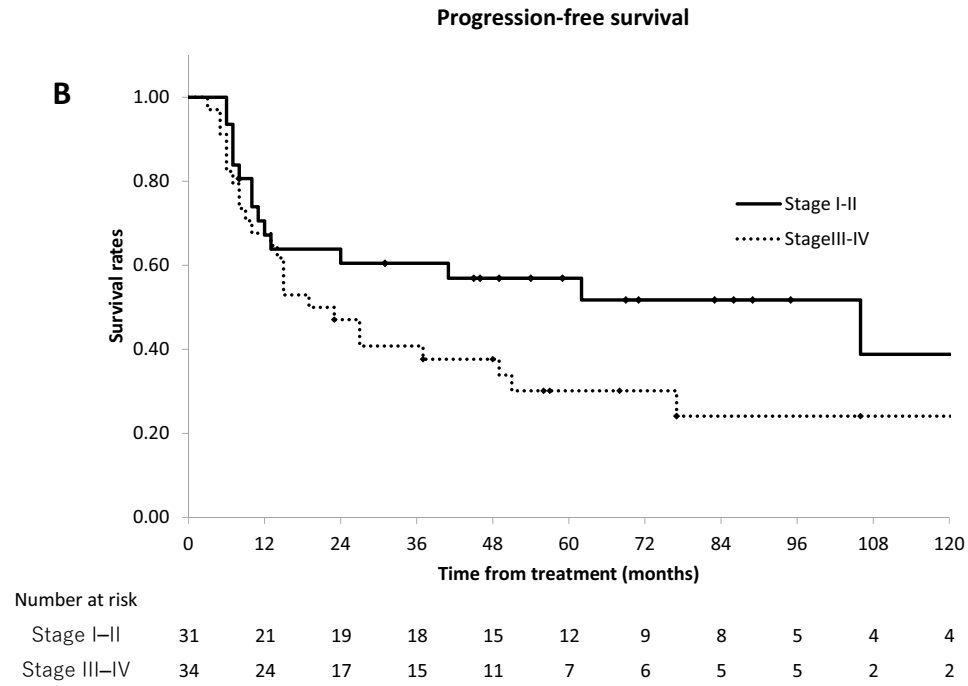


Fig. 2 OS and PFS rates by stage. The 5-year OS rates of stages I–II and III–IV were 67 and 42%, respectively ($P=0.0550$). The 5-year PFS rates of stages I–II and III–IV were 57 and 30%, respectively ($P=0.0584$). *OS* overall survival, *PFS* progression-free survival

Discussion

The current standard of care for resectable LA-ESCC is neoadjuvant chemotherapy or neoadjuvant CRT followed by esophagectomy, but no clinical trials have directly compared it to definitive CRT. Esophagectomy with three-field LN dissection is a highly invasive procedure. In definitive CRT with ENI, late AEs have also been problematic; however, most of the data are from 2D planning systems, and we believe that 3D planning systems can provide safer treatment. This study aimed to evaluate the efficacy and safety of definitive CRT using ENI in a 3D planning system. Despite a quarter of the patients being intolerant to surgery, the results were favorable, with a 2-year OS of 69%, 2-year PFS of 53%,

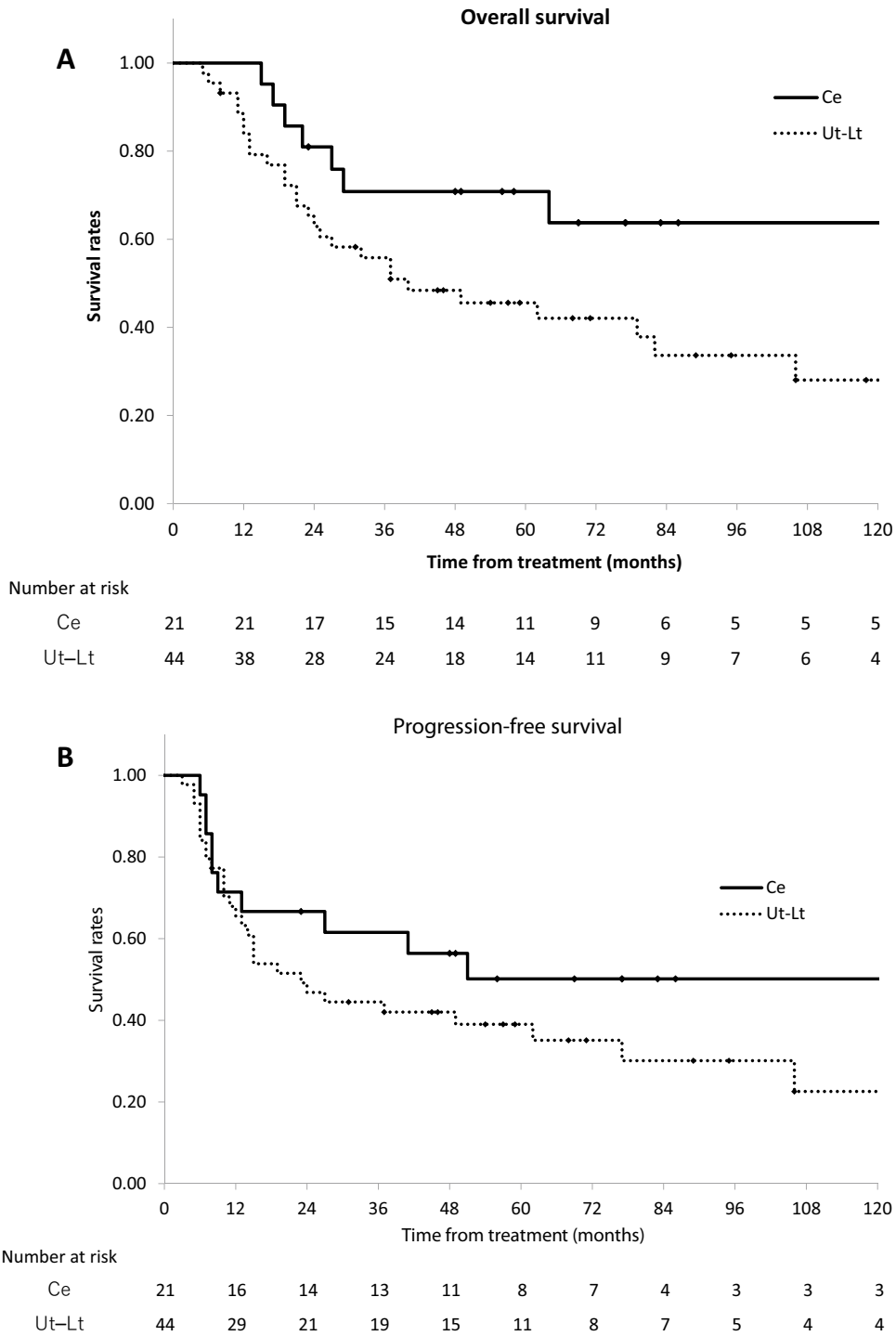


Fig. 3 OS and PFS rates by tumor location. The 5-year OS rates of the Ce and Ut–Lt groups were 71 and 46%, respectively ($P=0.0405$). The 5-year PFS rates for the Ce and Ut–Lt groups were 50 and 39%, respectively ($P=0.2749$). *OS* overall survival, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *PFS* progression-free survival

5-year OS of 54%, 5-year PFS of 43%, and grade 3 or higher late AEs of 12%. These results are comparable to those reported in the Japan Clinical Oncology Group (JCOG) 9907 trial (5-year OS, 55%; 5-year PFS, 44%) and the CROSS trial (2-year OS, 67%; 2-year PFS, 50%), which were clinical trials of esophagectomy following neoadjuvant therapy [2, 3]. A comprehensive registry of patients with esophageal cancer in Japan reported that the treatment-related mortality rate after esophagectomy was 2.75% (operative mortality rate, 0.75%; and hospital mortality rate, 2.0%) [14]. Moreover, Low et al. reported 30- and 90-day mortality rates of 2.4 and 4.5%, respectively [20]. These results were comparable to the 3% grade 5 late AEs in this study. Moreover, our study included patients who were unable to tolerate surgery; hence, we considered ENI with radiotherapy techniques an acceptable treatment.

Table 2 Relationship between predictive factors and treatment results

	N	5-year OS rate (%)	UVA *P* value	5-year PFS rate (%)	UVA *P* value
Age					
≤70	33	65	0.0821	47	0.5301
>70	32	42		39	
Sex					
Male	56	52	0.2305	40	0.5496
Female	9	67		56	
Performance status					
0	52	64	<0.0001	53	0.004
1–2	13	15		0	
Tumor location (Ce vs Ut–Lt)					
Ce	21	71	0.0405	50	0.2749
Ut–Lt	44	46		39	
Clinical stage (I–II vs III–IV)					
I–II	31	67	0.055	57	0.0584
III–IV	34	42		30	
T category (T1b–2 vs T3)					
T1b–2	25	75	0.0118	63	0.0085
T3	40	40		30	
N category (N0 vs N1–3)					
N0	30	65	0.1215	56	0.226
N1–3	35	45		33	
Reasons for receiving the CRT					
Request	49	56	0.6996	49	0.5331
Not suitable for surgery	16	46		24	
Diabetes mellitus					
Yes	10	57	0.9552	47	0.533
No	55	53		42	
Clinical tumor responses (CR vs others)					
CR	47	63	0.0033	47	0.017
Others	18	31		33	

OS overall survival, *PFS* progression-free survival, *UVA* univariate analysis, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *CR* complete responses

There are several important aspects of CRT performed at our institution. First, we used a 3D planning system. This is a currently matter of course, but until 20–30 years ago, 2D planning system was common, and most reports of late AEs in CRT were from this era [5, 19]. Several studies have reported that the use of IMRT can reduce the dose to organs at risk (OARs), thereby reducing the incidence of AEs [21, 22]. In 3D-conformal RT, multiple beams are used from the start, reducing the doses per fraction delivered to the OARs. Consequently, the biologically effective dose is reduced, and a lower AE rate can be expected [23]. In fact, grade 3 or higher late AEs occurred in more than 30% of patients when the 2D planning system was used, compared to a markedly lower rate of 12% in this study [5, 19].

Second, we used ENI for regional LNs. Onozawa et al. reported that ENI suppresses LN recurrence; however, further evaluation is needed to determine whether ENI improves OS [9]. Li et al. also reported that local and distant recurrences contribute to OS, and ENI does not contribute to OS because LN recurrence is rare [13]. Thus, the effectiveness of ENI remains controversial [9–13]. There are two main reasons why ENI does not improve the prognosis of LA-ESCC patients. The first argument is that even if only the LNs can be controlled when local control is not possible, it will not lead to long-term survival because of local recurrence. In previous reports, the most common failure pattern was local failure in advanced cases [19]. However, reports that ENI does not improve prognosis may include a large number of unresectable cases [11, 12]. In contrast, in

Table 3 Results of acute and late adverse events

Adverse events	Common terminology criteria for adverse events Ver 5.0							
	Grade 2		Grade 3		Grade 4		Grade 5	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Acute adverse events								
Leukopenia	22	33.8	38	58.5	–	–	–	–
Anemia	21	32.3	3	4.6	–	–	–	–
Thrombocytopenia	12	18.5	5	7.7	–	–	–	–
Increased creatinine	8	12.3	–	–	–	–	–	–
Hyponatremia	2	3.1	10	15.4	1	1.5	–	–
Esophagitis	36	55.4	4	6.2	–	–	–	–
Nausea	21	32.3	5	7.7	–	–	–	–
Stomatitis	5	7.7	3	4.6	–	–	–	–
Late adverse events								
Esophageal stricture	11	16.9	–	–	–	–	–	–
Pneumonitis	3	4.6	2	3.1	–	–	–	–
Pleural effusion	4	6.2	3	4.6	1	1.5	–	–
Pericardial effusion	23	35.4	2	3.1	1	1.5	–	–
Hypothyroidism	18	27.7	–	–	1	1.5	–	–
Heart failure	–	–	–	–	–	–	2	3.1

Table 4 Results of late adverse events of patients with thoracic esophageal cancer

Adverse events	Common terminology criteria for adverse events Ver 5.0					
	Grade 3		Grade 4		Grade 5	
	N	(%)	*N*	(%)	*N*	(%)
Esophageal stricture	–	–	–	–	–	–
Pneumonitis	2	4.5	–	–	–	–
Pleural effusion	3	6.8	1	2.3	–	–
Pericardial effusion	2	4.5	1	2.3	–	–
Hypothyroidism	–	–	1	2.3	–	–
Heart failure	–	–	–	–	2	4.5

this study, only resectable stages were included, and a high local control rate was achieved (CR rates: 72%, only in-field recurrence rates: 22%, etc.), suggesting that the inhibition of LN recurrence by ENI improved prognosis in resectable cases. Another argument is that the expansion of the irradiation field by ENI increases late toxicity and worsens prognosis [5, 9, 19]. However, many reports of late toxicity are from the 2D era, and we consider that ENI can now be performed safely for the aforementioned reasons. Notably, in this study, the median follow-up period of the surviving patients was 71 months, which is a long time, and late AEs were fewer than those reported in the past. In summary, ENI may be performed safely and has the potential to improve outcomes of definitive CRT for patients with LA-ESCC. Globally, ENI has been adopted in clinical trials conducted in recent years, such as ARTDECO, CONCORDE, and JCOG 0909, and ENI is now considered to be effective [24–26].

Third, our institution used to prescribe 60 Gy or more to many patients with the expectation that an increased dose would improve treatment efficacy. The results were good, but the extent to which the increased dose improved the outcomes was unclear. In Japan, a prescription of 60 Gy is standard, following the results of the JCOG 9906 trial [5]. However, the recently reported JCOG 0909 trial showed good survival and AE rates with a prescription of 50.4 Gy, albeit with the assumption of salvage surgery [26]. In addition, the results of clinical trials to evaluate dose-escalation strategies, such as ARTDECO (50.4 vs 61.6 Gy, NTR3532) and CONCORDE (50 vs 66 Gy, NCT01348217) trials, were also recently reported [24, 25]. In those trials, as in previous reports, local control rates did not improve with high-dose prescriptions and OS tended to be relatively low. Based on these results, for definitive CRT of locally advanced esophageal cancer, we consider that a prescription of 50–50.4 Gy is

preferable for patients who can undergo surgery. For patients who refuse surgery or cannot tolerate surgery, irradiation of approximately 60 Gy may be considered.

RT techniques have improved significantly in recent years, and the outcomes of resectable LA-ESCC may improve further in the future. The latest irradiation techniques include IMRT and proton therapy. Lin et al. reported that the use of IMRT can reduce all-cause mortality, including cardiac-related deaths [20, 21]. Unlike X-rays, proton beams do not spread around or stop after a certain distance. Taking advantage of this, proton therapy has been reported to improve survival rates and AEs in esophageal cancer patients even more than IMRT [27, 28]. With such high-precision treatments, local control rates and AE rates may be further improved.

The field of onco-cardiology has also gained attention in recent years in response to the growing number of cancer patients with cardiovascular diseases owing to the aging of the population [29]. It is an attempt to improve the prognosis and quality of life by preventing severe cardiovascular toxicity caused by chemotherapy and radiotherapy through periodic cardiac function monitoring (including electrocardiogram, echocardiography, and blood sampling) and early therapeutic intervention [30, 31]. For example, there is a gap in the treatment of heart failure, where the criteria for initiation of treatment in oncology are symptomatic cases (CTCAE Grade 3); however, in cardiology, treatment is initiated even in the absence of symptoms if risk factors are present. As thoracic irradiation itself is a risk factor for heart failure, periodic evaluation of cardiac function may be beneficial, especially in cases of thoracic irradiation in patients with cardiac complications. Onco-cardiology is not yet well established in the field of radiation oncology because radiation oncologists focus on reducing cardiac doses. However, it may become important in the future to reduce late cardiotoxicity after RT in patients with esophageal cancer.

This study was limited by its retrospective design and the fact that it is a single-center study. Furthermore, this report includes cases of cervical esophageal cancer. For cervical esophageal cancer, the dose to the heart and lungs is naturally lower; therefore, the frequency of late cardiopulmonary AEs is also lower. Notably, grade 3 or higher AEs were only observed in patients with thoracic esophageal cancer, and this difference may have led to the difference in OS across tumor locations. However, even if we analyzed only thoracic esophageal cancer in this study, 8 patients (18%) had grade 3 or higher late AEs. This study was followed for a longer period than most other reports, and on that basis, we considered this toxicity to be acceptable [5]. However, some degree of cardiopulmonary toxicity is still observed, and given that more people can expect a long-term prognosis, further dose reduction strategies for the heart and lungs are expected (e.g., IMRT and proton beams).

In conclusion, with a 3D planning system, ENI has the potential to contribute to the suppression of regional LN recurrence in definitive CRT for LA-ESCC, while reducing AEs.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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