

# Definitive chemoradiotherapy has comparable survival outcomes to esophagectomy in patients with clinical T1N0M0 esophageal squamous cell carcinoma: real world data

**Kentaro Sawada**

Kushiro Rosai Hospital: Kushiro Rosai Byoin <https://orcid.org/0000-0001-7952-2765>

**Hiroki Yukami**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Saori Mishima**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Hisashi Fujiwara**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Tomohiro Kadota**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Keiichiro Nakajo**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Yusuke Yoda**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Masaki Nakamura**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Hidehiro Hojo**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Tomonori Yano**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Takeo Fujita**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Takashi Kojima**

National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

**Daisuke Kotani** (✉ [dkotani@east.ncc.go.jp](mailto:dkotani@east.ncc.go.jp))

Department of Gastroenterology and Gastrointestinal Oncology <https://orcid.org/0000-0002-4196-555X>

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# Abstract

## Background

Recently, the JCOG0502 has shown a comparable efficacy of chemoradiotherapy and esophagectomy in patients with clinical T1N0M0 esophageal squamous cell carcinoma. However, few studies have compared the clinical outcomes of these treatments in esophageal squamous cell carcinoma patients (including elderly patients) based on real-world data.

## Methods

This retrospective study determined real-world outcomes in patients who underwent chemoradiotherapy or esophagectomy, including those with clinical T1N0M0 esophageal squamous cell carcinoma, between 2009 and 2017 at the National Cancer Center Hospital East.

## Results

Among a total of 156 patients, 120 and 36 patients underwent esophagectomy and chemoradiotherapy, respectively; 138, 12 and 6 patients had Eastern Cooperative Oncology Group performance status 0, 1, and 2, respectively; and 33 and 123 patients had clinical tumor depth MM-SM1 and SM2-SM3, respectively. In a median follow-up of 72 months, 5-year progression-free survival and overall survival were respectively 77.0% and 81.5% in the esophagectomy group and 74.4% and 82.6% in the chemoradiotherapy group ( $P = 0.48$  and,  $P = 0.89$ ). Moreover, no treatment-related death was detected in both groups. In elderly patients (75 years or older), 5-year progression-free survival and overall survival were not significantly different between esophagectomy and chemoradiotherapy groups (5-year progression-free survival: 72.3% vs. 81.8%,  $P = 0.38$ ; 5-year overall survival: 76.9% vs. 81.8%,  $P = 0.59$ ).

## Conclusions

This real-world study confirms the results of a previous clinical trial, and the present findings support chemoradiotherapy as one of the standard treatment options in patients of all ages with clinical T1N0M0 esophageal squamous cell carcinoma.

## Introduction

Esophageal cancer is the eighth most common cancer in the world, leading to about a half million of deaths each year [1]. Western populations have a high prevalence of esophageal or esophagogastric junction adenocarcinoma, while more than 90% of patients with esophageal cancer in Asia, including Japan, have esophageal squamous cell carcinoma (ESCC) [2, 3].

Endoscopic resection, including endoscopic mucosal resection and endoscopic submucosal dissection (ESD), is the standard treatment for clinical T1aN0M0 ESCC due to a potentially low risk of nodal metastasis [4, 5], while esophagectomy is regarded as the standard treatment for clinical T1bN0M0 ESCC because of 20–40% of lymph node metastasis [6, 7]. Although the 3-year overall survival (OS) in patients with clinical T1N0M0 (cT1N0M0) ESCC who underwent esophagectomy is over 80% [6, 8, 9], post-operative complications and declined quality of life after esophagectomy still remain major problems; therefore, less-invasive procedures have been desired as alternative treatments.

Chemoradiotherapy (CRT) showed promising efficacy in patients with cT1N0M0 ESCC in the Japan Clinical Oncology Group (JCOG) 9708, with a complete response rate of 87.5% and a 4-year survival rate of 80.5% [10]. More recently, the JCOG0502 demonstrated non-inferiority of CRT to esophagectomy in patients with cT1N0M0 ESCC in the non-randomized part (5-year OS rate: 85.5% in CRT versus 86.5% in esophagectomy) [11]. Therefore, CRT could be considered one of the standard treatment options for patients with cT1N0M0 ESCC. Therefore, this retrospective study aimed to assess whether CRT has equivalent survival outcomes compared to esophagectomy in patients with cT1N0M0. In addition, we also investigated the safety and efficacy of CRT and esophagectomy in elderly patients, who were not eligible to clinical trials.

## Methods

### Patients

This study included patients with cT1N0M0 ESCC who underwent esophagectomy or CRT as the first-line treatment at the National Cancer Center Hospital East between January 2009 and December 2017. The clinical tumor stages were determined by these modalities: Upper gastrointestinal endoscopy and computed tomography (CT) were performed for all patients, while endoscopic ultrasonography and positron emission tomography were performed optionally. In this study, an "elderly patient" was defined as a patient aged 75 years or older.

The main exclusion criteria were as follows: 1) tumor location at the cervical esophagus or abdominal esophagus; 2) prior treatment for ESCC, except those who were finally diagnosed with pathological T1a-muscularis mucosae or shallower invasion without lymphovascular invasion after endoscopic resection for other lesions; 3) synchronous or metachronous multiple cancers, except stage I, within the previous 5 years. Patients with medical comorbidities were not excluded from this study.

### Treatment

Esophagectomy included open or thoracoscopic radical esophagectomy with or without three-field lymphadenectomy. Transhiatal esophagectomy was also permitted. CRT, comprising radiotherapy and concurrent chemotherapy, mainly consisted of 5-fluorouracil (FU) and platinum. Patients were treated 5 days per week at 1.8 Gy/day in 28 fractions (total 50.4 Gy) or at 2 Gy/day in 30 fractions (total 60 Gy) with megavoltage equipment ( $\geq 6$  MV) using a multiple-field technique. In Patients treated with 50.4 Gy,

the clinical target volume (CTV) included the primary tumor and regional lymph nodes (LNs) with a 2 cm craniocaudal margin of the primary tumor. Planning target volume (PTV) was defined as CTV plus a 1–2 cm margin in the craniocaudal direction and 0.5–1 cm margin in the lateral direction. After treatment with 41.4 Gy to the PTV, a booster dose of 9.0 Gy was administered to the primary tumor. In patients treated with 60 Gy, CTV included the primary tumor with a 2 cm craniocaudal margin. PTV was defined the same as above. Irradiation of 60 Gy to the PTV was performed without prophylactic irradiation for regional LNs.

## **Clinical outcomes and statistical analysis**

OS was defined as the time from the initiation date of treatment to death, and progression-free survival (PFS) was defined as the time from the initiation date of treatment to recurrence or death. In the CRT group, esophageal preservation period was defined as the time from the initiation date of treatment to salvage surgery or death. Recurrence was defined as distant metastasis, LN metastasis, or local recurrence that needed surgical resection for cure. Local recurrence that can be cured with endoscopic treatment was not defined as a recurrence in this study. The adverse events of esophagectomy and CRT were evaluated with the Clavien–Dindo classification version 2.0 [12] and the Common Terminology Criteria for Adverse Events version 5.0. Early toxicity and hematological adverse events of the CRT group in particular were defined as events observed between the initiation day of treatment and 30 days after the end of treatment, and late toxicity was defined as events observed more than 30 days after the end of treatment.

Patients' clinical information was collected by retrospectively reviewing their medical records. This study was conducted in accordance with the Ethical Guidelines for Medical Research Involving Human Subjects and was approved by the Ethical Review Committee of the National Cancer Center Hospital East (2017 – 120).

The Fisher's exact test or the chi-square test was performed to compare categorical variables and the student t-test was performed to compare continuous variables. Survival curves were estimated using the Kaplan–Meier method and differences between the groups were tested by the log-rank test. Hazard ratios were estimated using the Cox proportional hazards model. All P values < 0.05 were considered statistically significant and statistical analyses were performed using the IBM SPSS statistical software package (version 23.0 for Mac, IBM Japan Ltd., Tokyo, Japan).

## **Results**

### **Characteristics of Patients**

This study included 120 patients in the esophagectomy group and 36 patients in the CRT group. Among them, 21 and 11 elderly patients were included in the esophagectomy and CRT groups, respectively (Supplementary Fig. 1). The esophagectomy and CRT groups had similar patients' characteristics, except clinical tumor depth (SM2/3: 84.2% in the esophagectomy group vs. 61.1% in the CRT group, P = 0.005) (Table 1). Synchronous stage 0 or I ESCC at diagnosis was detected in 18 patients in the esophagectomy

group (15.0%) and five patients in the CRT group (13.9%). Only two patients in the esophagectomy group had history of previous treatment with endoscopic resection for pathological T1a ESCC.

Table 1  
Baseline patient characteristics

	All patients (n = 156)			Elderly patients (n = 32)	
	Esophagectomy (n = 120) n, %	CRT (n = 36) n, %	P values	Esophagectomy (n = 21) n, %	CRT (n = 11) n, %
Age, year (median, range)	67 (46–87)	70 (38–85)	0.360*	78 (75–87)	77 (75–85)
Sex	96 (79.7)	32 (88.8)	0.322**	20 (95.2)	9 (81.8)
Male	24 (20.3)			1 (4.8)	
Female		4 (11.1)			2 (18.2)
ECOG PS	105 (87.5)	33 (91.7)	0.391***	16 (76.1)	10 (90.9)
0	11 (9.2)			5 (23.8)	
1	4 (3.3)	1 (2.8)		0	1 (9.1)
2		2 (5.6)			0
Tumor location	12 (10.0)	4 (11.1)	0.067***	3 (14.3)	1 (9.1)
Ut	61 (50.8)	26 (72.2)		10 (47.6)	8 (72.7)
Mt	47 (39.2)			8 (38.1)	
Lt		6 (16.7)			2 (18.2)
Clinical tumor depth	19 (15.8)	14 (38.9)	0.005**	2 (9.5)	6 (54.5)
MM/SM1	101 (84.2)			19 (90.5)	
SM2/SM3		22 (61.1)			5 (45.5)
Horizontal location	74 (61.7)	17 (47.2)	0.129**	15 (71.4)	5 (45.5)
≤ 3/4	46 (38.3)			6 (28.6)	
>3/4		19 (52.8)			6 (54.5)
Intramural metastasis	3 (2.5)	2 (5.6)	0.326**	1 (4.8)	1 (9.1)

\*Student t-test, \*\*Fisher's exact test, \*\*\*chi-square test, Esophagectomy vs. CRT in all patients. CRT: Chemoradiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; ESCC: esophageal squamous cell carcinoma; Lt: lower thoracic esophagus; MM: muscularis mucosae; Mt: Middle thoracic esophagus; SM: submucosa; Ut, upper thoracic esophagus.

	All patients (n = 156)			Elderly patients (n = 32)	
History of treatment for ESCC	2 (1.7)	0	1.000**	0	0
Synchronous other ESCC at diagnosis	18 (15.0)	5 (13.9)	1.000**	2 (9.5)	0
Synchronous other cancer at diagnosis	16 (13.3)	3 (8.3)	0.567**	3 (14.3)	0
Comorbidity	57 (47.5)	13 (36.1)	0.256**	16 (76.2)	6 (54.5)
Cardiovascular	13 (10.8)	2 (5.6)	0.523**	2 (9.5)	2 (18.2)
Respiratory	16 (13.3)	5 (13.9)	1.000**	4 (19.0)	1 (9.1)
Diabetes mellites	9 (7.5)	2 (5.6)	1.000**	2 (9.5)	0
Brain disease					

\*Student t-test, \*\*Fisher's exact test, \*\*\*chi-square test, Esophagectomy vs. CRT in all patients. CRT: Chemoradiotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; ESCC: esophageal squamous cell carcinoma; Lt: lower thoracic esophagus; MM: muscularis mucosae; Mt: Middle thoracic esophagus; SM: submucosa; Ut, upper thoracic esophagus.

Table 2  
Treatment details in patients with esophagectomy (A) and CRT (B)

A. Esophagectomy			
	All patients (n = 120)	Elderly patients (n = 21)	P values
	n (%)	n (%)	
Esophagectomy with a 3 FL	110 (91.7)	15 (71.4)	0.026*
Esophagectomy with a 2 FL	2 (1.7)	1 (4.8)	
Esophagectomy with 1 FL or others	8 (6.7)	5 (23.8)	
Open esophagectomy	8 (6.7)	0	0.026*
Thorascopic esophagectomy	104 (86.7)	16 (76.2)	
Transhiatal esophagectomy	8 (6.7)	5 (23.8)	
Resection margin	118 (98.3)	21 (100.0)	1.000**
R0	2 (1.7)	0	
R1			

\* Chi-square test, \*\* Fisher's exact test, All patients vs. Elderly patients. FL: field lymphasectomy

Table 3  
Complications in patients with esophagectomy (A) and CRT (B)

<b>B. CRT</b>			
	All patients (n = 36)	Elderly patients (n = 11)	P values*
	n (%)	n (%)	
Concurrent chemotherapy regimen	34 (94.4)	10 (90.9)	0.560
5-FU + platinum	2 (5.6)	1 (9.1)	
5-FU alone			
Treatment modality	21 (58.3)	6 (54.5)	1.000
X-ray	15 (41.7)	5 (45.5)	
Proton			
Radiation dose	16 (44.4)	5 (45.5)	1.000
50.4 Gy	20 (55.6)	6 (54.5)	
60 Gy			
Response to treatment	33 (91.7)	11 (100.0)	1.000
Complete remission	3 (8.3)	0	
Residual disease			
* Fisher's exact test, All patients vs. Elderly patients. CRT: Chemoradiotherapy; 5-FU: 5-fluorouracil.			
<b>A. Esophagectomy</b>			
	All patients (n = 120)	Elderly patients (n = 21)	P values*
	n (%)	n (%)	

\* Fisher's exact test, All patients vs. Elderly patients. RL nerve: Recurrent laryngeal nerve

<b>B. CRT</b>			
<b>Early complication</b>	72 (60.0)	14 (66.7)	0.634
Any	22 (18.3)	4 (19.0)	1.000
RL nerve paralysis	15 (12.5)	1 (4.8)	0.467
Anastomotic leakage	9 (7.5)	4 (19.0)	0.106
Surgical site infection	7 (5.8)	3 (14.3)	0.171
Pneumonia	6 (5.0)	1 (4.8)	1.000
Lymphorrhea	4 (3.3)	0	1.000
Chylothorax	3 (2.5)	0	1.000
Ileus	2 (1.7)	0	1.000
Bleeding	2 (1.7)	1 (4.8)	0.386
Pneumothorax	31 (25.8)	8 (38.1)	0.292
<b>Late complication</b>	26 (21.7)	6 (28.6)	0.572
Any	3 (2.5)	0	1.000
Esophageal stenosis	2 (1.7)	0	1.000
Ileus			
Bleeding			
* Fisher's exact test, All patients vs. Elderly patients. RL nerve: Recurrent laryngeal nerve			

### Treatment details

Treatment details and pathological outcomes in patients who received esophagectomy are shown in Table 2A and Supplementary Table 1. Esophagectomy with three-field lymphadenectomy was performed in 110 patients (91.7%). Post-operative histological findings revealed that 86 patients (77.3%) had pathological T1N0M0 disease, and 34 patients (30.9%) had a pathological non-T1N0M0 disease. Thirty-two patients (29.1%) had LN metastasis, and six patients (5.5%) had deeper tumor depth (four patients had both LN metastasis and deeper tumor). Although most of the patients achieved complete resection (R0), two patients (1.8%) had microscopic residual disease (R1). After esophagectomy, six patients with non-T1N0M0 disease underwent adjuvant chemotherapy.

Treatment details in the CRT group are shown in Table 2B. Concurrent chemoradiotherapy was performed for all patients. Thirty-four patients (94.4%) received the 5-FU plus platinum combination regimen. In addition, 21 patients (58.3%) received X-ray therapy, and 15 patients (41.7%) received proton beam therapy. Total doses of 60 Gy or Gy equivalents and 50.4 Gy were delivered to 20 patients and 16 patients, respectively. Post-treatment endoscopic evaluation showed that 33 patients (91.7%) achieved

complete remission, while three patients (8.3%) had residual disease. All three patients with residual diseases underwent additional salvage treatment (ESD in two patients and esophagectomy in one patient).

## Safety

Post-operative complications in the esophagectomy group are shown in Table 3A. Seventy-two patients (60.0%) had early complications; the main common complications were recurrent laryngeal nerve paralysis (22 patients, 18.3%), anastomotic leakage (15 patients, 12.5%), and surgical site infection (9 patients, 7.5%). Esophageal stenosis was the most frequent (26 patients, 21.7%) late complication. There was no post-operative mortality within 30 days of esophagectomy.

Adverse events in the CRT group are shown in Table 3B and Supplementary Table 2. Most of the patients experienced hematologic adverse events; particularly, grade 3 or higher leucopenia and neutropenia were observed in nine patients (25.0%). Esophagitis was observed in 31 patients (86.1%); it was the most common early toxicity. Radiation-related late toxicities including pleural effusion, pericardial fluid accumulation, and irradiation pneumonitis were observed in six (16.7%), four (11.1%), and three (8.3%) patients, respectively.

## Efficacy

With a median follow-up period of 71.8 months (72.8 months in esophagectomy group and 70.8 months in CRT group) with Kaplan-Meier estimate, the 5y-PFS was 77.0% in the esophagectomy group and 74.4% in the CRT group, with no significant difference between the two groups ( $P = 0.48$ ) (Fig. 1A). The 5y-OS was 81.5% in the esophagectomy group and 82.6% in the CRT group, with no significant difference between the two groups ( $P = 0.89$ ) (Fig. 1B). The results of univariate and multivariate analysis for PFS and OS with clinical factors are shown in supplementary table 4 and 5. Particularly, according to the clinical tumor invasion depth, which was based on clinical factors between the treatment groups, the 5y-PFS and OS in patients with cSM2/SM3 disease tend to be worse compared to those with MM/SM1 (5y-PFS, 87.9% vs. 73.4%; 5y-OS, 90.6% vs. 79.5%) (Supplementary Fig. 2). However, even in multivariate analysis, the adjusted hazard ratio of CRT was 1.299 (95%CI [0.627–2.689],  $p = 0.48$ ) for PFS and 1.007 for OS (95%CI [0.438–2.315],  $p = 0.99$ ), respectively; there was no significant difference in efficacy between esophagectomy and CRT. In the CRT group, the 3y- and 5y-survival rates with esophageal preservation were 80.4% and 76.9%, respectively.

## Treatments after recurrence

During the follow-up period, 21 patients (17.5%) in the esophagectomy group and nine patients (25.0%) in the CRT group experienced disease recurrence. The details of recurrence sites and additional treatments are shown in Table 4 and Supplementary Table 3. The rates of local recurrence (0% vs. 2.8%), regional LN metastasis (5.8% vs. 8.3%), and distant metastasis (11.7% vs. 13.9%) were similar between the esophagectomy and CRT groups; however, bone metastasis ( $n = 5$ ) was observed only in the

esophagectomy group. Among the 30 patients with recurrence, salvage surgery was performed in three of 21 patients in the esophagectomy group (14.3%) and five of nine patients in the CRT group (55.5%), and their recurrence site was regional LN (n = 4), lung (n = 3), and local (n = 1) recurrence. Salvage CRT was performed in five of 21 patients in the esophagectomy group (23.8%), and all of them had regional LN recurrence. In each group, palliative chemotherapy was selected in four patients who had recurrence in distant LN, lung, and liver. Particularly, nine of 21 patients in the esophagectomy group received best supportive care (BSC) alone after recurrence due to their poor general condition. There were no significant differences in the recurrence rates between the two treatment groups; however, BSC alone was selected more frequently in the esophagectomy group (P = 0.029).

Table 4  
Details about recurrence sites and additional treatments

	All patients (n = 156)		Elderly patients (n = 32)	
	Esophagectomy (n = 120) n (%)	CRT (n = 36) n (%)	Esophagectomy (n = 21) n (%)	CRT (n = 11) n (%)
<b>Recurrence</b>	21 (17.5)	9 (24.3)	5 (23.8)	1 (9.1)
<b>Recurrence site</b>	0	1 (2.8)	0	0
Local recurrence	7 (5.8)	3 (8.3)	2 (9.5)	1 (9.1)
Regional lymph node	14 (11.7)	5 (13.9)	3 (14.3)	0
Distant metastasis				
<b>Additional treatment after recurrence</b>	3 (14.3)	5 (55.5)	1 (20.0)	1 (100.0)
Salvage surgery	5 (23.8)	0	1 (20.0)	0
Salvage CRT	4 (19.0)	4 (44.4)	0	0
Palliative chemotherapy	9 (42.9)	0	3 (60.0)	0
BSC alone				

CRT: Chemoradiotherapy; BSC: best supportive care.

### Safety and efficacy in elderly patients

Among a total of 32 elderly patients, 21 patients underwent esophagectomy and 11 patients received CRT. The rate of clinical SM2/3 tumor was higher in esophagectomy group than that in CRT group (90.5% vs.45.5%, P = 0.01). In the esophagectomy group, the rate of three-field lymphadenectomy in elderly patients was lower than that in the total population (71.4% vs. 91.7%, P = 0.026) and the rate of

transhiatal esophagectomy was higher (23.8% vs. 6.7%,  $P = 0.026$ ) (Table 2A). On the contrary, details of treatment modality and radiation doses in the CRT group were similar between elderly patients and all patients (Table 2B). In the safety profile, there were no significant differences in the frequency of post-operative complications in the esophagectomy group (Table 3A) and the frequency of adverse events in the CRT group between all patients and elderly patients, although pleural effusion after CRT tended to be higher in elderly patients (Table 3B). The 5y-PFS was 72.3% and 81.8% (HR 0.55; 95% CI, 0.14–2.13) and the 5y-OS was 76.9% and 81.8% (HR 0.68; 95% CI, 0.16–2.81) in the esophagectomy group and the CRT group, respectively (Fig. 2). After adjusting the clinical tumor depth on Cox regression analysis, there were still no statistical differences between the esophagectomy and CRT groups in the survival outcomes; PFS, adjusted HR = 0.34, 95%CI [0.061–1.856],  $p = 0.211$ ; OS, adjusted HR = 0.32, 95%CI [0.044–2.243],  $p = 0.249$ .

## Discussion

We retrospectively evaluated the safety and efficacy of esophagectomy and CRT in patients with cT1N0M0 ESCC, including elderly patients, using real-world data. There were no significant differences in the safety and efficacy between the esophagectomy and CRT groups, irrespective of age.

Both National Comprehensive Cancer Network (NCCN) guidelines and European Society of Medical Oncology (ESMO) Clinical Practice Guidelines recommend esophagectomy as a standard of care for cT1-2N0 ESCC disease, and chemoradiation is only referred in locally advanced disease, not in cT1-2N0 disease, in these guidelines [13, 14]. Notably, the Japanese guideline mentions that chemoradiation is a treatment option in patients with cT1N0M0 disease who are not fit for or unwilling to undergo esophagectomy. Indeed, the similar OS of esophagectomy and CRT found in the JCOG0502 supports the recommendations in the Japanese guideline, despite the non-randomized findings.

In this study, the PFS in the CRT group seems to be slightly worse than that of the esophagectomy group, although it was not statistically significant (HR = 1.26, 95%CI [0.64–2.56]), which was consistent with the results of JCOG0502. Notably, local recurrence or regional lymph node recurrence were observed in four of nine patients with recurrent disease; then, all four patients underwent salvage surgery (supplementary table 3). These facts may lead to a similar OS between the treatment groups. If patients choose CRT for cT1N0M0 ESCC, careful follow-up is important to ensure that the timing for salvage surgery for recurrent disease is not missed.

We also assessed the efficacy in elderly patients who underwent esophagectomy or CRT. A large-scale cohort study with the Japanese National database of Hospital-Based Cancer Registries found that survival outcomes of CRT were comparable to those of esophagectomy in elderly patients with clinical stage I esophageal cancer [15]. Although there was a selection bias because elderly patients included in our study were all clinically fit for esophagectomy or CRT, our results were consistent with those in the cohort study, showing the comparable efficacy of CRT and esophagectomy in elderly patients with cT1N0M0 ESCC. In addition, our study showed acceptable complications in elderly patients with CRT,

although most of them underwent CRT with concurrent doublet chemotherapy. These findings indicate that CRT is a promising optional treatment for patient of all ages with cT1N0M0 ESCC.

This study has some limitations. First, this was a single-center, retrospective study. Patients' selection bias due to the retrospective nature, including higher proportion of patients with cSM2/SM3 disease in the esophagectomy group, might have led to decreased 5y-PFS and 5y-OS in the esophagectomy group as compared to the CRT group. However, comparable results in the multivariate analysis support the similar survival outcomes of CRT and esophagectomy in our study. Second, the sample size of this study was small; only 21 and 11 elderly patients were included in the esophagectomy and CRT groups, respectively. Despite these limitations, our findings would help decide the treatment strategy for patients with cT1N0M0 ESCC in clinical practice as it is difficult to conduct randomized trials to compare the efficacy of esophagectomy versus CRT.

## **Conclusion**

Our real-world study showed acceptable safety and favorable efficacy of CRT in patients with cT1N0M0 ESCC, including elderly patients. This study confirms that CRT is one of the standard treatment options for patients of all ages with cT1N0M0 ESCC in clinical practice.

## **Abbreviations**

BSC: best supportive care; CRT: Chemoradiotherapy; CT: computed tomography; CTV: clinical target volume; ESCC: esophageal squamous cell carcinoma; ESD: endoscopic submucosal dissection; ESMO: European Society of Medical Oncology; FU: fluorouracil; JCOG: Japan Clinical Oncology Group; LNs: lymph nodes; NCCN: National Comprehensive Cancer Network; OS: overall survival; PFS: progression-free survival; PTV: planning target volume,

## **Declarations**

### **Ethics approval and consent to participate**

This study was conducted in accordance with the Ethical Guidelines for Medical Research Involving Human Subjects and was approved by the Ethical Review Committee of the National Cancer Center Hospital East (2017-120).

### **Consent for publication**

Not applicable

### **Availability of data and materials**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

TK declare that he receives research funding to institutions from MSD, Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Astellas Amgen BioPharma, Taiho Pharmaceutical, Chugai, Shionogi.

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## Author contributions

KS, DK, TK and HF designed the research; HF, HY, SM, TK and KN collected the data; KS analyzed the data; KS and DK wrote the manuscript; HF, HY, SM, DK, TK, YY, MN, HH, TY, TF and TK reviewed and approved the final version of the manuscript.

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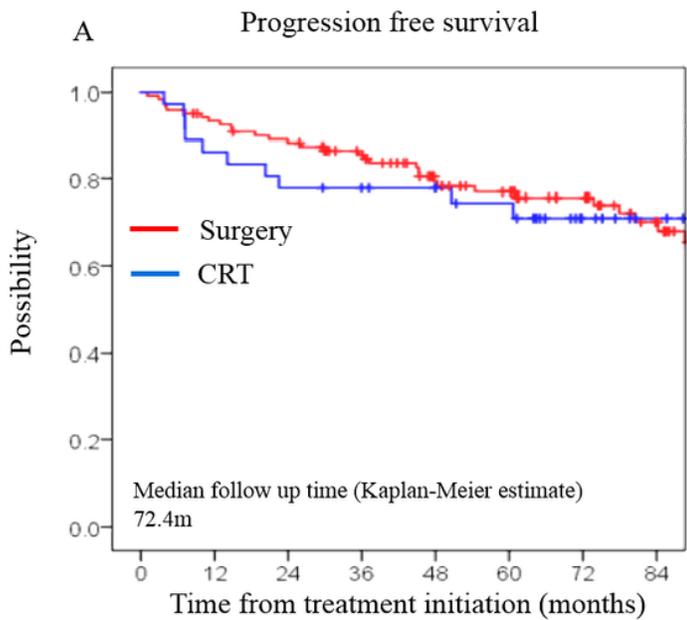
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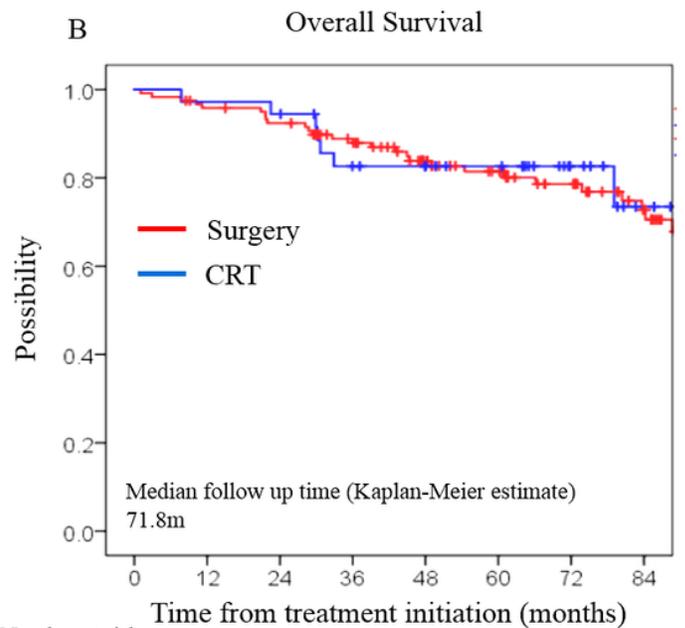
## Figures



Number at risk

Surgery	120	110	103	91	70	61	49	33
CRT	36	31	28	26	24	21	10	5

Group	3y-PFS	5y-PFS	HR (95%CI)	P
Surgery	85.5%	77.0%	Ref	-
CRT	77.8%	74.4%	1.28 (0.64-2.56)	0.48



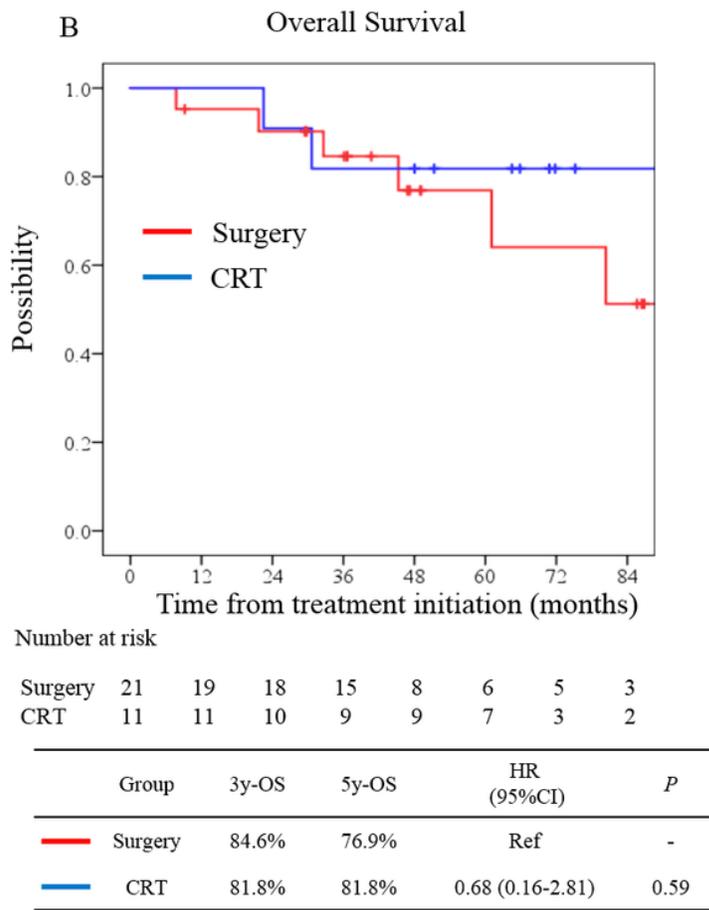
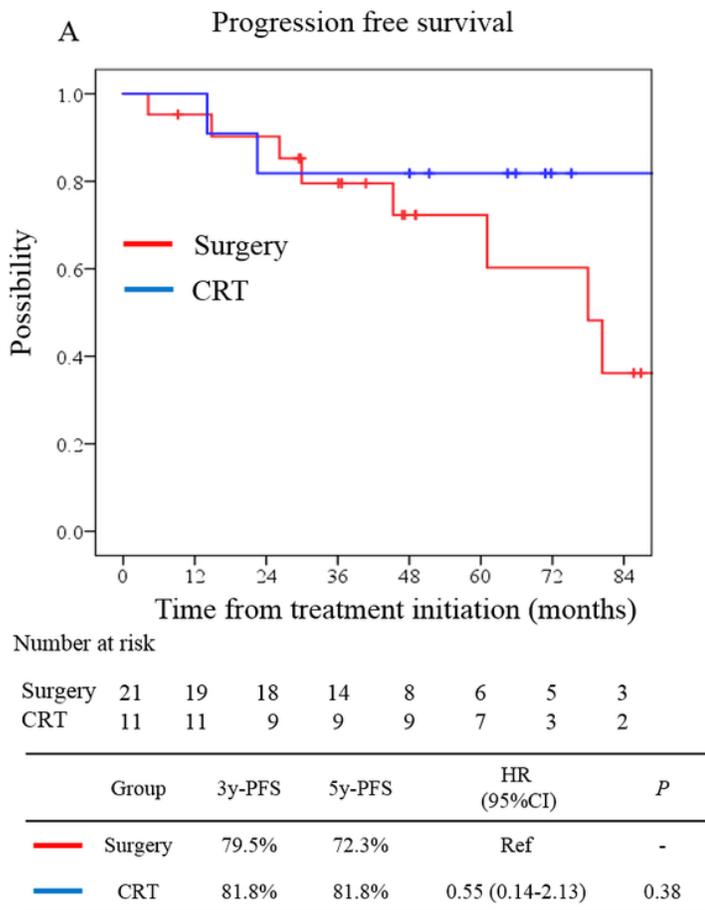
Number at risk

Surgery	120	113	108	95	74	63	50	34
CRT	36	35	34	27	25	22	12	5

Group	3y-OS	5y-OS	HR (95%CI)	P
Surgery	88.9%	81.5%	Ref	-
CRT	82.6%	82.6%	1.06 (0.48-2.34)	0.89

**Figure 1**

PFS in all patients (A) and elderly patients (B)



**Figure 2**

OS in all patients (A) and elderly patients (B)

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterialver2.6.docx](#)