



Esophageal cancer patients' survival after complete response to definitive chemoradiotherapy: a retrospective analysis

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Abstract

Background Chemoradiotherapy is an alternative to surgery for esophageal cancer, with a putatively equivalent outcome. However, disease recurrence after a complete response is common and if follow-up surveillance detects recurrence, salvage treatments for potentially curable disease must follow.

Methods We conducted a nation-wide questionnaire survey of institutions in Japan certified by the Japanese Esophageal Society to investigate outcomes of primary thoracic esophageal cancer patients initially treated by chemoradiotherapy with complete response diagnoses. The primary endpoint was overall survival, the secondary endpoint disease recurrence. Outcomes of patients who had undergone salvage treatments were also investigated. Cases were excluded from analysis if endoscopic study, endoscopic biopsy, or computed tomography data were lacking.

Results At 41 institutes 544 case records were collected; valid data on 392 patients were obtained; 5-year survival was 74.8%, 5-year disease-free survival, 66.8%. Clinical staging before treatment significantly affected both overall and disease-free survival rates, but differences between adjoining stages were unexpectedly small. The primary relapse site was classified as primary site ($n = 58$), regional lymph nodes ($n = 36$), or distant disease ($n = 34$). Salvage treatments with curative intent (surgery, endoscopic treatments, and additional radiation) were performed on 38, 23, and 4 cases; 5-year survival after esophagectomy ($n = 22$), endoscopic treatment ($n = 23$), and lymphadenectomy ($n = 9$) was 47.4%, 70.9%, and 33.3%, respectively.

Conclusions A quarter of patients developed recurrent disease, mostly locoregional, after complete response. Complete response patients with originally advanced stage disease had fair clinical outcomes; salvage treatments after locoregional recurrence achieved modest long-term survival.

Keywords Chemoradiation · Salvage · Survey · Esophageal squamous cell carcinoma

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Introduction

In the treatment of esophageal carcinoma, chemoradiotherapy (CRT) is an option and considered an attractive alternative to surgical treatment [1, 2]. Clinical data on the outcome of esophageal cancer patients treated by CRT have accumulated and point to advantages in comparison with surgical treatment [3–5]. Although randomized controlled trials are lacking, currently available retrospective data show survival after surgical treatment superior to CRT [6–8]. In a recent review of 1964 definitive chemoradiotherapy cases in Japan, complete response (CR) was achieved in 40% of patients, 76% and 30% for cT1 and cT2-4 disease, respectively [9]. However, the 5-year survival of the CR cases in this series was 59.5%. Although the disease-specific survival rates in these patients were not surveyed in this study, disease recurrence after CR presumably accounts for most deaths. A clinical diagnosis of “complete response” is not equivalent to a disease cure and should be regarded as a putative diagnosis, a required step in the process of decision-making for further treatments. While patients with evident remnant disease require additional treatment, CR patients are generally not candidates for planned surgery, but they are followed up by regular surveillance. If recurrent disease is detected at follow-up visits, salvage surgery, defined as surgery targeting disease in radiation fields irradiated over 50 Gy, is normally performed; data on long-term outcomes of such salvage surgery has accumulated [10–14]. More recently, endoscopic treatments such as endoscopic mucosal resection, argon plasma coagulation, and photodynamic therapy have come to be indicated for early forms of disease recurrence at a primary site [15–17]. Because R0 resection has been suggested as an established prognostic factor in salvage surgery, locoregional recurrence should be carefully monitored through follow-up surveillance including endoscopy and computed tomography (CT) [18, 19]. Reliable guidelines for follow-up surveillance after CRT have yet to be established, however.

We conducted a nation-wide survey to investigate the disease status and outcome of salvage treatments for esophageal carcinoma. This survey was confined to patients with a putative diagnosis of CR after definitive CRT. Through this survey, we investigated the clinical outcome and the effectiveness of the salvage treatments performed on esophageal cancer patients after reaching CR status.

Materials and methods

Survey strategy

This study was a retrospective study of the thoracic esophageal cancer patients primarily treated by CRT and appropriately diagnosed as CR within one year after the termination of chemoradiotherapy. It was conducted as an official study approved by the Japan Esophageal Society (JES); only specialty institutions certified by JES were requested to collaborate. The study group consisted of the University of Tokyo Hospital, the Japanese Foundation for Cancer Research, Kitasato University Hospital, Tokai University Hachioji Hospital, the Osaka International Cancer Institute, and Tohoku University Hospital. In total, 41 institutions participated in this survey. The study design was approved by each of the institutional review boards in this study group. Patients’ informed consent was replaced by opt-out of this study on the website of each institute.

Study population, eligibility criteria

The patients included in this study were histologically confirmed esophageal carcinoma (squamous cell carcinoma or adenocarcinoma) patients treated initially by definitive CRT started between January 2010 and December 2014 with or without preceding induction chemotherapy. Eligibility was confined to patients in whom the main location of the carcinoma was the thoracic esophagus; the radiation dose was 50 Gy or more; irradiation was accompanied by at least one cycle of concurrent chemotherapy; the patient’s performance status was 0, 1, or 2; pretreatment and post-treatment surveillance included endoscopy, CT, and biopsy; and follow-up exceeded 2 years. Exclusion criteria were distant nodal metastasis other than to the supraclavicular nodes and synchronous or metachronous esophageal, pharyngeal or laryngeal malignancy.

Radiation field

Extended-field radiotherapy encompassing the whole esophagus and both the supraclavicular and the abdominal fields was standardly administered in 13 institutes (182 cases). Meanwhile, radiotherapy confined to primary and metastatic sites with lateral and longitudinal margins was the standard in six institutes (139 cases). Twelve institutes (175 cases) applied the mixture of the two types of radiotherapy. As for the other 10 institutes (48 cases), information on the field of radiation was not available.

Criteria of CR definition

The diagnosis of complete response had been made in each collaborative institute in accordance with the criteria described in the 11th edition of Japanese Classification of Esophageal Cancer edited by JES. Cases with inadequate post-therapeutic surveillance (e.g. lack of biopsy within one year after CRT) were excluded from analysis. Therefore, triple-negative findings from CT, endoscopy, and biopsy were mandatory for the inclusion of data in our current study.

Case records

The main query items were followings; patient’s background (gender, age), clinical staging (Tumor-Node-Metastasis, Union of International Cancer Control 7th Edition), detailed CRT regimen, findings of post-therapeutic clinical surveillance, disease-free survival, salvage treatment; overall survival. An electronic file of the endoscopic image on the definition of complete response was also provided. The questionnaire form was sent via electronic file to each institute and returned with endoscopic images to the study group after completing and anonymizing the form.

Survival analysis

The primary endpoint was overall survival and the secondary endpoint was disease status. For patients undergoing any salvage treatments with curative intent, such as surgical or endoscopic intervention with the intent to cure disease, the clinical outcome after the salvage was also investigated. Survival curves were drawn by the Kaplan–Meier method and comparisons between clinicopathological groups were made by the log-rank test and Cox regression analysis. A value of $P < 0.05$ was regarded as statistically significant. All analyses were performed using JMP Pro software version 14.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

544 questionnaires were collected; 151 cases were excluded owing to inadequate post-therapeutic evaluations ($n = 97$), follow-up loss within two years ($n = 20$), synchronous or metachronous disease of the esophagus and/or head and neck ($n = 16$), non-thoracic disease ($n = 4$), or other causes ($n = 14$). Among the 393 eligible patients, only one patient was diagnosed with adenocarcinoma of the thoracic esophagus. Therefore, the analysis in this study was confined to 392 esophageal squamous cell carcinoma cases. The demographics and the treatment profile of the 392 patients are shown in Table 1.

The commonest dose of radiation was 60 Gy. The most frequently used concurrent chemotherapy regimen was 5-FU combined with cisplatin (300 cases); a combination of oral fluorouracil and platinum (cisplatin or nedaplatin) came second (51 cases), and a three-drug regimen comprising fluorouracil, platinum, and docetaxel (19 cases) third in frequency. Induction chemotherapy was given in 91 cases. The overall survival and disease-free survival rates of the 392 patients are shown in Fig. 1a and b.

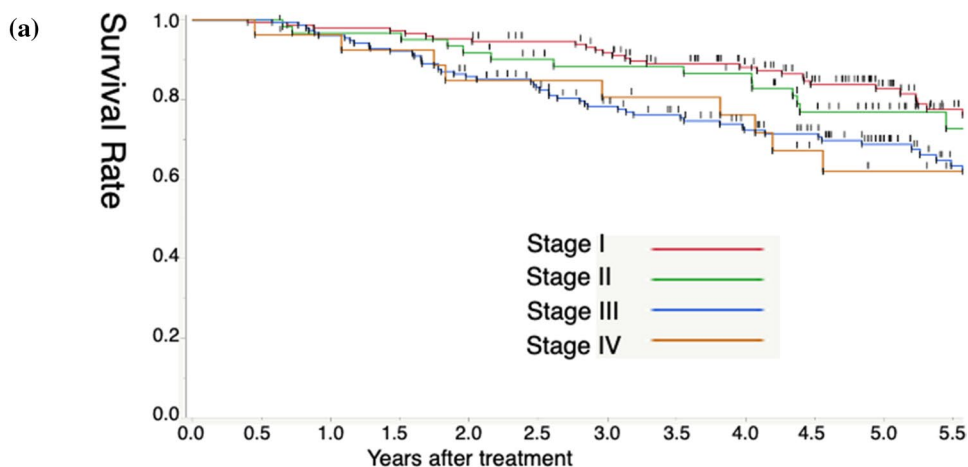
5-year survival was 74.8% with a median follow-up of 5.0 years and there were small but significant differences in overall survival among clinical stages (Fig. 1. $P = 0.0105$). The 5-year survival of Stage I (including I_A and I_B), II (including II_A and II_B), III (including III_A, III_B and III_C), and IV were 82.7%, 76.9%, 68.7%, and 61.9%, respectively. 5-year disease-free survival was 66.8% with a median follow-up of 5.1 year. Although the log-rank test showed significant differences among the four stages ($P < 0.001$), the 5-year disease-free survival was 77.5%, 74.3%, 53.4%, and 68.3% and clinical stage III showed the worst survival. Table 2 shows the clinical factors contributing to the development of each type of recurrence.

Table 1 Patients’ characteristics disease stage and treatment profiles

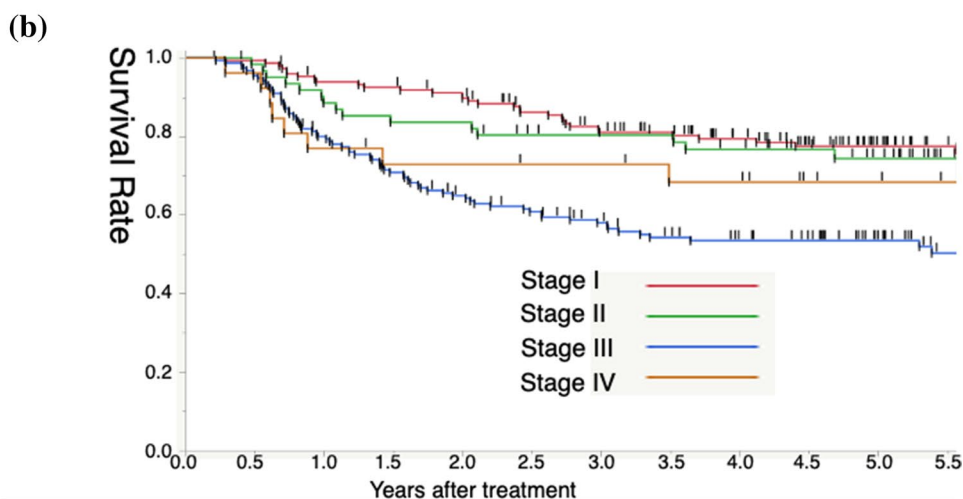
Age	Median (range)	69 (40–90)
Gender	Male/Female	332/60
Location	Ut/Mt/Lt	91/211/90
cT stage	1/2/3/4a/4b	131/56/105/7/93
cN stage	0/1/2/3	201/102/71/18
cM stage	0/1	365/27
cStage	IA/IB/IIA/IIB/IIIA/ IIIB/ IIIC/ IV	110/39/36/25/35/25/95/27
Dose of radiation	50 Gy/50.4 Gy/50.5–59.9 Gy/60 Gy/ > 60 Gy	6/78/29/237/42
Concurrent chemotherapy ¹	FP/Modulated FP/DCF/Others	300/51/19/22
Induction chemotherapy	Yes/No	91/301

1. FP: 5FU plus cisplatin, Modulated FP: Oralfluorouracils and nedaplatin were used as substitutes for 5FU and cisplatin, respectively, DCF:docetaxel,cisplatin plus 5FU,Others: Monotherapies: 21 (5FU:11, Docetaxel:7, Cisplatin:1,Taxotere: 1),5FU,Cisplatin plus Adriamycin: 1,5FU,cisplatin plus Nimotuzumab: 1)

Fig. 1 a Overall survival of 392 complete-response patients. 5-year survival was 74.8% (Stage I, 82.7%; Stage II, 76.9%; Stage III, 68.7%; Stage IV, 61.9%). **b** Disease-free survival of 392 complete-response patients. 5-year survival was 66.8% (Stage I, 77.5%; Stage II, 74.3%; Stage III, 53.4%; Stage IV, 68.3%)



		0	1	2	3	4	5
All	Numbers at risk	392	378	350	310	262	175
	Deaths	0	12	38	57	72	90
Stage I	Numbers at risk	149	146	142	130	107	73
	Deaths	0	3	7	12	17	23
Stage II	Numbers at risk	61	59	56	50	47	29
	Deaths	0	2	5	7	8	13
Stage III	Numbers at risk	155	148	130	111	91	62
	Deaths	0	6	22	33	41	45
Stage IV	Numbers at risk	27	25	22	19	17	11
	Deaths	0	1	4	5	6	9



		0	1	2	3	4	5
All	Numbers at risk	392	333	294	250	209	139
	Recurrences	0	53	86	111	121	124
Stage I	Numbers at risk	149	137	129	109	88	59
	Recurrences	0	9	15	27	29	31
Stage II	Numbers at risk	61	54	51	45	41	27
	Recurrences	0	7	10	12	14	15
Stage III	Numbers at risk	155	122	96	79	65	43
	Recurrences	0	31	54	64	70	70
Stage IV	Numbers at risk	27	20	18	17	15	10
	Recurrences	0	6	7	8	8	8

As shown, clinical T factor was an independent contributor to all types of ($P=0.004$) and locoregional recurrence ($P=0.03$) while clinical N factor was to the distant form of recurrence ($P=0.02$). In addition, the radiation dose

smaller than 60 Gy weakly contributed to all forms of disease recurrence ($P=0.03$).

The disease status and treatment flow of the 392 patients is summarized in Fig. 2.

Table 2 Clinical factors associated with each form of disease recurrence (Cox hazards model)

Factors	All forms of recurrence			Locoregional recurrence			Distant form of recurrence		
	Univariate			Univariate			Univariate		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age > 65	1.19	0.86–1.64	0.3	1.17	0.82–1.69	0.39	1.23	0.75–2.03	0.41
Male	1.38	0.86–2.20	0.18	1.37	0.81–2.31	0.24	2.03	0.88–4.69	0.1
Location									
Ut	1.2	0.82–1.74	0.35	1.12	0.73–1.71	0.6	1.17	0.65–2.12	0.6
Mt	Ref			Ref			Ref		
Lt	1.15	0.79–1.67	0.46	1.01	0.66–1.55	0.96	1.37	0.79–2.38	0.26
cT3–4 (vs.cT1–2)	1.89	1.38–2.60	<0.001	1.53	1.08–2.16	0.02	1.48	1.04–2.10	0.03
cN2–3 (vs.cN0–1)	1.67	1.19–2.34	0.003	1.31	0.87–1.96	0.2	2.49	1.53–4.05	<0.001
cM1 (vs.cM0)	1.27	0.72–2.23	0.42	1.08	0.55–2.13	0.82	2.15	1.07–4.34	0.03
Radiation dose < 60 Gy	1.49	1.08–2.05	0.01	1.45	0.48–0.99	0.04	1.2	0.73–2.00	0.47
Induction chemotherapy	1	0.69–1.45	0.99	1.08	0.72–1.62	0.71	0.56	0.29–1.10	0.09
CR diagnosis < 6 months	1.19	0.82–1.73	0.35	1.36	0.88–2.08	0.16	0.98	0.57–1.68	0.93

HR hazard ratio, 95% CI 95% Confidence interval

Recurrent disease-free patients

Thirty-two patients, including six cases with late radiation-related adverse events, died without evident disease recurrence; 232 patients were alive at the last follow-up visit and remained free of disease; five among these 232 patients had undergone esophagectomy without evident recurrent disease and CR was confirmed pathologically after surgery.

Patients with recurrent disease

One hundred twenty-eight patients had developed the recurrent disease; their initial recurrence was at the primary esophageal site in 58 cases, in regional nodes in 36 cases, or a form of the distant disease in 34 cases. Salvage esophagectomy was performed in 22 cases (19 cases of primary-site recurrence and three cases of regional lymph node recurrence); other types of radical interventions for recurrence were regional lymph node resection (9 cases), distal node resection (2 cases), salvage endoscopic interventions (23 cases including 18 cases of endoscopic resection, three cases of argon laser coagulation therapy and two cases of photodynamic therapy), and additional radiotherapy (lung metastasis: 1 case, and nodal metastasis: 3 cases). Of the 94 patients who developed locoregional recurrence, 57 patients (61%) were offered some form of radical treatment; 68 patients (including 37 patients with locoregional recurrence) were treated with the best supportive care or palliative chemotherapy.

The clinicopathological characteristics of patients who underwent salvage surgery or endoscopic interventions are shown in Table 3. A larger proportion of cT1 disease was noted in the patients who underwent endoscopic treatment ($P=0.0281$, Fisher’s exact test); endoscopic treatment was performed in predominantly older patients ($P=0.009$, Wilcoxon’s rank-sum test). The clinical outcomes of these salvage treatments are shown in Fig. 3. The 5-year survival rates were 47.4%, 70.9%, and 33.3% in the esophagectomy ($n=22$), endoscopic treatment ($n=23$), and lymphadenectomy ($n=9$) groups, respectively (Table 4).

Discussion

The primary site of esophageal cancer is basically unmeasurable; we define “complete response” as the disappearance of macroscopic tumor confirmed by both endoscopy and CT [21]. Histological confirmation by biopsy is also mandated. However, other criteria, such as a thickened esophageal wall or mucosal break, may persist for months even in true CR cases with a long survival, and the optimal timing of the initial evaluations defining CR is unclear. Even with positron emission tomography, reliable

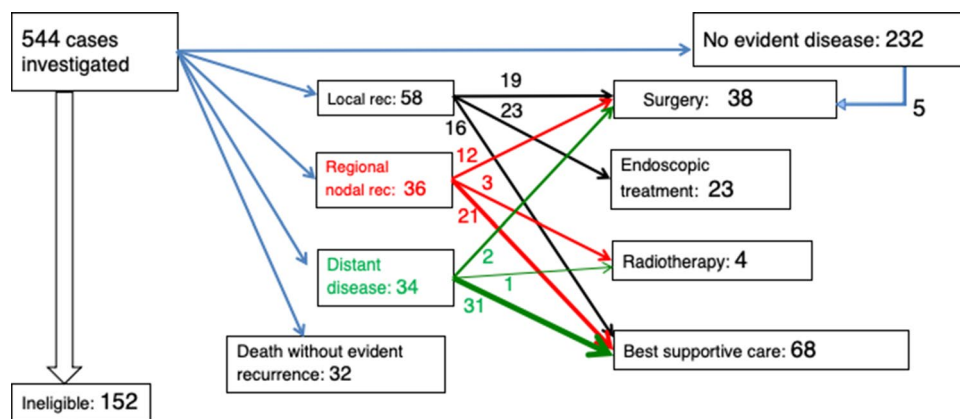


Fig. 2 Disease status and treatment flow of 544 investigated cases. 152 cases were excluded from the analysis mainly because of the lack of post-therapeutic surveillance for disease evaluations. A total of 128 cases developed disease recurrence and most (94 cases, 73.4%) were

defined as locoregional. Of the 94 cases with locoregional recurrence, 57 cases (60.6%) underwent some form of salvage treatment with curative intent while the remaining 37 cases were treated with best supportive care with or without palliative chemotherapy

Table 3 Clinicopathological factors of patients undergoing salvage treatments

		Esophagectomy <i>n</i> = 22	Lymphadenectomy <i>n</i> = 9	Endoscopic treatment <i>n</i> = 23	<i>P</i> value
Gender	Male/Female	21/11	8/11	18/15	0.267*
Age	Median (Range)	65 (50–75)	72 (63–76)	71 (42–88)	0.009**
cTfactor	1/2/3/4	3/2/6/11	3/2/2/2	12/2/7/2	0.0225*
cN factor	0/1/2/3	8/7/6/1	6/2/1/0	14/8/1/0	0.227*
Tumor location	Ut/Mt/lt	7/11/4	1/7/1	5/12/6	0.648*
pT	0/1/2/3/4	2/4/2/14/0	NA	NA	
pN	0/1/2/3	15/5/1/1	NA	NA	
DFS (Days)	Median (Range)	303 (105/2788)	755 (211–1319)	567 (104 to 2036)	0.0652**

NA not available, DFS disease free survival

*Fisher's exact test

**Wilcoxon rank-sum test

diagnostic criteria and the optimal timing for clinical evaluation after CRT are challenging [22, 23]. The median disease-free survival was 14.1, 19.7 and 17.1 months in local, nodal and distant types of recurrence, respectively. The disease recurrence was frequently observed within two years after the completion of CRT but late recurrence was not rare in all types of recurrence form (data not shown). Designation as “complete response” at the initial evaluation should not be regarded as definitive: clinical evaluations should be repeated for years.

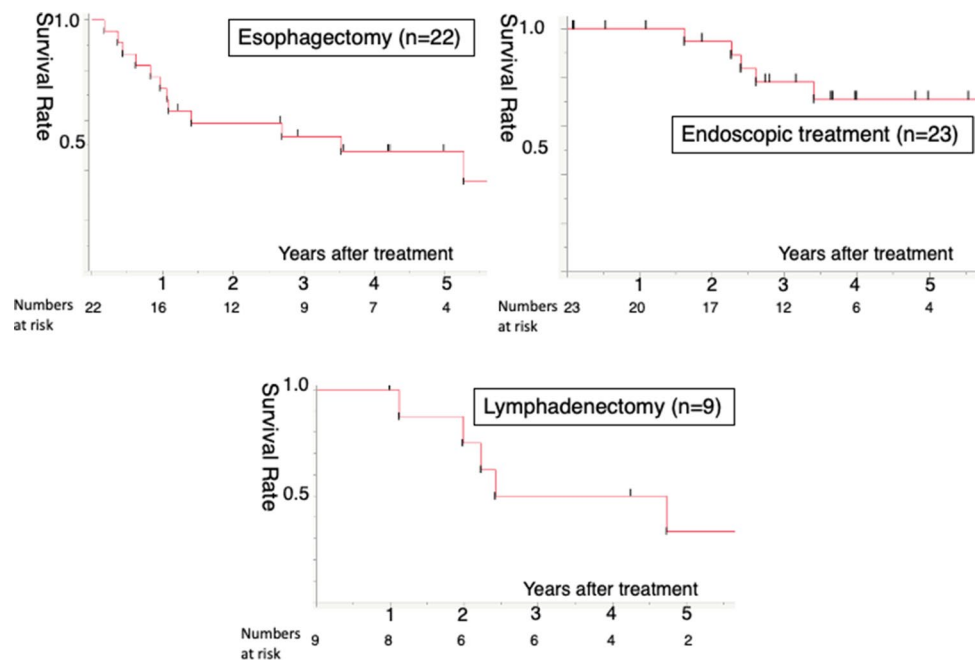
In this study, a majority of the CR patients (5-year disease-free survival 66.8%) maintained their disease-free status, while 94 out of 392 patients (24%) developed locoregional recurrence, which was found in about three quarters (94 of 128) of all recurrent disease types. Careful follow-up surveillance aiming to detect early forms of locoregional recurrence would presumably contribute to successful salvage interventions and to improved clinical outcome.

Although the pretreatment clinical stage is presumed to be a significant prognostic factor, differences among the 5-year survival rates at each stage were unexpectedly small. None of the individual comparisons of overall survival between two adjoining stages was significant (data not shown); only comparison between cStage I and cStage III showed a significant difference with a hazard ratio of 1.96 in Cox regression analysis (cStage I as a standard; 95% confidence interval: 1.27 to 3.01). Notably, CR cases in cStage IV showed 61.9% 5-year survival and the disease-free survival was superior to Stage III patients. These observations may be explained by the design of this study which excluded Stage IV patients with distant disease other than supraclavicular metastasis. Supraclavicular lymph node has been categorized as regional lymph node of thoracic esophageal cancer in Japan because supraclavicular-node-positive patients showed 5-year survival of 42.3% after esophagectomy according to the survey conducted by Japan Esophageal

Table 4 Collaborative institutions

Shizuoka Cancer Center	Tokushima University Hospital
University of Tokyo Hospital	Hakodate National Hospital
Cancer Institute Hospital of Japanese Foundation for Cancer Research	Kochi Medical School Hospital
Niigata Cancer Genier Hospilal	Yamaguchi University Hospital
Tohoku University Hospital	University of Yamanashi Hospital
University Hospital, Kyoto Prefectural University of Medicine	Toho University Omori Medical Center
Akita University Hospital	Jikei University Hospital
Kitasato University Hospital	Tokyo Medical and Dental University Hospital Faculty of Medicine
National Hospital Organization Kyushu Cancer Center	Shimane University hospital
Hiroshima University Hospital	Osaka International Cancer Institute
Saitama Medical Center	Dokkyo Medical University Hospital
Kurume University Hospital	Saitama Medical University International Medical Center
Kumamoto University Hospital	Kagawa Prefectural Central Hospital
Yokohama City University Medical Center	Mie University Hospital
Kindai University Hospital, Faculty of Medicine	Yokohama City University Hospital
Hokkaido University Hospital	St. Luke’s International Hospital
Chiba University Hospital	Okayama University Hospital
Nagoya City University Hospital	Tokai University Hachioji Hospital
Shizuoka General Hospital	Saiseikai Fukuoka General Hospital
Kanazawa University Hospital	Yamagata University Hospital
Oita University Hospital	

Fig. 3 Overall survival after detection of disease recurrence in each type of salvage treatment. The 5-year survival rates were 47.4%, 70.9%, and 33.3% in the esophagectomy ($n = 22$), endoscopic treatment ($n = 23$), and lymphadenectomy ($n = 9$) groups, respectively



Society [24]. These “responder” cases can expect a remarkably improved survival compared to overall cStage IV cases. However, multivariate analyses in Table 2 suggested that locally advanced disease and greater nodal involvement were respectively associated with locoregional and distant disease

recurrence. Locally advanced disease with fewer lymph node metastases might deserve frequent and careful post therapeutic observations to facilitate successful salvage interventions although this observation should be confirmed with more mightier analyses in the future.

Salvage esophagectomy has been associated with high morbidity and mortality and is indicated only for selected patients with low perioperative risk [13, 14, 25, 26]. R0 resection has been suggested as a definite prognostic factor after salvage esophagectomy [12, 14, 17]. In our analysis, only two patients underwent non-R0 surgery; their 5-year survival (47.4%) was deemed acceptable, and sufficient for salvage esophagectomy to be feasible. To further improve the clinical outcome of CR cases, an immediate surgery after CRT, so called “tri-modality therapy”, may prevent future locoregional recurrences [27]. However, such a strategy must be verified by a prospective trial. Meanwhile, a close observation policy without immediate surgery for patients receiving neoadjuvant CRT regimen is now ongoing [28]. We have to wait for a convincing evidence established by such clinical trials.

Salvage endoscopic intervention showed an even better, indeed excellent, outcome: 70.9% 5-year survival, in older patients. It is also to be noted, however, that the endoscopic salvage group included a larger proportion of formerly early-stage disease and/or late recurrence (over one year), in other words, disease with possibly less aggressive behavior.

Because this study was a retrospective study, it provided no convincing evidence for the benefit of early detection of disease recurrence after CR. However, it did suggest that a majority of the post-complete-response recurrent esophageal squamous cell carcinoma cases were locoregional, and salvage treatments for such disease showed modest long-term survival regardless of the pretreatment clinical stage.

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Compliance with ethical standards

Conflict interest Kazuhiko Mori, Kotaro Sugawara, Susumu Aikou, Hideomi Yamashita, Tsugufumi Yamashita, Mariko Ogura, Keisho Chin, Masayuki Watanabe, Hisahiro Matsubara, Yasushi Toh, Yoshihiro Kakeji and Yasuyuki Seto declare that they have no conflict of interest.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

References

- Hironaka S, Ohtsu A, Boku N, et al. Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2–3) N(any) M(0) squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys.* 2003;57:425–33.
- Yamada K, Murakami M, Okamoto Y, et al. Treatment results of chemoradiotherapy for clinical stage I (T1N0M0) esophageal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;64(4):1106–11.
- Gillham CM, Aherne N, Rowley S, et al. Quality of life and survival in patients treated with radical chemoradiation alone for oesophageal cancer. *Clin Oncol.* 2008;20(3):227–33.
- Yamashita H, Okuma K, Seto Y, et al. A retrospective comparison of clinical outcomes and quality of life measures between definitive chemoradiation alone and radical surgery for clinical stage II–III esophageal carcinoma. *J Surg Oncol.* 2009;100:435–41.
- Ariga H, Nemoto K, Miyazaki S, et al. Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys.* 2009;75(2):348–56.
- Yamashita H, Nakagawa K, Yamada K, et al. A single institutional non-randomized retrospective comparison between definitive chemoradiotherapy and radical surgery in 82 Japanese patients with resectable esophageal squamous cell carcinoma. *Dis Esophagus.* 2008;21:430–6.
- Wang BY, Hung WH, Wu SC, et al. Comparison between esophagectomy and definitive chemoradiotherapy in patients with esophageal cancer. *Ann Thorac Surg.* 2019;107(4):1060–7.
- Nomura M, Kato K, Ando N, et al. Comparison between neoadjuvant chemotherapy followed by surgery and definitive chemoradiotherapy for overall survival in patients with clinical Stage II/III esophageal squamous cell carcinoma (JCOG1406-A). *Jpn J Clin Oncol.* 2017;47(6):480–6.
- Toh Y, Numasaki H, Tachimori Y, et al. Current status of radiotherapy for patients with thoracic esophageal cancer in Japan, based on the Comprehensive Registry of Esophageal Cancer in Japan from 2009 to 2011 by the Japan Esophageal Society. *Esophagus.* 2020;17(1):25–32.
- Booka E, Haneda R, Ishii K, et al. Appropriate candidates for salvage esophagectomy of initially unresectable locally advanced T4 esophageal squamous cell carcinoma. *Ann Surg Oncol.* 2020;27(9):3163–70.
- Borghesi S, Hawkins MA, Tait D. Oesophagectomy after definitive chemoradiation in patients with locally advanced oesophageal cancer. *Clin Oncol.* 2008;20:221–6.
- D’Journo XB, Michelet P, Dahan L, et al. Indications and outcome of salvage surgery for oesophageal cancer. *Eur J Cardiothorac Surg.* 2008;33(6):1117–23.
- Tachimori Y, Kanamori N, Uemura N, et al. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg.* 2009;137:49–54.
- Miyata H, Yamasaki M, Takiguchi S, et al. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. *J Surg Oncol.* 2009;100:442–6.
- Noordzij IC, Curvers WL, Huysentruyt CJ, et al. Salvage endoscopic resection in patients with esophageal adenocarcinoma after chemoradiotherapy. *Endosc Int Open.* 2018;6(9):E1126–9.
- Matsutani T, Nomura T, Hagiwara N, et al. Salvage endoscopic argon plasma coagulation after chemoradiotherapy for inoperable esophageal cancer. *Surg Laparosc Endosc Percutan Tech.* 2017;27(5):384–90.
- Yano T, Muto M, Minashi K, et al. Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal squamous cell carcinoma: a phase II study. *Int J Cancer.* 2012;131(5):1228–34.
- Seto Y, Chin K, Gomi K, et al. Treatment of thoracic esophageal carcinoma invading adjacent structures. *Cancer Sci.* 2007;98:937–42.
- Chao YK, Chan SC, Chang HK, et al. Salvage surgery after failed chemoradiotherapy in squamous cell carcinoma of the esophagus. *Eur J Surg Oncol.* 2009;35(3):289–94.

20. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus*. 2017;14:1–36.
21. Tahara M, Ohtsu A, Hironaka S, et al. Clinical impact of criteria for complete response of primary site to treatment of esophageal cancer. *Jpn J Clin Oncol*. 2005;35(6):316–23.
22. Valkema MJ, Noordman BJ, Wijnhoven BPL, et al. Accuracy of ¹⁸F-FDG PET/CT in Predicting Residual Disease After Neoadjuvant Chemoradiotherapy for Esophageal Cancer. *J Nucl Med*. 2019;60(11):1553–9.
23. Huang YC, Li SH, Lu HI, et al. Post-chemoradiotherapy FDG PET with qualitative interpretation criteria for outcome stratification in esophageal squamous cell carcinoma. *PLoS ONE*. 2019;14(1):e0210055.
24. Tachimori Y, Ozawa S, Numasaki H, et al. Efficacy of lymph node dissection by node zones according to tumor location for esophageal squamous cell carcinoma. *Esophagus*. 2016;13:1–7.
25. Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. *J Thorac Cardiovasc Surg*. 2002;123:175–83.
26. Cohen C, Tessier W, Gronnier C, et al. Salvage surgery for esophageal cancer: how to improve outcomes? *Ann Surg Oncol*. 2018;25(5):1277–86.
27. Piessen G, Messager M, Mirabel X, Briez N, et al. Is there a role for surgery for patients with a complete clinical response after chemoradiation for esophageal cancer? An intention-to-treat case-control study. *Ann Surg*. 2013;258(5):793–9.
28. Noordman BJ, Wijnhoven BPL, Lagarde SM, et al. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial. *BMC Cancer*. 2018;18(1):142.

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