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ORIGINAL ARTICLE

Treatment outcomes according to the macroscopic tumor type in locally advanced esophageal squamous cell carcinoma treated by chemoradiotherapy

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Abstract

Purpose To identify predictive factors for local control of locally advanced esophageal cancer by chemoradiotherapy, the relationship between clinical features, including macroscopic tumor type, and treatment outcome was analyzed in 83 patients.

Materials and methods Macroscopic tumor type was defined by endoscopy as follows: type 1: protruding type; type 2: ulcerative and localized type; type 3: ulcerative and infiltrative type; type 4: diffusely infiltrative type; and type 5: unclassifiable type. We analyzed the overall survival, cause-specific survival, local progression-free rate, and predictive factors for locally advanced esophageal cancer after chemoradiotherapy.

Results The median follow-up period at the time of evaluation was 59 months among survivors. The 5-year overall survival, cause-specific survival, and local progression-free rates for type 1 and other types were 37.0% and 23.3% ($P=0.4255$), 71.8% and 30.3% ($P=0.0325$), and 100% and 63.3% ($P=0.0246$), respectively. Macroscopic tumor type (type 1) was the most significant predictive factor of cause-specific survival and local progression-free rates.

Conclusions Macroscopic tumor type 1 was the significant favorable predictive factor for local control. The study results suggested that the macroscopic tumor type was useful in predicting tumor responses.

Keywords Esophageal cancer · Chemoradiotherapy · Endoscopy

Introduction

Esophageal cancer is a serious and aggressive disease that remains difficult to treat. The lack of a serosal barrier in the esophagus facilitates the radial spread of tumors to invade adjacent local structures such as the tracheobronchial tree, pleura, or aorta. In addition, esophageal cancer is associated with a high frequency of lymph node metastases, observed in approximately 70% of patients at autopsy. The prognosis of advanced esophageal cancer remains poor, and an estimated 11,483 deaths occurred due to this disease in Japan in 2016 [1, 2]. Progression of esophageal cancer causes dysphagia, and various other symptoms result from infiltration of the surrounding organs. Therefore, local control of esophageal cancer is very important.

Surgical resection is the curative treatment for esophageal cancer. However, esophagectomy remains one of the most demanding surgical procedures, and not all patients are suitable for surgery. Chemoradiotherapy (CRT) is the standard treatment option in patients with esophageal cancer who are ineligible for surgery. Numerous studies have proven the effectiveness of CRT [3–8]. However, CRT is associated with a relatively higher local recurrence rate than surgery [9, 10]. Treatment outcomes of CRT differ from case to case, and various factors are related to these outcomes. If the predictive factors for CRT outcomes are identified, selection of CRT as the definitive treatment for patients with positive predictive factors may be feasible. Many authors have reported various predictive factors for local control after CRT for esophageal cancer [11–16]. However, few studies have assessed the relationship between macroscopic tumor type and responses following CRT.

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Therefore, in this study, we analyzed the clinical features, including macroscopic tumor type, and treatment outcomes after CRT for locally advanced esophageal cancer and aimed to identify the predictive factors for local control following CRT.

Materials and methods

Patients

From June 2008 to June 2017, a total of 120 patients with esophageal cancer underwent CRT at Hiroshima Prefectural Hospital. Among these patients, we analyzed those who met the following criteria:

1. Histological diagnosis of squamous cell carcinoma.
2. T2–T4 disease and no organic metastasis. Patients with supraclavicular lymph node metastasis were included. T1 disease was excluded.
3. Macroscopic tumor type diagnosed by endoscopy.
4. Patients who received concurrent CRT.

Before therapy, all patients underwent clinical evaluation by assessment of previous medical history, physical and laboratory examinations, upper gastrointestinal endoscopy, and radiographic studies. Laboratory examination included complete blood cell count, liver function studies, renal function studies, and measurement of electrolytes. Radiographic studies included chest radiography and computed tomography (CT) of chest, abdomen, and pelvis. The clinical TNM stage was defined according to the Tumor Node Metastasis classification (Union for International Cancer Control 7th edition). The study protocol was approved by the Human Ethics Review Committee of Hiroshima Prefectural Hospital, and each subject provided written informed consent.

Treatment

Three-dimensional conformal radiation therapy was used for treatment planning in all patients. In principle, elective nodal irradiation (ENI) was performed. Elective nodal areas were determined as follows: supraclavicular to middle mediastinal regions for cervical and upper thoracic tumors; upper mediastinal to perigastric regions for middle and lower thoracic tumors; and lower mediastinal to celiac regions for abdominal tumors. The dose of ENI was 40 Gy using 6–10 MV photon beams (2 Gy/fraction). After ENI, boost radiotherapy to primary tumor and lymph node metastasis was initiated. The total prescribed dose was 60 Gy. For patients with poor lung function or very large tumor lesions, a decreased dose was selected to avoid adverse effects. The concurrent chemotherapy regimen was two cycles of cisplatin 70 mg/m^2 on day 1 and 5-fluorouracil 700 mg/m^2 on day 1 to day 4 at an interval of 4 weeks. Another two cycles of cisplatin and 5-fluorouracil were administered 4 and 8 weeks after CRT.

Definitions

Macroscopic tumor type was defined according to the Japanese Classification of Esophageal Cancer 11th edition as follows [17]:

Type 1

Protruding type Localized protruding lesion. The definitely protruding lesion commonly has an erosive surface. However, the lesion is occasionally covered by intact squamous epithelium continuous with the surroundings.

Type 2

Ulcerative and localized type The ulcerative lesion has a well-demarcated surrounding ridge.

Type 3

Ulcerative and infiltrative type The ulcerative lesion has an ill-demarcated surrounding ridge circumferentially or semi-circumferentially.

Type 4

Diffusely infiltrative type Lesion with wide intramural invasion, generally without conspicuous ulceration or protrusion. Even if the lesion has ulcerative and/or protruding components, it is defined as type 4.

Type 5

Unclassifiable type The lesion has a complicated macroscopic appearance that is unclassifiable as any of macroscopic tumor types 1–4.

All patients underwent follow-up CT and upper gastrointestinal endoscopy every 4–6 months after CRT. Local esophageal tumor progression was defined as progressive disease of local esophageal tumor on CT or endoscopy, and local progression-free (LPF) status was defined as the absence of local esophageal tumor progression.

Statistical analysis

Univariate analyses using the Mantel–Haenszel χ^2 test were performed to determine the statistical significance of differences in treatment results. Investigated factors included age at CRT, sex, tumor location, T stage, N stage, M stage,

macroscopic tumor type, tumor length, and maximum tumor diameter. The maximum tumor diameter was the major axis in transverse planes in CT images. The Kaplan–Meier method was used to calculate the overall survival (OS), cause-specific survival (CSS), and LPF rates. The OS was calculated from the date of initiation of CRT to the date of the final follow-up or death from any cause. The CSS was estimated from the CRT start date until death from esophageal cancer, and patients who died of other diseases were censored. The LPF was estimated from the CRT start date until the date of local esophageal tumor progression, and patients without local progression at the time of death were censored. In estimation of LPF, local esophageal tumor progression was defined as the enlargement of the tumor from its state after CRT, as observed by CT or endoscopic findings, even in patients who did not achieve complete response following CRT. Ekuseru-Toukei 2015 (version 1.02; Social Survey Research Information Co., Ltd., Tokyo, Japan) was used to perform the statistical analyses. Statistical significance was defined as $P < 0.05$.

Results

Patients

Of the 120 patients who underwent definitive CRT, 37 were excluded from the analysis because 22 patients had T1 disease, the details of endoscopic findings before CRT in 13 patients were not available and 2 patients had adenocarcinoma. Therefore, 83 patients were enrolled in this study. Characteristics of the eligible patients are summarized in Table 1. Macroscopic tumor type 1, type 2, and type 3 were observed in 15 patients (18%), 36 patients (43%), and 30 patients (36%), respectively. Type 4 and type 5 were each observed in one patient (1%). The median patient age was 71 years (52–86 years) and almost 90% of patients were men. T2, T3, and T4 disease were observed in 9 patients (11%), 36 patients (43%), and 38 patients (46%), respectively. Regarding lymph node metastases, regional lymph node metastases were observed in 66 patients (80%) and supraclavicular lymph node metastases in 17 patients (20%). Stage I, Stage II, Stage III, and Stage IV disease were observed in 5 patients (6%), 8 patients (10%), 53 patients (64%), and 17 patients (20%), respectively. In 10 patients (12%), a decreased dose (less than 60 Gy) was selected. The median follow-up period at the time of evaluation was 59 months in survivors.

Table 1 Patient characteristics

	Total	
	$n = 83$	
Age, years, median (range)	71 (52–86)	
Sex		
Male	73	88%
Female	10	12%
Location		
Cervical esophagus	16	19%
Upper thoracic esophagus	12	14%
Middle thoracic esophagus	27	33%
Lower thoracic esophagus	24	29%
Esophago-gastric junction	4	5%
T stage		
T2	9	11%
T3	36	43%
T4	38	46%
N stage		
N0	16	19%
N1	33	40%
N2	25	30%
N3	9	11%
M stage		
M0	66	80%
M1	17	20%
Stage		
Stage I	5	6%
Stage II	8	10%
Stage III	53	64%
Stage IV	17	20%
Macroscopic tumor type		
Type 1	15	18%
Type2	36	43%
Type 3	30	36%
Type 4	1	1%
Type 5	1	1%
Tumor length, mm, median (range)	60 (10–160)	
Maximum diameter, mm, median (range)	33 (15–57)	
Dose, Gy, median (range)	60 (43.2–66)	

Treatment outcome of all patients

Figure 1 shows the OS, CSS, and LPF rates in all patients. The 5-year OS rate was 25.6% (95% confidence interval [CI] 15.3–35.9%). During the follow-up period, 57 patients died; among these, 43 died of esophageal cancer and 14 died of other diseases. The 5-year CSS rate was 36.3% (95% CI 23.8–48.7%). The 5-year LPF rate was 69.6% (95% CI 56.9–82.3%). Disease progression was observed in 46 patients. As the pattern of first recurrence, 18 patients experienced treatment failure at the site of the local esophageal tumor, 5 patients had lymph node metastasis, and 20 patients had distant metastasis.

The 5-year OS rates of Stage I, Stage II, Stage III, and Stage IV were 20.0% (95% CI 0–55.1%), 18.8% (95% CI

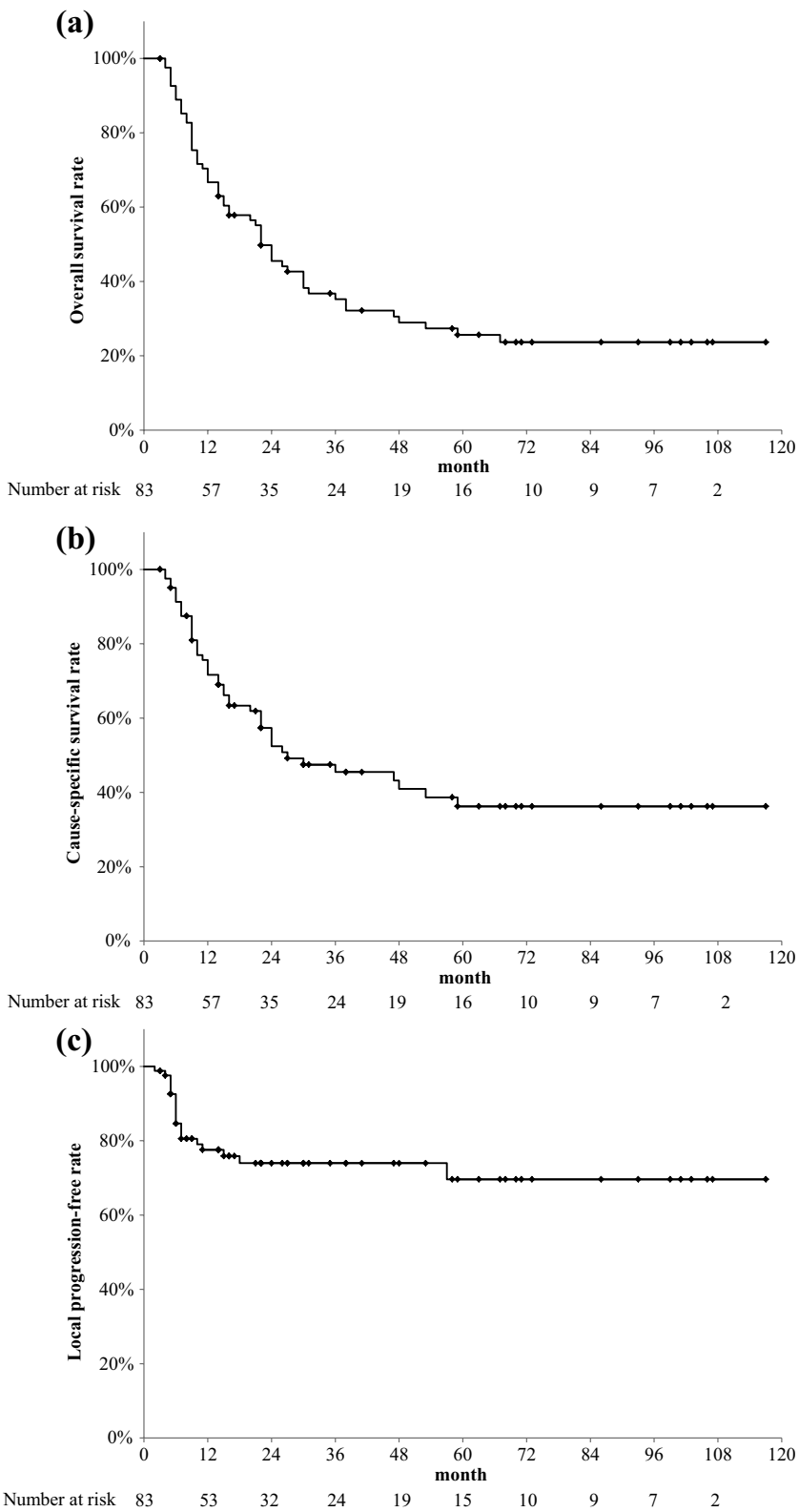

Fig. 1 Treatment results of chemoradiotherapy for esophageal cancer. **a** Overall survival rate. The 5-year overall survival rate was 25.6%. **b** Cause-specific survival rate. The 5-year cause-specific survival rate was 36.3%. **c** Local progression-free rate. The 5-year local progression-free rate was 69.6%

0–49.7%), 34.7% (95% CI 20.6–48.7%), and 6.6% (95% CI 0–19.1%), respectively. The 5-year CSS rates of Stage I, Stage II, Stage III, and Stage IV were 33.3% (95% CI 0–86.7%), 42.9% (95% CI 6.2–79.5%), 43.4% (95% CI 28.3–58.6%), and 12.9% (95% CI 0–34.6%), respectively. The 5-year LPF rates Stage I, Stage II, Stage III, and Stage

IV were 75.0% (95% CI 32.6–100%), 75.0% (95% CI 45.0–100%), 71.5% (95% CI 58.8–84.2%), and 42.9% (95% CI 0–100%), respectively.

Treatment outcome by macroscopic tumor type

Type 4 and 5 tumors were excluded from these analyses because of the small number of cases. The 5-year OS rates of type 1, type 2, and type 3 were 37.0% (95% CI 11.7–62.4%), 17.7% (95% CI 3.2–32.1%), and 31.9% (95% CI 14.2–49.7%), respectively. The 5-year CSS rates of type 1, type 2, and type 3 were 71.8% (95% CI 44.3–99.3%), 24.6% (95% CI 6.7–42.4%) and 36.8% (95% CI 17.3–56.3%), respectively. The 5-year LPF rates of type 1, type 2 and type 3 were 100% (95% CI 100–100%), 47.8% (95% CI 22.8–72.8%) and 80.5% (95% CI 64.9–96.2%), respectively. The complete response rates of type 1, type 2 and type 3 were 86.7%, 55.6% and 73.3%, respectively. The 5-year CSS and LPF rates of type 1 were better than those of type 2 and type 3.

Predictive factors for CSS and LPF

Table 2 shows the univariate analyses of the predictive factors for CSS and LPF. For both CSS and LPF, macroscopic tumor type 1 showed a better treatment outcome than the other types. In our study, macroscopic tumor type had a greater influence on treatment outcome than sex, TNM stage, and tumor volume, and was the only significant predictive factor.

Comparison between macroscopic tumor type 1 and other types (types 2–5)

Table 3 summarizes the characteristics of macroscopic tumor type 1 and other types (types 2–5). There was no statistical difference in the clinical characteristics of the groups. Figure 2 shows the OS, CSS, and LPF rates of a comparison of type 1 and other types. The 5-year OS rates of type 1 and other types were 37.0% (95% CI 11.7–62.4%) and 23.3% (95% CI 12.2–34.4%), respectively ($P = 0.4255$). The

Table 2 Relationship between predictive factors and treatment results

	n	Five-year CSS rate (%)	UVA *P* value	Five-year LPF rate (%)	UVA *P* value
Age					
< 70	46%	36.4	0.5921	78.4	0.1914
≥ 70	54%	35.2		62.9	
Sex					
Male	88%	31.3	0.0804	71.6	0.6304
Female	12%	66.7		75.0	
Location					
Cervical esophagus	19%	25.5	0.8114	50.9	0.8546
Others	81%	38.5		72.9	
T stage					
T2 and 3	54%	43.7	0.1536	75.4	0.5948
T4	46%	27.4		61.7	
N stage					
N0	19%	42.4	0.4392	69.2	0.9213
N1–3	81%	35.1		69.4	
M stage					
M0	80%	41.9	0.0803	71.6	0.6374
M1	20%	12.9		42.9	
Macroscopic tumor type					
Type 1	18%	71.8	0.0325	100	0.0246
Other types	82%	30.3		63.3	
Tumor length					
< 60 mm	45%	38.5	0.5310	78.6	0.2349
≥ 60 mm	55%	33.7		61.3	
Maximum diameter					
< 33mm	47%	39.8	0.1896	70.7	0.5060
≥ 33mm	53%	33.9		70.2	

CSS cause-specific survival, *UVA* univariate analysis, *LPF* local progression free

Table 3 Comparison of macroscopic tumor type 1 and other types

	Type 1		Other types		*P* value
	n = 15		*n* = 68		
Age, years, median (range)	71 (59–83)		71 (52–85)		0.3402
Sex					0.8659
Male	13	87%	60	88%	
Female	2	13%	8	12%	
Location					0.1758
Cervical esophagus	6	40%	10	15%	
Upper thoracic esophagus	2	13%	10	15%	
Middle thoracic esophagus	2	13%	25	37%	
Lower thoracic esophagus	4	27%	20	29%	
Esophago-gastric junction	1	7%	3	4%	
T stage					0.7518
T2	1	7%	8	12%	
T3	6	40%	30	44%	
T4	8	53%	30	44%	
N stage					0.2493
N0	5	33%	11	16%	
N1	5	33%	28	41%	
N2	5	33%	20	29%	
N3	0	0%	9	13%	
M stage					0.4485
M0	13	87%	53	78%	
M1	2	13%	15	22%	
Tumor length, mm, median (range)	60 (20–110)		60 (10–160)		0.7945
Maximum diameter, mm, median (range)	29 (18–55)		34 (15–57)		0.6308
Dose, Gy, median (range)	60 (56–66)		60 (43.2–66)		0.3064

5-year CSS rates of type 1 and other types were 71.8% (95% CI 44.3–99.3%) and 30.3% (95% CI 17.3–43.3%), respectively ($P = 0.0325$). The 5-year LPF rates of type 1 and other types were 100% (95% CI 100–100%) and 63.3% (95% CI 48.5–78.1%), respectively ($P = 0.0246$). Among patients with type 1 disease, 9 died; of these, 3 (33%) died of esophageal cancer and 6 (67%) died of other diseases. Among patients with other types, 48 died; of these, 40 (83%) died of esophageal cancer and 8 (17%) died of other diseases. The 5-year CSS and LPF rates of type 1 were significantly better than those of other types, but there was no significant difference in OS because the frequency of death from other diseases was high in patients with type 1 disease.

Discussion

In patients with locally advanced esophageal cancer who are medically and surgically fit, preoperative chemotherapy followed by surgery should be considered. CRT is considered in patients who are not suitable for surgery or who refuse it. Consequently, patients who undergo CRT include those with advanced stage disease and/or poor general condition who were not suitable for surgery. Therefore, it is not appropriate to simply compare surgery and CRT. However, in the case of stage II–III operable esophageal cancer, the 5-year OS and PFS rates were 55% and 44% for surgery, and 37% and 26% for CRT, respectively [9, 10]. It seemed that the treatment outcome of surgery was better than that of CRT. We suspected that the difference in outcomes between the two treatment modalities stemmed largely from the frequency of local recurrence. With preoperative therapy followed by surgery, local recurrence ranged from about 20–30%. On the other hand, local recurrence after CRT occurred in 30–50% of patients [2, 9, 10, 12, 13, 15, 18–20]. To improve the treatment outcomes of CRT, we felt that local control was the most important factor. Several previous studies described recurrence patterns in patients with esophageal cancer who received CRT [12, 19, 20]. The majority of these patients experienced treatment failure at the site of the primary tumor, and the incidence of distant metastasis in patients who achieved complete response after CRT was not high. For these reasons, local control might be the key in improving treatment outcome, and it is also important to predict local control after CRT.

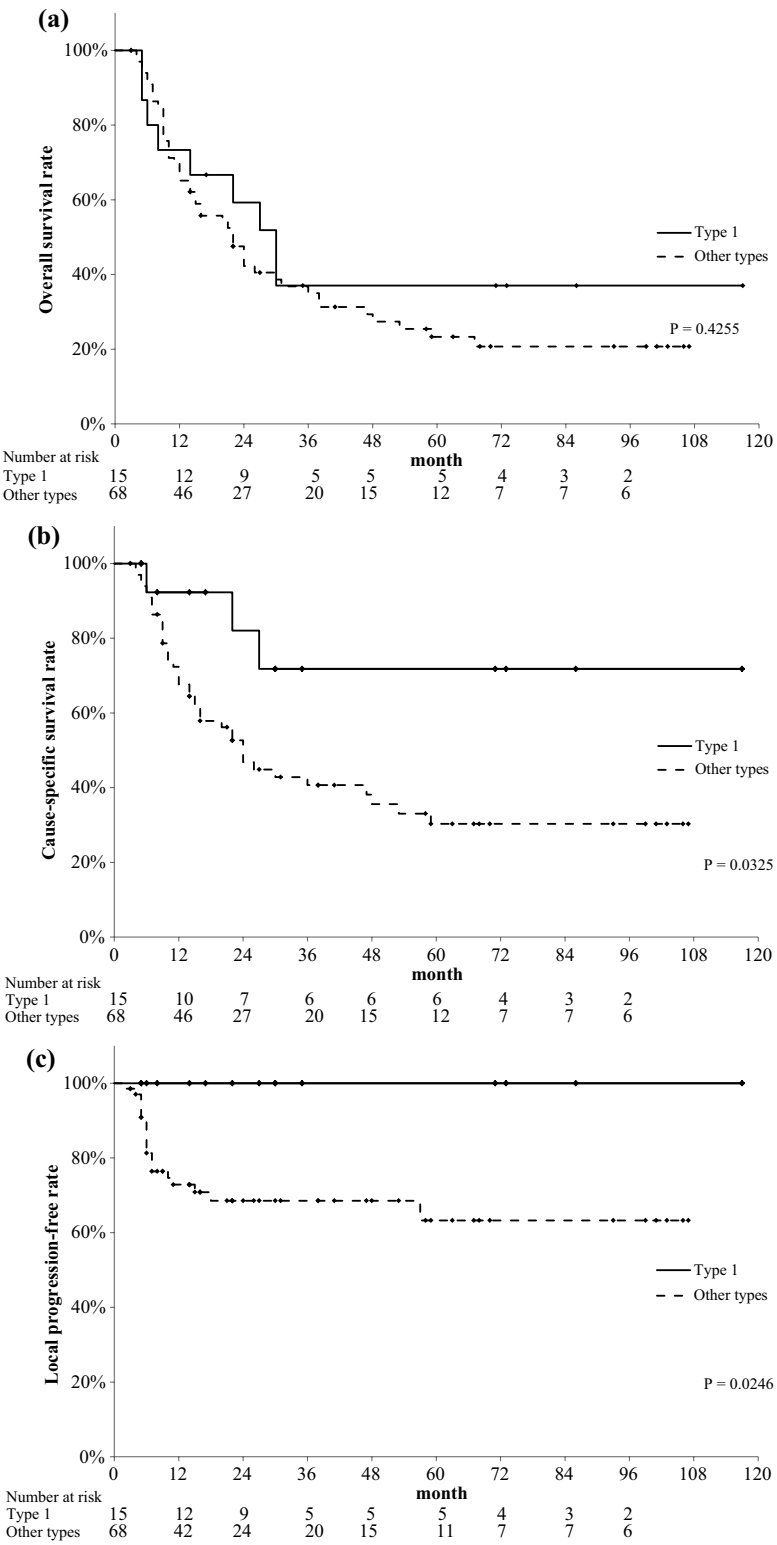

Fig. 2 Comparison of treatment results of 15 patients with macroscopic tumor type 1 and 68 patients with other types. **a** Overall survival rate. **b** Cause-specific survival rate. **c** Local progression-free rate

Many studies have identified various predictive factors related to the results after CRT, such as TNM stage, tumor volume, and radiation dose [11–16]. In the present study, the impact of macroscopic tumor type identified by endoscopy on the treatment outcome was greater than other factors, such as TNM stage and tumor length. Local control was particularly superior in patients with type 1 disease compared to other types. The complete response rate of type 1 was higher than those of other types and the 5-year CSS and LPF rates of type 1 were 71.8% and 100%, respectively.

While the sample size was small, these treatment results were remarkable. In patients with unresectable advanced esophageal cancer, or patients who do not wish to undergo surgery, knowledge of the efficacy of CRT for esophageal tumor type 1 would be beneficial in treatment decisions.

Morita et al. previously reported a relationship between the radiologic features of esophageal cancer and the local control by radiation therapy [21]. The authors found that patients with superficial or proliferative type disease (type 1 in the current study) had better treatment outcomes than patients with ulcerative or infiltrative type disease (types 2 and 3 in the current study). These findings were similar to our results, and it is clear that the macroscopic tumor type is closely related to local control following CRT. However, current CRT differs in both the anticancer drugs and the radiation therapy technique from the treatments used in the study of Morita et al., and the tumor types in their study were evaluated with barium examination. In addition, their study included T1 disease, which was considered to have better local control than T2–T4 disease. No previous studies have described a relationship between macroscopic tumor type and responses after current CRT for locally advanced esophageal cancer. The present study is a unique investigation that suggests the possibility that the effect of current CRT for locally advanced esophageal cancer can be predicted by macroscopic tumor type.

Despite good local control, the 5-year OS rate was not significantly different between type 1 and other types in the current study. The reason for this finding was death from other diseases. Patients with locally advanced esophageal cancer often have comorbid diseases, such as chronic obstructive lung disease, alcoholic liver disease, cardiovascular disease, and other cancers. According to a Japanese nationwide survey, almost 20% of patients with esophageal cancer died from other diseases [2]. In our study, 17% of all patients died from other diseases, a finding similar to the results of the survey. However, in patients with type 1 disease, two-thirds of deaths were due to other diseases. We believe that this outcome was due to chance, but it will be necessary in a future study to confirm these results by increasing the number of cases to avoid such potential incidental findings.

At the same time, this study had several limitations, including its retrospective and single-institution design, which introduced potential biases, as well as its small sample size. In addition, detailed pathological information, such as degree of differentiation and nuclear grade, was not available in our study owing to the retrospective design. However, in this study population, since the backgrounds and treatment procedures were well balanced, we felt that these shortcomings did not significantly affect the credibility of our study. Therefore, despite these limitations, macroscopic tumor type as determined by endoscopy was the most significant predictive factor for outcomes of locally advanced esophageal cancer after CRT, and we believe that these findings are useful and meaningful.

In conclusion, macroscopic tumor type 1 was the significant favorable predictive factor for local control after CRT. The study results suggested that the macroscopic tumor type was useful in predicting tumor responses. Further study is warranted to evaluate the impact on prognosis.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

References

1. National Cancer Center, Center for Cancer Control and Information Services. Latest cancer statistics 2016. https://ganjoho.jp/reg_stat/statistics/stat/summary.html. Accessed 31 Oct 2018.
2. Ozawa S, Tachimori Y, Baba H, Matsubara H, Muro K, Numasaki H, et al. Comprehensive registry of esophageal cancer in Japan, 2002. Esophagus. 2010;7:7–22.
3. Murakami M, Kuroda Y, Nakajima T, Okamoto Y, Mizowaki T, Kusumi F, et al. Comparison between chemoradiation protocol intended for organ preservation and conventional surgery for clinical T1–T2 esophageal carcinoma. Int J Radiat Oncol Biol Phys. 1999;45:277–84.
4. Hironaka S, Ohtsu A, Boku N, Muto M, Nagashima F, Saito H, 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.
5. Ohtsu A, Boku N, Muro K, Chin K, Muto M, Yoshida S, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol. 1999;17:2915–21.
6. Nishimura Y, Suzuki M, Nakamatsu K, Kanamori S, Yagyu Y, Shigeoka H. Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol Biol Phys. 2002;53:134–9.
7. Ishida K, Ando N, Yamamoto S, Ide H, Shioda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG) /Japan Clinical Oncology Group trial (JCOG9516). Jpn J Clin Oncol. 2004;34:615–9.
8. Wong RK, Malthaner RA, Zuraw L, Rumble RB. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. Int J Radiat Oncol Biol Phys. 2003;55:930–42.
9. Kato K, Muro K, Minashi K, Ohtsu A, Ishikura S, Boku N, et al. Phase II study of chemoradiotherapy with 5-fluorouracil

and cisplatin for stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys. 2011;81:684–90.
10. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluoroiracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG 9907). Ann Surg Oncol. 2012;19:68–74.
11. Amini A, Ajani J, Komaki R, Allen PK, Minsky BD, Blum M, et al. Factors associated with local-regional failure after definitive chemoradiation for locally advanced esophageal cancer. Ann Surg Oncol. 2014;21:306–14.
12. Kim HW, Kim JH, Lee IJ, Kim JW, Lee YC, Lee CG, et al. Local control may be the key in improving treatment outcomes of esophageal squamous cell carcinoma undergoing concurrent chemoradiation. Digestion. 2014;90:254–60.
13. Haefner MF, Lang K, Krung D, Koerber SA, Uhlmann L, Kieser M, et al. Prognostic factors, patterns of recurrence and toxicity for patients with esophageal cancer undergoing definitive radiotherapy or chemo-radiotherapy. J Radiat Res. 2015;56:742–9.
14. Chen Y, Zhang Z, Jiang G, Zhao K. Grass tumor volume is the prognostic factor for squamous cell esophageal cancer patients treated with definitive radiotherapy. J Thorac Dis. 2016;8:1155–61.
15. Luo Y, Mao Q, Wang X, Yu J, Li M. Radiotherapy for esophageal carcinoma: dose, response and survival. Cancer Manag Res. 2018;10:13–211.
16. Sakanaka K, Ishida Y, Fujii K, Itasaka S, Miyamoto S, Horimatsu T, et al. Long-term outcome of definitive radiotherapy for cervical esophageal squamous cell carcinoma. Radiat Oncol. 2018;13:7.
17. Japan Esophageal Society. Japanese classification of esophageal cancer, 11th edition: part II and III. Esophagus. 2017;14:37–65.
18. Murakami Y, Hamai Y, Emi M, Hihara J, Imano N, Takeuchi Y, et al. Long-term results of neoadjuvant chemoradiotherapy using cisplatin and 5-fluorouracil followed by esophagectomy for resectable, locally advanced esophageal squamous cell carcinoma. J Radiat Res. 2018;59:616–24.
19. Versteijine E, van Laarhoven HW, van Hooft JE, van Os RM, Geijsen ED, van Berge Henegouwen MI, et al. Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern. Dis Esophagus. 2015;28:453–9.
20. Shen WB, Zhu SC, Gao HM, Li YM, Su JW, Li J, et al. Analysis of failure patterns in patients with resectable esophageal squamous cell carcinoma receiving chemoradiotherapy. J Cancer Res Ther. 2016;12:62–8.
21. Morita K, Takagi I, Watanabe M, Niwa K, Kanazawa H. Relationship between the radiologic features of esophageal cancer and the local control by radiation therapy. Cancer. 1985;55:2668–766.