Original Article

Does protruding type 1 esophageal cancer really have a good response to radiation therapy?—a retrospective observational study

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Background: It is now well-established that esophageal cancer can be more accurately classified macroscopically on the basis of endoscopic rather than esophagographic findings. Thus far, no studies have reported correlations between responses to radiation therapy (RT) and endoscopically-determined macroscopic type of locally advanced esophageal cancer. In this retrospective study, we therefore aimed to determine such correlations in patients who had undergone at least two follow-up endoscopies.

Methods: Our study cohort comprised 30 patients who had received radiotherapy for locally advanced squamous cell carcinoma (SCC) of the esophagus from January 2012 to November 2017 at our hospital. The lesions had been classified endoscopically into one of the five types specified by the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Disease. All patients had received radiotherapy and 27 had received chemotherapy. In accordance with those guidelines, responses to treatment were evaluated endoscopically, a median of 74 days after initiating radiotherapy. Follow-up endoscopy had been performed at least twice in 18/30 patients.

Results: The primary complete response (CR) rate was significantly higher in patients with type 1 disease (protruding) than in those with the other types (χ^2 test, P=0.041). The only correlation revealed by logistic regression analysis was between CR rate and macroscopically classified type 1 disease (P=0.05). Disease-specific survival (DSS) did not differ between macroscopically classified types (P=0.31). Patients with clinical T2 disease and ≤ stage IIIA had better outcomes than those with other stages (P=0.041 and 0.025, respectively).

Conclusions: Macroscopic classification of esophageal carcinoma by endoscopy accurately identifies a group with a higher primary CR rate to chemoradiotherapy (CRT): those with type 1 disease (protruding). However, median DSS did not differ between patients with type 1 disease and those with other types.

Keywords: Macroscopic classification; protruding type 1; esophageal cancer; squamous cell carcinoma (SCC); radiation therapy (RT)

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Introduction

Polypoid or exophytic carcinoma of the esophagus has long been reported to have a better outcome with surgery and/or radiation therapy (RT) than other types of esophageal cancer. However, these studies were conducted in the 1980s and 1990s, when responses to RT in "proliferative" or "tumorous" disease types were evaluated by esophagography (1-3). With recent advances in endoscopic technology, accurate tumor typing is commonly achieved on the basis of macroscopic endoscopic findings (4). RT is frequently used to treat locally advanced esophageal cancer; however, no studies have evaluated the association between responses to RT and type of esophageal cancer as determined endoscopically. In this retrospective study, we therefore compared responses to RT in patients with locally advanced esophageal cancer according to the macroscopic disease type determined on the basis of endoscopic findings. We also assessed responses to RT in patients who had undergone at least two follow-up endoscopies.

Methods

Patients

Table 1 lists relevant patients' characteristics and their treatment regimens.

Data on 30 patients (26 men and 4 women) with endoscopic and pathological diagnoses of squamous cell carcinoma (SCC) of the thoracic esophagus who had not undergone surgery after RT were reviewed. All patients had undergone RT to the primary lesion and lymph node regions from January 2012 to November 2017 at our hospital. All tumor samples had been collected before treatment. Patient age at RT initiation ranged from 51 to 86 years (median, 70 years). Clinical stage was assessed according to the TNM classification [the International Union Against Cancer (UICC), 2009; stages IB/IIA/IIB/IIIA/IIIB/IIIC =1/1/2/7/12/7, respectively]. This retrospective study was approved by the Institutional Review Board of Nihon University School of Medicine. The patients had provided informed consent for all treatment procedures.

Macroscopic classification of esophageal cancer

In accordance with the Guidelines for Clinical and Pathologic Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Disease (11th edition) (4), advanced disease was classified on the basis of endoscopic findings as one of the following types: (I) protruding; (II) ulcerative and localized; (III) ulcerative and infiltrative; (IV) diffusely infiltrative; and (V) unclassified. Eight patients had type 1 disease, 11 type 2, 11 type 3, none type 4, and none type 5. Type 1 lesions are tall and protruding with an eroded surface but no ulceration; they correspond with polypoid or exophytic type tumors on esophagography images *(Figure 1)*. In this study, type 1 lesions were diagnosed by pathological examination as moderately differentiated (M/D) SCC in seven patients and well differentiated (W/D) in one. Other types were diagnosed as M/D in 11 patients, W/D in two, poorly differentiated in one, and only SCC in eight. There was no difference in degree of differentiation between type 1 and other types of tumor.

RT

A linear accelerator was used to deliver beam energy of 10 MV to all patients except one, who received beam energy of 4 MV. Multiple fields were used with an anterior-posterior opposed field that included at least the primary tumor, lymph nodes harboring metastases and, when appropriate, regional lymph nodes. The total dose ranged from 40 to 66 Gy (median, 50 Gy) and was 40 Gy in patients who either did not consent to post-chemoradiation surgery or had a good response to RT; these patients were followed closely. Two patients who had undergone RT alone each received a total dose of 66 Gy. The dose per fraction was 2 Gy except in two patients with a wide radiation field, for whom 1.8 Gy was used.

Chemotherapy

Twenty-seven of the 30 patients received concurrent chemotherapy. The regimen used was 5-fluorouracil (5-FU) + cisplatin [cis-diamine dichloroplatinum (CDDP)] in 26 patients and 5-FU + nedaplatin [cis-Diammine(glycolato-O^1,O^2)platinum (CDGP)] in one. All patients except one completed the 5-FU + CDDP regimen specified by the Japan Clinical Oncology Group Trial (JCOG9516) schedule. Three patients underwent RT alone because of advanced age and renal impairment.

Response to RT

The response of the primary lesions was assessed on the basis of endoscopic findings approximately 1 month after

Table 1 Patient characteristics

Characteristic	Number (%)
Age (years), median [range]	70 [51–86]
Sex	
Male	26 (86.7)
Female	4 (13.3)
Macroscopic classification	
Type 1	8 (26.6)
Type 2	11 (36.7)
Type 3	11 (36.7)
T stage	
T2	6 (20.0)
T3	22 (73.3)
T4	2 (6.7)
UICC stage	
I	1 (3.3)
II	3 (10.0)
III	26 (86.7)
Total radiation dose (Gy)	
40	11 (36.7)
50	5 (16.6)
59.4	2 (6.7)
60	10 (33.3)
66	2 (6.7)
Chemotherapy	
5-FU + cisplatin	26 (86.7)
5-FU + nedaplatin	1 (3.3)
None	3 (10.0)

UICC, International Union against Cancer; FU, fluorouracil.

completion of RT; the first endoscopic examination being performed 38 to 174 days after initiation of RT (median, 74 days). These responses were evaluated according to the criteria for endoscopic complete response (CR) of primary lesions in the Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Disease (11th edition) (5,6). CR was diagnosed when all of the following criteria were met: (I) resolution of all endoscopic findings suggesting the presence of a tumor; (II) negative endoscopic biopsy findings in the area of the primary tumor; (III) entire esophagus observed by endoscopy; and (IV) no endoscopic evidence of active esophagitis. Lesions that appeared to be residual tumors that had diminished in size, biopsies of which showed no malignant cells, and with no tumor growth noted at the second and subsequent follow-up endoscopic examinations were also diagnosed as achieving CR. Responses of the primary lesions were assessed at the last endoscopic examination (performed 71 to 779 days after initiation of RT; median, 397 days) in the 18 patients who had undergone follow-up endoscopy at least twice.

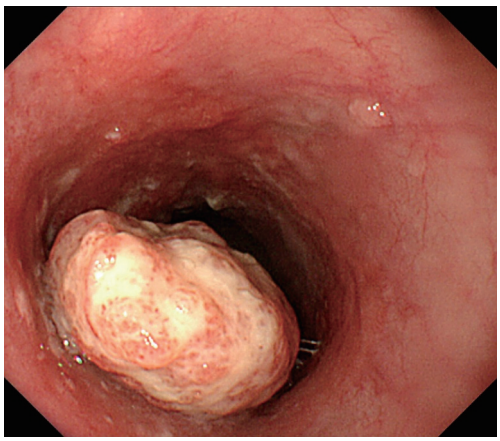

Figure 1 Endoscopic image of protruding type 1 esophageal cancer shows a tall protruding lesion without ulceration. The surface of this lesion is white.

Statistical methods

SPSS ver. 21.0 (IBM, Armonk NY, USA) was used for statistical analysis. Univariate analysis using Pearson's χ^2 test and multivariate analysis using stepwise logistic regression were performed to analyze primary responses to RT. The following patient characteristics were evaluated: age (< median 70 *vs.* ≥70 years), clinical T staging (T2 *vs.* T3–4), macroscopic findings on endoscopy (type 1 *vs.* other types), and radiation dose (< median 50 *vs.* ≥50 Gy). The Kaplan-Meier method was used to calculate the probability of disease-specific survival (DSS) from the date of RT initiation. Differences in survival between subgroups of patients according to clinical stage (IB/IIA/IIB/IIIA *vs.* IIIB/IIIC) and the above variables were analyzed using Mantel's log-rank test.

Table 2 Type 1 disease and other types according to primary response to RT

Macroscopic classification	No. of patients	CR	Non-CR	CR rate (%)	P
Type 1	8	5	3	62.5	0.041*
Other types	22	5	17	22.7	–

*, χ^2 test. CR, complete response; RT, radiation therapy.

Table 3 Results of multivariate analysis for correlation between listed factors and complete response of primary tumor

Characteristics	P
Age (years)	
<70 *vs.* ≥70	0.33
T stage	
T2 *vs.* T3–4	0.13
Macroscopic classification	
Type 1 *vs.* other types	0.05*
Total radiation dose (Gy)	
<50 *vs.* ≥50	0.94

*, stepwise logistic regression analysis.

Results

Comparisons between patients with type 1 disease and those with other disease types according to primary response to RT are shown in *Table 2*. The χ^2 test revealed that patients with type 1 disease had a significantly higher CR rate than those with other types (P=0.041). Univariate analysis showed no significant differences for the other variables.

The results of multivariate analysis aimed at determining correlations between the studied factors and CR of the primary tumor are shown in *Table 3*. According to stepwise logistic regression analysis, only macroscopic classification type 1 showed a higher CR rate than other types (P=0.05). Changes in primary tumor response between the first and last endoscopy in the 18 patients who had undergone at least two follow-up endoscopies are shown in *Table 4*. After the first endoscopy, additional therapy with oral tegafur-gimestat-otastat potassium (TS-1) was administered to 11 patients and paclitaxel (PTX) to one. Six patients received no additional therapy. According to the χ^2 test, patients with type 1 disease had a significantly higher CR rate than those with other types (P=0.019) at the time of the last endoscopy. The mean DSS was 684 days for all patients; DSS did not differ between patients with type 1 disease and those with other types (P=0.31; *Figure 2*). Patients with clinical T2 disease and ≤ stage IIIA showed better outcomes than those with other stages (P=0.041 and 0.025, respectively).

Discussion

Polypoid carcinoma of the esophagus is relatively rare, reportedly accounting for 2% to 8% of esophageal tumors and 7% of definite SCCs of the esophagus (7-9). In our study, 8 of 30 patients (26.6%) had type 1 disease, which is a higher percentage than that reported in previous studies. The percentage may have been lower if we had also enrolled patients who had undergone surgery. It has long been reported that clinical and histopathological features differ between type 1 disease and the other types. Type 1 disease also reportedly has better therapeutic outcomes than the other types. A meta-analysis has demonstrated that preoperative chemoradiotherapy (CRT) improves the prognosis of locally advanced esophageal cancer (10). Another study has shown that definitive CRT improves the prognosis of unresectable locally advanced esophageal cancer; these findings have led to increased use of RT in such patients (11). In the present study, we evaluated primary responses to RT in patients who had endoscopic macroscopic diagnoses of protruding disease type; endoscopy provides more accurate diagnoses than esophagography. To the best of our knowledge, this is the first report on responses to RT in patients with endoscopically diagnosed type 1 polypoid carcinoma of the esophagus. Only one published study has reported associations between macroscopic type of primary lesion and responses to RT. In that study, four of 15 patients had type 1 disease, three of whom achieved CR at the primary site following definitive CRT; however, responses were not evaluated according to disease type in that study (12). In our study, patients with macroscopic type 1 disease on endoscopy had better primary responses to RT than those with other types. The results of our study, in which we classified lesions macroscopically on the basis of endoscopic findings, thus supported the findings of previous studies

Table 4 Endoscopically assessed primary tumor response at first and last endoscopy

Case	Macroscopic classification	T stage	Radiation dose (Gy)	First endoscopy	Additional therapy	Last endoscopy
1	Type 1	2	40	CR	TS-1	CR
2	Type 1	3	40	Non-CR	None	CR
3	Type 1	4	60	CR	TS-1	CR
4	Type 1	3	40	CR	TS-1	CR
5	Type 1	3	40	Non-CR	None	Non-CR
6	Type 1	2	60	Non-CR	TS-1	CR; CR rate 83.3%, P=0.019*
7	Type 2	3	60	Non-CR	None	Non-CR
8	Type 2	3	40	Non-CR	TS-1	Non-CR
9	Type 2	3	40	Non-CR	TS-1	Non-CR
10	Type 2	3	40	Non-CR	TS-1	Non-CR
11	Type 2	3	60	Non-CR	TS-1	Non-CR
12	Type 3	2	40	CR	TS-1	Recurrence
13	Type 3	3	40	Non-CR	None	Non-CR
14	Type 3	2	60	CR	TS-1	CR
15	Type 3	3	40	CR	TS-1	CR
16	Type 3	3	60	Non-CR	None	Non-CR
17	Type 3	3	60	CR	None	CR
18	Type 3	2	59.4	Non-CR	PTX	Non-CR; CR rate 25%

*, χ^2 test. CR, complete response; additional therapy, additional therapy after the first endoscopy; TS-1, tegafur-gimestat-otastat potassium; PTX, paclitaxel.

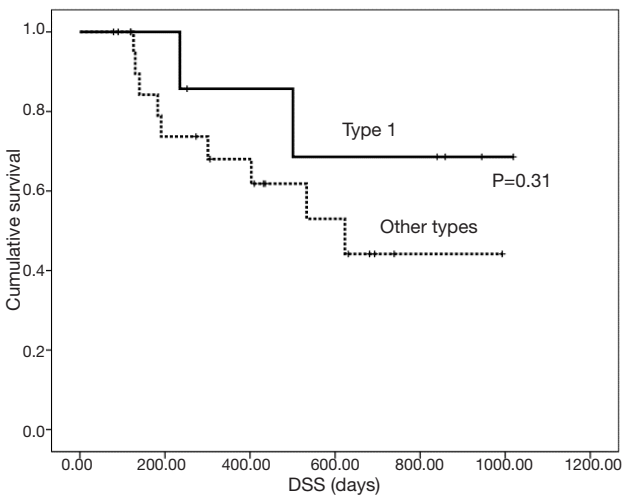

Figure 2 Kaplan-Meier curve of DSS according to endoscopically classified macroscopic type of disease. DSS, disease-specific survival.

that used esophagography findings. Of the 18 patients who had undergone follow-up endoscopy at least twice, four with type 1 disease and six with other disease types had received RT at a total dose of 40 Gy, which is lower than the recommended dose of 50.4–60 Gy for esophageal cancer (5,13). Interestingly, in those 10 patients, CR of the primary tumor (i.e., a good response to RT even at a lower than recommended total dose) was diagnosed on the last endoscopy in three of the four patients with type 1 disease (75%), whereas it was only diagnosed in one of the six patients with the other disease types (16.7%). These findings suggest that type 1 polypoid carcinoma of the esophagus is more susceptible to RT than the other types.

We have identified three studies on histopathological findings that may explain the better response of type 1 disease than of the other types to RT. One study on histopathological features of resected specimens of polypoid carcinoma of the esophagus reported that their

depth of invasion was shallow (14). In another study that evaluated features of polypoid SCC in resected specimens, the incidence of adventitial involvement was lower in the polypoid type than in the other types (9). A third study used immunostaining with an anti-CD34 antibody (found in vascular endothelial cells) to compare the number of blood vessels in resected specimens of SCCs of the esophagus (15). There tended to be more numerous blood vessels per unit area in type 1 carcinoma than in the other types. The higher density of blood vessels may result in minimal numbers of hypoxic tumor cells, resulting in greater susceptibility to RT. Moreover, type 1 SCCs diagnosed endoscopically as having a white protruding portion are reportedly less common and have narrower bases and less frequent T3 adventitial involvement than those with a red protruding portion (16). In our study, the lesions of only two of eight patients with type 1 disease had a white protruding portion and no evidence of adventitial involvement on computed tomography images. Given that we examined endoscopically-obtained biopsies rather than resected specimens, it is possible that the biopsied parts were not always representative of all of the tumor. For example, esophageal carcinosarcoma (ES) is commonly polypoid. One study reported that, although polypoid ES tumors are mostly sarcomatous, their bases are characteristically mainly SCC (17). Hence, biopsy of the base of a type 1 ES tumor may result in a diagnosis of SCC. ES is more likely to be localized than other pathological tumor types and the 5-year overall survival rate is significantly better than that of esophageal carcinoma (18). Another tumor type in which biopsy specimens may be unrepresentative is esophageal basaloid SCC (EBSCC), which is characterized by submucosal tumor-like growth and can form a polypoid tumor. Hence, biopsy of the superficial portion of such a type 1 tumor may result in a diagnosis of SCC (19). We have previously reported a case of EBSCC with a good response to RT (20).

We assessed the responses of primary lesions to RT endoscopically at a median of 74 days after initiation of RT; however, this may have been too early. The single published study on the optimal timing of endoscopic evaluation of esophageal cancer after definitive CRT found that the mean time to CR at the primary site was 97 days after initiation of CRT/RT. In that study, biopsy specimens showed residual viable cancer cells within 75 days of CRT/RT initiation in four patients, these cells not being identified in subsequent biopsies (21). These authors recommended that tumor response should be evaluated endoscopically 75 to 90 days after initiation of CRT/RT. Because most patients in our institution were receiving preoperative RT, responses to RT had to be assessed earlier than this, which is why we evaluated responses to RT only in those study patients who had undergone follow-up endoscopy at least twice; at a median of 397 days after initiation of RT, the response of type 1 tumors to RT was significantly better than that of the other types and better than that at the time of the first endoscopy. In contrast, type 1 disease and the other types did not differ significantly in DSS rate, which may be partly because a radiation dose of 40 Gy is too low to treat lymph node metastases, the optimal dose being 50.4–60 Gy (5,13).

Conclusions

In future studies, we plan to evaluate responses to RT according to macroscopic disease type by histopathological examination of specimens resected after RT in a larger cohort of patients receiving radical dose RT. We will also further explore findings and optimal timing of evaluation of response.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board of Nihon University School of Medicine and patient informed consent to treatments and procedures was obtained.

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