TABLE II.
Patient and Tumor Characteristics.

	With Local Recurrence, n = 17	Without Local Recurrence, n = 22	P
Sex			
Male	16	20	.598
Female	1	2	
Age, yr, median (range)	68 (50–84)	65 (48–77)	.257
Brinkman index, median (range)	830 (0–1600)	820 (0–3,840)	.849
T stage			
1a	11	9	.399
1b	3	7	
2	3	6	
Degree of differentiation			
Poorly differentiated	1	1	.07
Moderately differentiated	10	4	
Well differentiated	3	7	
Carcinoma in situ	0	3	
N/A	3	7	
Exophytic tumor			
Yes	7	7	.546
No	10	15	
Anterior commissure invasion			
Yes	6	9	.721
No	11	13	

N/A = not available. Because of the small amount of biopsy specimens, it was impossible to assess differentiation of the tumor.

those without a tumor recurrence matched for age, gender, T stage, dose per fraction, and total dose. The demographic and tumor characteristics are summarized in Table II. There was no statistical difference with respect to gender, age, Brinkman index, T stage, degree of differentiation, exophytic or nonexophytic tumor, and presence of anterior commissure invasion between the patients with or without local recurrences. Table III shows the treatment details. No difference was noted in the rate of group 1/2 between patients with or without local recurrences. Table IV summarizes the results of the immunohistological analyses. There was a statistically significant difference in the expression of BerEP4 between patients with or without local recurrences ($P = .01$), whereas p53 and p16 did not reach statistical significance. As shown in Table IV and Figure 2, among tumors with intense expression of BerEP4 (++), as many as 10 of 11 patients (91%) experienced local recurrences.

DISCUSSION

In study I, the distribution of EpCAM-positive HNSCCs was studied prospectively. It was shown that the incidence of positive expression of EpCAM was higher in HNSCCs from the oropharynx, hypopharynx, and larynx than those from the oral cavity. In particular, HNSCCs from the hypopharynx had a higher incidence of intense expression of EpCAM than other primary sites, which was considered to be an attractive site for future investigation for the relationship between EpCAM and radiosensitivity. Because the follow-up period of the patients in study I was quite limited, study II was planned to determine the result of radiation therapy and tumor expression of EpCAM. Early-stage glottic cancer was selected because the radiation therapy technique was nearly the same, and chemotherapy was not administered to this population. In study II, it was shown that only expression of EpCAM was statistically different between patients with or without local recurrences. Up to 90.9% of patients with intense expression of EpCAM had a local recurrence after primary radiation therapy, suggesting that there is a strong biological correlation with the expression of EpCAM and response to radiation therapy. Imadome et al.[16] reported the relationship between radiosensitivity and expression of EpCAM detected immunohistochemically using CD326 in uterine cervical cancer; however, because the background of the patients with or without EpCAM expression was not clarified, there was a possibility for bias, such as stage, administration of chemotherapy, and total radiotherapy dose between the two groups. In contrast, the current study clearly showed that expression of EpCAM is associated with response to radiation therapy, whereas patient and treatment factors were equally distributed among the patients with or without local recurrences. A study exists that showed an association between high levels of EpCAM expression and high frequencies of nodal metastasis in squamous cell carcinoma of the larynx[25]; however, this study did not focus on prognosis, especially with respect to radiotherapy. The current study is the first report that showed the relationship between expression of EpCAM and response to radiation therapy in the treatment of HNSCCs.

There exist several treatment strategies in the management of advanced-stage hypopharyngeal cancer. For advanced-stage disease, the tumor control rate resulting from primary concurrent chemoradiation (cCRT) is not favorable.[2] Therefore, primary surgery followed by postoperative cCRT is a reasonable treatment strategy but at the expense of the patient's quality of life.[3] In contrast, salvage total laryngectomy after primary cCRT is difficult compared with primary surgery because of the higher postoperative morbidity associated with fibrotic change after radiation therapy.[26] Thus, if a poor response to radiation therapy is predicted before treatment, primary surgery would be performed without radiation. It was shown in study I that the rate of intense expression of EpCAM in HNSCCs from the hypopharynx was higher than other sites. If a poor radiation response of HNSCCs from the hypopharynx with intense expression of EpCAM is demonstrated in a future study using the cohort from study I with longer follow-up, a new finding about more accurate patient selection for primary surgery will be provided.

This study had some limitations. Because the control rate of primary radiation therapy for early-stage glottic cancer is favorable, the number of recurrent

TABLE III.
Treatment Details.

	With Local Recurrence, n = 17	Without Local Recurrence, n = 22	P
Energy			
^{60}Co (1.17 MV–1.33 MV)	7	3	.129
4 MV	6	13	
6 MV	4	6	
Dose per fraction, Gy			
2 (conventional fractionation)	14	15	.265
2.4 (accelerated fractionation)	3	7	
Total dose, Gy (range)			
T1 (conventional fractionation	66 (60–70)	66	.44
T1 (accelerated fractionation	60	60	
T2 (conventional fractionation	68 (60–70)	66	
T2 (accelerated fractionation)	64.8	64.8 (60–64.8)	
Wedge			
15° wedge	13	21	.297
30° wedge	1	0	
No wedge	3	1	
Bolus			
5-mm bolus	1	0	.436
No bolus	16	22	
Total treatment time, d (range)	48 (34–55)	47 (35–52)	.37
Radiation technique			
Group 1	6	9	.721
Group 2	11	13	

patients was small. Additionally, this study was a retrospective study.

This study found that expression of EpCAM might be associated with a poor radiation response, but did not reveal the mechanism underlying radiosensitivity. Future research should therefore focus on understanding the biology of EpCAM in relation to radiosensitivity.

TABLE IV.
Immunohistological Analyses.

	With Local Recurrence, n = 17	Without Local Recurrence, n = 22	*P*
p53			
With mutation	15	14	.083
Without mutation	2	8	
p16			
HPV-infected pattern	0	1	.564
HPV-uninfected pattern	17	21	
BerEP4			
(−)	4	15	.01*
(+)	3	6	
(++)	10	1	

*A *P* value <.05 was considered statistically significant.
HPV = human papillomavirus.

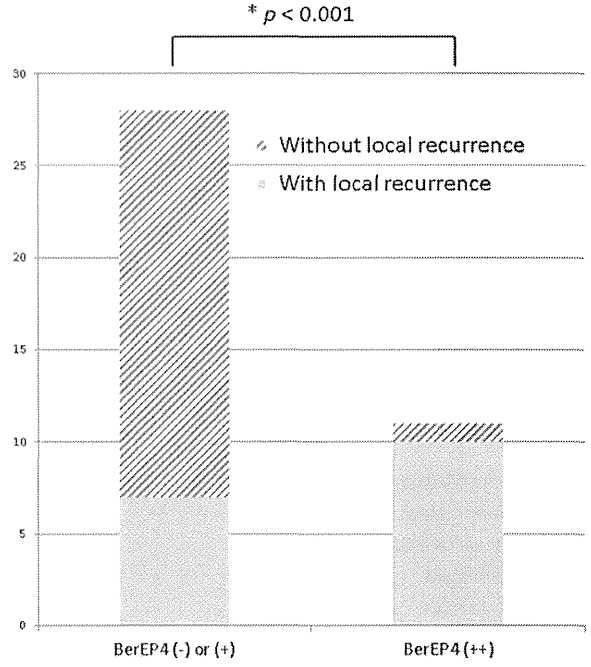

Fig. 2. Among tumors showing intense expression of BerEP4 (++), as many as 10 of 11 patients (91%) experienced local recurrence (*P* <.001).

CONCLUSION

A higher incidence of intense expression of EpCAM was found in HNSCCs from the hypopharynx. A strong relationship between expression of EpCAM and radiation response was demonstrated in early-stage glottic cancer. With longer follow-up, the relationship between expression of EpCAM and radiosensitivity can be investigated for HNSCC patients, especially involving the hypopharynx.

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Is the Outcome of a Salvage Surgery for T4 Thoracic Esophageal Squamous Cell Carcinoma Really Poor?

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Abstract

Background Among patients with T4 thoracic esophageal squamous cell carcinoma (TESCC), it is unclear whether the outcomes of late responders who undergo high-dose chemoradiotherapy (CRT) followed by salvage esophagectomy differs from those of early responders who undergo low-dose CRT followed by esophagectomy.

Methods A total of 153 patients with T4 TESCC were treated with CRT. The first evaluation was performed after 40 Gy of CRT for downstaging. Of these, 28 patients could be downstaged, and underwent subsequent surgery (early responders). For the remaining patients, additional CRT was administered, and patients were re-evaluated after treatment and underwent salvage surgery. In total, 40 patients (early + late responders) were analyzed.

Results The primary tumors exhibited a grade 3 response in six (21.4 %) of the early responders and two (16.7 %) of the late responders ($p = 1.000$). The rate of residual tumor in the primary tumor was 80 % (32/40 patients). The proportions of resected lymph nodes and positive metastatic nodes were similar between early and late responders ($p = 0.406$ and $p = 0.859$, respectively). The 5-year overall survival rates among the early and late responders were 25.9 and 36.5 %, respectively, and the median survival times were 24.8 and 24.3 months ($p = 0.925$), respectively. The 5-year cause-specific survival rates in the early and late responder groups were 61.5 and 72.9 % ($p = 0.425$), respectively.

Conclusion The outcomes of both early and late responders to CRT were similar, and salvage surgery for T4 TESCC outweighs the risks in patients with T4 TESCC.

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Introduction

Esophageal cancer is a malignant neoplasm of the digestive organs and carries a poor prognosis [1]. One reason for the severity of this malignancy is that esophageal cancer easily metastasizes to the lymph nodes, even at an early stage [2, 3]. Another reason is that the esophagus is located in the mediastinum and is surrounded by crucial organs, allowing esophageal cancer to easily invade adjacent organs such as the aorta (42 %), the major airway (22 %), the lung (12 %), the diaphragm (4 %), the pulmonary vein (3 %), and pericardium (3 %) [4]. Because of these particular features, the disease is often at an advanced stage at the time of diagnosis.

Recently, the outcome of chemoradiotherapy (CRT) has improved in esophageal cancer [5], and CRT is an appropriate modality for T4 esophageal cancer without distant metastases [6–8]. Following CRT, such tumors can become resectable (downstaging) in some cases, and a complete response (CR) can be obtained in some cases [9]. Moreover, long-term survival is possible if curative resection can be performed [4, 10]. The high dose of radiation leads to frequent postoperative mortality and morbidity. Therefore, comparatively low-dose radiation is recommended if esophagectomy is possible [11, 12]. For this reason, if downstaging can be achieved by low-dose CRT, needless

radiation can be avoided. However, it is not always easy to achieve downstaging with low-dose CRT, and high-dose CRT is often necessary for patients with T4 to be downstaged. Although 40–60 % of patients can achieve CRs after definitive CRT, tumor regrowth is frequently observed in the post-treatment course. This is because residual tumor remains in the primary site at a certain rate [13, 14]. For such patients, salvage surgery is the only curative method, although it is often accompanied by high rates of morbidity and mortality. Regrettably, there are few data to determine whether salvage surgery for T4 thoracic esophageal squamous cell carcinoma (TESCC) is beneficial. Additionally, it is unclear whether the outcomes for such late responders who undergo salvage esophagectomy after high-dose CRT differs from those of early responders who undergo low-dose CRT followed by esophagectomy. To answer this question, we compared these two groups and discussed the current status of salvage surgery for T4 TESCC.

Methods

Patient selection

First, patients with distant metastases were excluded on the basis of findings from positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT) in this study. Patients with clinical T4 diagnosed by CT and MRI were then selected. Consequently, we excluded patients with cervical or abdominal ESCC, those with double cancers, those who did not undergo esophagectomy with right thoracotomy, those with a poor performance status, and those who received radiation alone or best supportive care, leaving only patients with T4 TESCC. Between 2001 and 2012, a total of 153 patients with T4 TESCC were selected and treated with CRT according to the prescribed treatment strategy (Fig. 1). Ten patients (6.5 %) withdrew from treatment, and the remaining 143 patients (93.5 %) completed CRT (40 Gy), after which the first evaluation for downstaging was performed. Of these, 28 patients (18.3 %) exhibited downstaging of the primary tumor, and these patients underwent subsequent surgery (early responders). Among the remaining 115 patients (75.2 %), 102 received additional CRT, and an evaluation for downstaging was performed after the additional treatment. Among these patients, 12 (7.8 %) achieved downstaging and underwent salvage surgery (late responders). In total, 40 patients (26.1 %) (early responders + late responders) achieved downstaging and underwent surgery and 113 patients (73.9 %) did not (non-surgery patients). In non-surgery patients, one case that received definitive CRT followed by simple thoracotomy, because the primary tumor was still T4 during surgery, was included. Then, various factors and survival were compared between early and late responders. All evaluations of clinical diagnoses were performed using CT, endoscopy, and MRI; PET was also performed for some patients.

Treatment strategy and outcome

CRT was performed with concurrent chemotherapy (5-fluorouracil [5-FU] 500 mg/m^2/day from day 0 to day 4; cisplatin 15 mg/m^2/day from day 1 to day 5) and radiation, as described previously [9]. The radiation schedule was as follows: a dose of 2 Gy/day on days 1–5, 8–12, 15–19, and 22–26 (total of 40 Gy) before the first evaluation for resectability. Following this regimen, if the patients exhibited resectability with downstaging, then no additional CRT was undertaken, and a subsequent surgery was performed 3 or 4 weeks after the final day of CRT. These patients who underwent low-dose CRT were categorized as the 'early responders.' For the remaining patients, additional CRT was prescribed, followed by a re-evaluation for surgery. If downstaging and resectability were achieved, then the patients underwent salvage surgery; these patients who underwent high-dose CRT were defined as the 'late responders.' Various clinical factors, such as gender, age, tumor location, initial tumor size, and initial lymph node status, were compared between the early and the late responders.

Evaluation of the response

After 40 Gy of CRT, the clinical response was evaluated and restaged by CT. We additionally used diffusion-weighted MRI imaging for precise evaluation of the clinical staging as described previously [15]. In some cases, PET, endoscope, and endoscopic ultrasound (EUS) were added. The radiologic interpretations for downstaging of the primary tumor and resectability were performed by at least two doctors, and resectability was defined when an obvious space was present between the tumor and the adjacent organs. With respect to the pathologic effectiveness of CRT in the resected specimens, the following criteria of the Japanese Classification of Esophageal Cancer (tenth edition) were used [16, 17]: no viable carcinoma cells were present in the main tumor (markedly effective, grade 3); less than one-third of the residual cancer cells were viable (moderately effective, grade 2); more than one-third of the residual cancer cells were viable (slightly effective, grade 1); and no effect was found (non-effective, grade 0). The residual tumor in the resected lymph nodes was simultaneously evaluated pathologically.

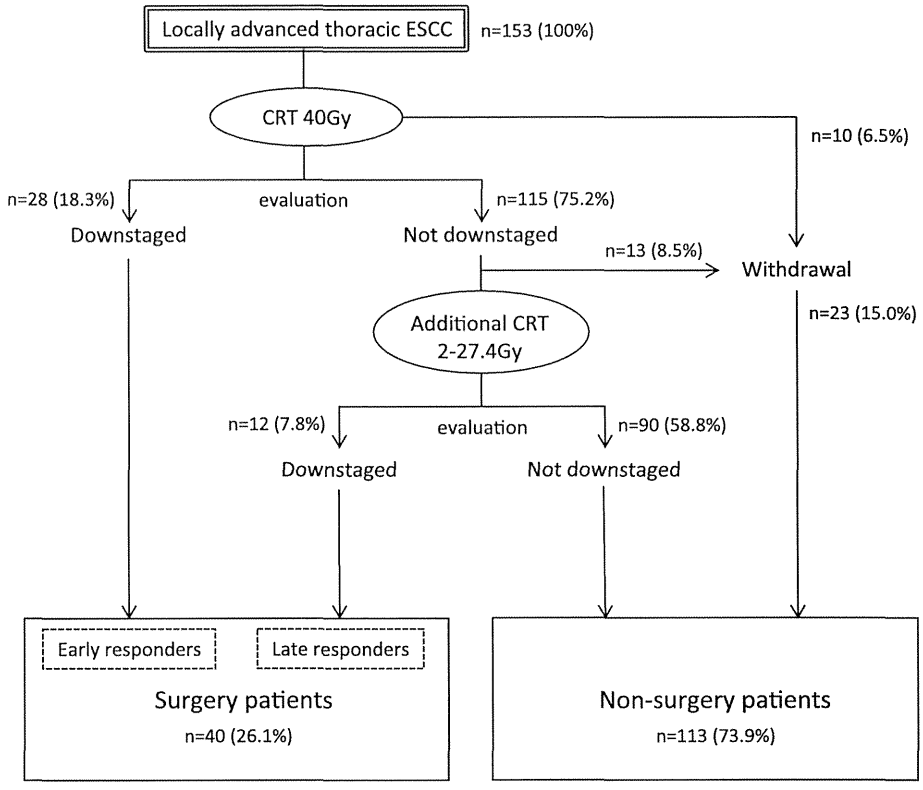

Fig. 1 Treatment strategy and outcome. The percentage of the surgery low-dose group was 18.3 % and that of the surgery high-dose group was 7.8 %. The total surgery group was 26.1 % and the non-surgery group were 73.9 %. *CRT* chemoradiotherapy, *ESCC* esophageal squamous cell carcinoma

Follow-up and survival

The patients were closely observed and followed up for recurrence with blood examinations, CT every 3 months, and endoscopy every 6 months for the first year after the surgery. The CT interval was then extended to every 4–6 months. If a new lesion appeared in the CT finding, then recurrence was considered to be present and MRI and PET were also performed to verify the recurrence.

Statistical analysis

Fischer's exact test was used to compare the gender distribution, tumor location, initial lymph node status, residual cancer rate, and proportion of patients with recurrence between the groups. Student's t test was used for comparisons of age, initial tumor size, mean total radiation dose, and mean total dose of chemotherapy between the groups. Overall survival (OS) was defined as the duration from the initial day of treatment to the day of death from any cause or the last day of follow-up. Cause-specific survival (CSS) was defined as the duration from the initial day of the treatment to the day of death from esophageal cancer or the last day of follow-up. The survival rate was calculated using the Kaplan–Meier method, and in univariate analysis, comparisons between the two groups were performed using the log-rank test. All tests were two-sided, and the significance level was set at $p < 0.05$. The software program SPSS version 18 (SPSS Japan Inc., Tokyo, Japan) was used for all statistical analyses.

Results

Analysis of the background between early and late responders

Factors with the potential to affect responses to CRT were evaluated (Table 1). No differences in gender distribution, age, tumor location, initial tumor size, and initial lymph node status were observed between the groups ($p = 0.298$, $p = 0.475$, $p = 0.444$, $p = 0.436$, and $p = 0.085$, respectively). Next, we evaluated the treatment intensity. The total dose of radiation was, of course, statistically greater among the late responders than among the early responders ($p < 0.001$). However, the total doses of 5-FU and cisplatin did not differ between the groups ($p = 0.729$ and $p = 0.515$, respectively). This was because the second round of chemotherapy was not administered to many patients because of the suppression of myeloid function. From these results, a response to CRT could not be estimated by clinical factors.

Table 1 Patient background

	Early responders	Late responders	*p* value
Patient number	28	12	
Sex			
Male	23	12	0.298[a]
Female	5	0	
Age	63.8 ± 8.0	62.0 ± 5.4	0.475[b]
Tumor location			
Upper third	8	2	0.444[a]
Middle third	14	9	
Lower third	6	1	
Initial tumor size (cm)	6.8 ± 2.4	7.5 ± 3.2	0.436[b]
Initial lymph node status			
Negative	0	2	0.085[a]
Positive	28	10	
Total radiation dose (Gy)	38.9 ± 3.0	53.2 ± 8.0	<0.001[b]
Total 5-FU dose (mg)	4,003 ± 697	3,927 ± 386	0.729[b]
Total cisplatin dose (mg)	106.8 ± 16.8	110.4 ± 12.9	0.515[b]

Data are presented as mean ± SD unless otherwise indicated

SD standard deviation, *5-FU* 5-fluorouracil

[a] Fisher's exact test

[b] *t*-test

Table 2 Pathological effectiveness of chemoradiotherapy in the resected specimens

	Early responders (%)	Late responders (%)	*p* value
Patient number	28	12	
Primary tumor			
Grade 3 (%)	6 (21.4)	2 (16.7)	1.000[a]
Grade 0–2 (%)	22 (78.6)	10 (83.3)	
Lymph node			
Node-negative cases (%)	16 (57.1)	10 (83.3)	0.157[a]
Node-positive cases (%)	12 (42.9)	2 (16.7)	
Mean resected lymph node	38.5	34.3	0.406[b]
Mean metastatic lymph node	1.1 ± 1.6	1.3 ± 3.5	0.859[b]

[a] Fisher's exact test

[b] *t*-test

Pathological effectiveness of CRT in resected specimens

Next, we evaluated the pathologic effectiveness of CRT in resected specimens from both early and late responders (Table 2). Primary tumors displayed a grade 3 response in six (21.4 %) of the early responders and two (16.7 %) of the late responders ($p = 1.000$). The overall rate of residual tumor was 80 % (32/40 patients). These results indicate that surgery was required even if the tumor was downstaged after CRT, regardless of dose of CRT. Concerning lymph node metastases, the proportions of resected lymph nodes and positive metastatic nodes were similar between the groups ($p = 0.406$ and $p = 0.859$, respectively).

Survival

To evaluate whether the early and late responders had different outcomes, each survival rate was compared (Fig. 2). The 5-year OS rates of the early and late responders were 25.9 and 36.5 %, respectively, and the median survival times (MSTs) of these groups were 24.8 [95 % confidence interval (CI) 0.00–46.18] and 24.3 months (95 % CI 14.3–34.26) ($p = 0.925$), respectively. Regarding CSS, the 5-year survival rates among the early and late responders were 61.5 and 72.9 %, respectively, and the MST of the late responders was 74.5 months (95 % CI 0.00–157.59) ($p = 0.425$). Unexpectedly, these results indicate that the duration of response does not affect patient outcome; in other words, salvage surgery outweighs the risks for such patients. In terms of the causes of death other than primary disease among the early responders, two patients died from pneumonia, and one patient each died of heart failure, gastric ulcer, and lung cancer. Among the late responders, pneumonia and suicide were the causes of death in two (included one instance of surgery-related death) and one patient, respectively, whereas one patient died of an unknown cause (data not shown). In total, five (17.9 %) and four patients (33.3 %) died for non-cause-specific reasons in the early and late responder groups, respectively.

Recurrence patterns

The patterns of recurrence after surgery in the early and late responder groups were evaluated (Table 3). Postoperative recurrence occurred in 13 (46.4 %) of the early responders and six (50.0 %) of the late responders; the frequency of recurrence did not differ between the groups ($p = 0.544$). In the patients with recurrence, lymphatic recurrence was the most frequent type among the early responders (76.9 %), whereas 50.0 % of the recurrences among the late responders were lymphatic. Hematological recurrence was observed in six (46.2 %) of the early responders and three (50.0 %) of the late responders. Dissemination was observed in three (23.0 %) of the early responders. The recurrence patterns not differ statistically between the groups ($p = 0.680$).

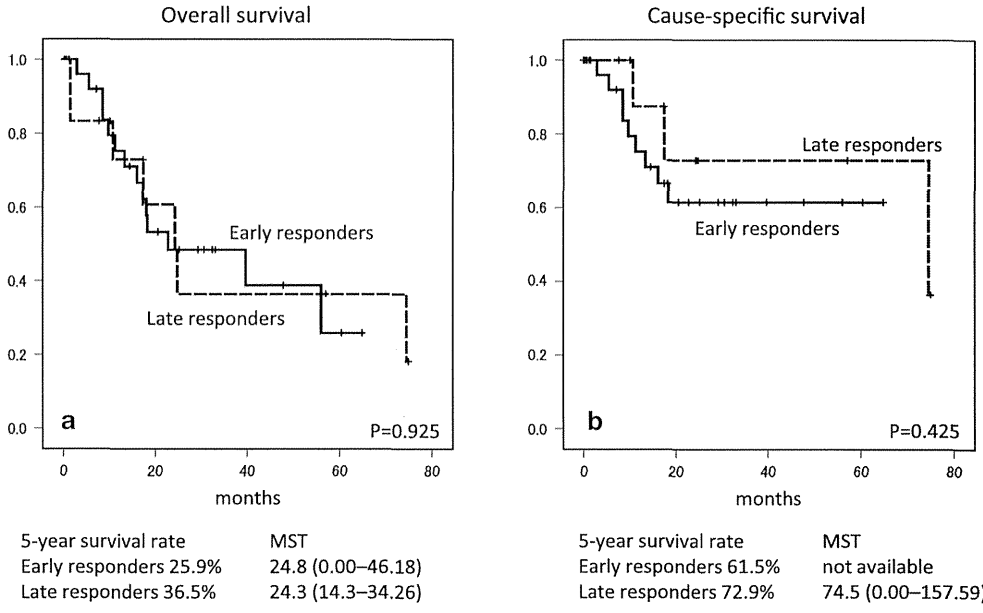

Fig. 2 **a** Overall survival: 5-year survival was 25.9 % in early responders and 36.5 % in late responders ($p = 0.925$). **b** Cause-specific survival: 5-year survival was 61.5 % in early responders and 72.9 % in late responders ($p = 0.425$). *MST* median survival time

Table 3 Recurrence patterns

	Early responders	Late responders	p value[a]
Total cases	28 (100)	12 (100)	0.544
Recurrences	13 (46.4)	6 (50.0)	
Lymphatic	10/13 (76.9)	3/6 (50.0)	
Hematological	6/13 (46.2)	3/6 (50.0)	0.680
Dissemination	3/13 (23.0)	0/6 (0)	

Data are presented as n (%) unless otherwise indicated

[a] Fisher's exact test

Discussion

Recent diagnostic developments have improved the accuracy of diagnosing distant metastases. This means that patients with T4 lesions without distant metastases, namely patients for whom the only non-curative factor is T4 disease, can be clearly delineated from other patients with unresectable disease. For such patients, residual primary tumor is the major concern for curative treatment, and esophagectomy should be re-considered. Therefore, if downstaging of the primary tumor can be achieved and patients can undergo subsequent surgery, then better survival can be expected.

One concern is the feasibility of esophagectomy following definitive CRT, also termed 'salvage surgery,' as salvage surgery is frequently associated with worse postoperative mortality and morbidity rates than surgery following low-dose CRT [12, 18]. Furthermore, whether salvage surgery is beneficial for T4 TESCC remains unclear. To answer this question, we first noted the high rate of residual tumor in the resected specimens (Table 2). This means that residual tumor is likely to remain, [19–21] and a major portion of T4 TESCC lesions cannot be cured by CRT alone, even if a good response is observed after CRT. Therefore, we concluded that patients in whom downstaging was achieved by CRT should be treated with esophagectomy, although there is some controversy and few available data regarding this issue [22]. The residual tumor rates were 78.6 and 83.3 % in the early and late responder groups, respectively, and no difference was noted according to the dose of CRT ($p = 1.000$). From this result, surgery is similarly beneficial for suppressing local failure after surgery between the early and the late responders. In other words, salvage surgery after definitive CRT for patients with T4 TESCC is similarly effective as surgery after low-dose CRT for preventing local failure [23].

Of course, local tumor control is only one of the factors that affect treatment outcome, and various other factors, such as lymph node recurrence, hematological recurrence, and dissemination, should be noted because they influence the outcome of treatment [24]. Therefore, we compared the recurrence patterns after surgery between early and late responders. Lymphatic recurrence was more common among the early responders (76.9 %) than among the late responders (50.0 %). Additionally, lymph node metastasis was less common among the late responders (16.7 %) than among the early responders (42.9 %) (Table 2). This difference in node-positive rates may explain the different rates of lymphatic recurrence according to the dose of CRT, although a significance difference was not observed. As our previous study indicated, lymph node metastasis is a significant risk factor even among patients who undergo CRT, and the control of metastatic lymph nodes is required

for better outcomes [24–26]. Possibly, high-dose CRT followed by salvage surgery is preferable for the control of lymphatic metastasis.

As previously mentioned, salvage surgery is frequently associated with high rates of morbidity and mortality after surgery. Although local control and lymphatic control are superior after salvage surgery following high-dose CRT, the associated high rates of morbidity and mortality may result in worse outcomes for salvage surgery in patients with T4 TESCC. Therefore, we evaluated the outcomes of early and late responders. Unexpectedly, the 5-year OS rate of the late responders was statistically similar (36.5 %) to that of the early responders (25.9 %) (Fig. 2). Although the reason for the similar outcomes between the groups was not clarified, there are some potential explanations. Death due to reasons other than the primary disease was more common among late responders with high-dose CRT (four patients, 33.3 %) than among early responders with low-dose CRT (five patients, 17.9 %) (data not shown). On the contrary, the treatment intensity was greater for the late responders. These opposing factors may explain why OS was similar between the groups.

Our study revealed that the outcome of salvage surgery after definitive CRT for T4 TESCC is not poor. However, curative resection should be performed to improve outcomes because it is the most important factor for cure [13, 27]. In the current status of diagnosis for T4 lesions, it remains difficult to precisely evaluate resectability after CRT. We previously investigated curative resection rates according to the organ being invaded from the primary tumor [4]. From this evaluation, curative resection rates were higher for major airway, lung, and diaphragm invasion than for aortic invasion. Therefore, to improve the curative resection rate, preoperative assessment for aortic invasion is the most crucial point in the treatment of T4 TESCC. The second important factor to improve treatment outcome is to suppress postoperative recurrence. As shown in Table 3, the recurrence rate was high even after downstaging followed by surgery. In the present study, lymphatic metastasis, hematological metastasis, and dissemination were inevitable. Therefore, additional treatments, if possible, should be performed before or after surgery.

Conclusion

Salvage surgery for T4 TESCC outweighs the risks, and there is no reason to avoid salvage surgery even for late responders. Therefore, if the lesion can be downstaged after definitive CRT, then salvage surgery should be considered without hesitation. However, the outcome remains unsatisfactory, and further improvements in this field are required.

Conflict of interest There are no conflicts of interest that should be disclosed.

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SPECIAL ARTICLE

Comprehensive Registry of Esophageal Cancer in Japan, 2006

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Preface

We deeply appreciate the great contributions of many physicians in the registry of esophageal cancer cases. The Comprehensive Registry of Esophageal Cancer in Japan, 2006, was published here, despite some delay. The registry complies with the Act for the Protection of Personal Information. The encryption with a HASH function is used for ''anonymity in an unlinkable fashion''.

We briefly summarized the Comprehensive Registry of Esophageal Cancer in Japan, 2006. Japanese Classification of Esophageal Cancer 9th and UICC TNM Classification 6th were used for cancer staging according to the subjected year. A total of 4994 cases were registered from 239 institutions in Japan. Tumor locations were cervical: 4.2 %, upper thoracic: 13.4 %, middle thoracic: 48.7 %, lower thoracic: 26.0 % and EG junction: 6.7 %. Superficial carcinomas (Tis, T1a, T1b) were 35.9 %. As for the histologic type of biopsy specimens, squamous cell carcinoma and adenocarcinoma accounted for 90.8 and 3.9 %, respectively. Regarding clinical results, the 5-year survival rates of patients treated using endoscopic mucosal resection, concurrent chemoradiotherapy, radiotherapy alone, chemotherapy alone, or esophagectomy were 84.5, 25.8, 22.0, 3.0, and 48.0 %, respectively. Esophagectomy was performed in 2545 cases. Concerning the approach used for esophagectomy, 15.4 % of the cases were treated

These data were first made available on July 1, 2013, as the Comprehensive Registry of Esophageal Cancer in Japan, 2006. Not all the pages are reprinted here; however, the original table and figure numbers have been maintained.

The authors were members of the Registration Committee for Esophageal Cancer, the Japan Esophageal Society, and made great contributions to the preparation of this material.

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thoracoscopically. The operative mortality (within 30 days after surgery) was 1.0 % and the hospital mortality was 2.1 %.

We hope that this Comprehensive Registry of Esophageal Cancer in Japan for 2006 will help to improve all aspects of the diagnosis and treatment of esophageal cancer in Japan.

Contents

I. Clinical factors of esophageal cancer patients treated in 2006

Institution-registered cases in 2006

Institution
Aichi Cancer Center
Aizawa Hospital
Akita University Hospital
Arao Municipal Hospital
Asahikawa Medical College Hospital
Chiba Cancer Center
Chiba Medical Center
Chiba Prefecture Sawara Hospital
Chiba University Hospital
Chibaken Saiseikai Narashino Hospital
Dokkyo Medical University Hospital
Foundation for Detection of Early Gastric Carcinoma
Fuchu Hospital
Fujioka General Hospital
Fujisawa Shounandai Hospital
Fujita Health University
Fukui Red Cross Hospital
Fukui University Hospital
Fukuoka Saiseikai General Hospital
Fukuoka University Hospital
Gifu Prefectural General Medical Center
Gifu University Hospital
Gunma Central General Hospital
Gunma Prefectural Cancer Center
Gunma University Hospital
Hakodate Goryokaku Hospital
Hakodate National Hospital
Hamamatsu University School of Medicine, University Hospital
Hannan Chuo Hospital
Health Insurance Naruto Hospital
Hiratsuka City Hospital
Hiratsuka Kyosai Hospital
Hiroshima City Asa Hospital
Hiroshima University Research Institute for Radiation Biology Medicine
Hitachi General Hospital
Hokkaido Kin-Ikyo Chuo Hospital
Hokkaido P.W.F.A.C Obihiro-Kosei General Hospital
Hokkaido University Hospital
Hyogo College of Medicine
Ibaraki Prefectural Central Hospital
Imazu Surgical Clinic
Inazawa City Hospital
International University of Health and Welfare Mita Hospital
Ishikawa Prefectural Central Hospital
Ishinomaki Red Cross Hospital
Iwakuni Medical Center
Iwate Medical University Hospital
Iwate Prefectural Chubu Hospital
Japanese Red Cross Shizuoka Hospital
Juntendo University Hospital
Juntendo University Shizuoka Hospital
Junwakai Memorial Hospital
Kagawa Prefectural Central Hospital
Kagawa Rosai Hospital
Kagawa University Hospital
Kagoshima Kenritsu Satsunan Hospital
Kagoshima University Hospital
Kanazawa Medical University Hospital
Kanazawa University Hospital
Kansai Medical University Hirakata Hospital
Kansai Rosai Hospital
Kasamatsu Hospital
Kashiwa Kousei General Hospital
Kawakita General Hospital
Kawasaki Medical School Hospital
Kawasaki Municipal Hospital
Kawasaki Municipal Ida Hospital
Keio University Hospital
Keiyukai Sapporo Hospital
Kikuna Memorial Hospital
Kinki Central Hospital
Kinki University Hospital
Kinki University Sakai Hospital
Kiryu Kosei General Hospital
Kishiwada City Hospital
Kitakyushu Municipal Medical Center
Kitasato University Hospital
Kitasato University Kitasato Institute Medical Center Hospital
Kobe City Medical Center General Hospital
Kochi University Hospital
Kumamoto University Hospital
Kurashiki Central Hospital
Kurume Daiichi Social Insurance Hospital
Kurume University Hospital
Kuwana West Medical Center
Kyorin University Hospital
Kyoto University Hospital
Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers
Kyushu University Beppu Hospital
Kyushu University Hospital
Matsuda Hospital
Matsushita Memorial Hospital

continued

Institution
Matsuyama Red Cross Hospital
Mie University Hospital
Minoh City Hospital
Mito Red Cross Hospital
Mitsui Memorial Hospital
Murakami General Hospital
Musashimurayama Hospital
Nagahama City Hospital
Nagano Red Cross Hospital
Nagasaki University Hospital
Nagayoshi General Hospital
Nagoya City University Hospital
Nagoya Daiichi Red Cross Hospital
Nagoya University Hospital
Nanpuh Hospital
Nara Medical University Hospital
National Cancer Center Hospital
National Defense Medical College Hospital
National Hospital Organization Chiba Medical Center
National Hospital Organization Fukuoka-higashi Medical Center
National Hospital Organization Hokkaido Cancer Center
National Hospital Organization Iwakuni Medical Center
National Hospital Organization Kure Medical Center
National Hospital Organization Kyushu Cancer Center
National Hospital Organization Matsumoto National Hospital
National Hospital Organization Nagoya Medical Center
National Hospital Organization Osaka National Hospital
National Hospital Organization Sendai Medical Center
National Hospital Organization Tokyo Medical Center
Nihon University Itabashi Hospital
Niigata Cancer Center Hospital
Niigata City General Hospital
Niigata Prefectural Shibata Hospital
Niigata University Medical and Dental Hospital
Nikko Memorial Hospital
Nippon Medical School Chiba Hokusoh Hospital
Nippon Medical School Hospital
Nippon Medical School Musashi Kosugi Hospital
Nippon Medical School Tama Nagayama Hospital
Nishi-Kobe Medical Center
Nishinomiya Municipal Central Hospital
Nomura Medical Park Hospital
NTT East Japan Kanto Hospital
Numazu City Hospital
Ohta General Hospital Foundation Ohta Nishinouchi Hospital
Oita Red Cross Hospital
Oita University Hospital
Oizumi Gastrointestinal Medical Clinic

continued

Institution
Okayama Saiseikai General Hospital
Okayama University Hospital
Onomichi Municipal Hospital
Osaka City General Medical Center
Osaka City University Hospital
Osaka Hospital of Japan Seafarers relief Association
Osaka Koseinenkin Hospital
Osaka Medical Center for Cancer and Cardiovascular Diseases
Osaka Medical College Hospital
Osaka Prefectural Hospital Organization Osaka General Medical Center
Osaka Red Cross Hospital
Otsu Red Cross Hospital
Ryukyu University Hospital
Saga University Hospital
Saiseikai General Hospital
Saiseikai Kyoto Hospital
Saiseikai Utsunomiya Hospital
Saitama City Hospital
Saitama Medical Center
Saitama Medical Center Jichi Medical University
Saitama Medical University Hospital
Saitama Medical University International Medical Center
Saitama Prefectural Cancer Center
Saitama Red Cross Hospital
Saitama Social Insurance Hospital
Sakai Municipal Hospital
Saku Central Hospital
Sanno Hospital
Sano Kousei General Hospital
Sato Clinic
Sendai City Hospital
Shiga Medical Center for Adults
Shiga University of Medical Science Hospital
Shikoku Cancer Center
Shimada Hospital
Shimane University Hospital
Shimizu Welfare Hospital
Shinshiro Municipal Hospital
Shinshu University Hospital
Shizuoka Cancer Center
Shizuoka City Shimizu Hospital
Shizuoka City Shizuoka Hospital
Shizuoka General Hospital
Showa University Hospital
Showa University Northern Yokohama Hospital
Showa University Toyosu Hospital
Social Insurance Omuta Tenryo Hospital

continued

Institution
Social Insurance Tagawa Hospital
Social Insurance Yokohama Central Hospital
Sonoda Daiichi Hospital
St. Luke's International Hospital
Sugita Genpaku Memorial Obama Municipal Hospital
Suita Municipal Hospital
Takaoka Hospital
Takasago Municipal Hospital
Tenri Hospital
The Cancer Institute Hospital of JFCR
The Jikei University Hospital
Tochigi Cancer Center
Toho University Omori Medical Center
Toho University Sakura Medical Center
Tohoku Kosai Hospital
Tohoku University Hospital
Tokai University Hachioji Hospital
Tokai University Hospital
Tokushima Red Cross Hospital
Tokushima University Hospital
Tokyo Medical and Dental University Hospital
Tokyo Medical University Ibaraki Medical Center
Tokyo Medical University Hospital
Tokyo Metropolitan Cancer and Infectious Center Komagome Hospital
Tokyo Metropolitan Health and Medical Corporation Toshima Hospital
Tokyo University Hospital

continued

Institution
Tokyo Women's Medical University Hospital
Tokyo Women's Medical University Medical Center East
Tonan Hospital
Toranomon Hospital
Tottori Prefectural Central Hospital
Tottori University Hospital
Toyama Prefectural Central Hospital
Toyama University Hospital
Tsuchiura Kyodo Hospital
Tsukuba University Hospital
University Hospital, Kyoto Prefectural University of Medicine
University of Miyazaki Hospital
Yamagata Prefectural and Sakata Municipal Hospital Organization
Yamagata Prefectural Central Hospital
Yamagata Prefectural Shinjo Hospital
Yamagata University Hospital
Yamaguchi-ken Saiseikai Shimonoseki General Hospital
Yamaguchi University Hospital
Yamanashi Prefectural Central Hospital
Yamanashi University Hospital
Yao Municipal Hospital
Yatsu Hoken Hospital
Yokohama City Municipal Hospital
Yokohama City University Hospital
Yokohama City University Medical Center
Yuri General Hospital

(Total 239 institutions)

Patient background

Table 1 Age and gender

*Excluding 54 missing cases of gender

Age	Male	Female	Unknown	Cases (%)	
~29	7	1	0	8	(0.2%)
30~39	6	4	0	10	(0.2%)
40~49	132	42	0	174	(3.6%)
50~59	889	174	1	1064	(21.7%)
60~69	1757	238	1	1996	(40.8%)
70~79	1203	163	1	1367	(27.9%)
80~89	203	56	0	259	(5.3%)
90~	11	3	0	14	(0.3%)
Total	4208	681	3	4892	
Missing	40	8	0	48	

Table 11 Types of primary treatment

Treatments	Cases (%)	
Surgery	2705	(54.4%)
Esophagectomy	2545	(51.2%)
Palliative	160	(3.2%)
Chemotherapy/Radiotherapy	1315	(26.4%)
Endoscopic treatment	697	(14.0%)
others	43	(0.9%)
None/Unknown	213	(4.3%)
Total	4973	
Missing	21	

Table 12 Tumor location

*** Excluding 277 treatment unknown, missing cases of treatment types**

Location of tumor	Total (%)	
Cervical	198	(4.2%)
Upper thoracic	631	(13.4%)
Middle thoracic	2290	(48.7%)
Lower thoracic	1224	(26.0%)
Abdominal	247	(5.3%)
EG	31	(0.7%)
EG-Junction(E=G)	26	(0.6%)
Cardia (G)	6	(0.1%)
Unknown	46	(1.0%)
Total	4699	
Missing	5	

EG: esophago-gastric

Table 15 Histologic types of biopsy specimens

*** Excluding 277 treatment unknown, missing cases of treatment types**

Histologic types	Total (%)	
Not examined	65	(1.4%)
SCC	4258	(90.8%)
SCC	2650	(56.5%)
Well diff.	323	(6.9%)
Moderately diff.	971	(20.7%)
Poorly diff.	314	(6.7%)
Adenocarcinoma	182	(3.9%)
Undifferentiated	17	(0.4%)
Carcinosarcoma	14	(0.3%)
Malignant melanoma	9	(0.2%)
Other tumors	50	(1.1%)
Dysplasia	0	(0.0%)
Unknown	97	(2.1%)
Total	4692	
Missing	25	

Table 16 Depth of tumor invasion, cT (UICC TNM 6th)

*** Excluding 277 treatment unknown, missing cases of treatment types**

cT	Total (%)	
cTX	13	(0.3%)
cT0	12	(0.3%)
cTis	154	(3.3%)
cT1	211	(4.5%)
cT1a	560	(11.9%)
cT1b	763	(16.3%)
cT2	592	(12.6%)
cT3	1666	(35.5%)
cT4	616	(13.1%)
Unknown	108	(2.3%)
Total	4695	
Missing	22	

Table 17 Lymph node metastasis, cN (UICC TNM 6th)

*** Excluding 277 treatment unknown, missing cases of treatment types**

cN	Total (%)	
cNX	42	(0.9%)
cN0	2173	(46.3%)
cN1	2340	(49.8%)
Unknown	140	(3.0%)
Total	4695	
Missing	22	

Table 18 Distant metastasis, cM (UICC TNM 6th)

*** Excluding 277 treatment unknown, missing cases of treatment types**

cM	Total (%)	
cMX	40	(0.9%)
cM0	3895	(82.9%)
cM1	169	(3.6%)
cM1a	108	(2.3%)
cM1b	382	(8.1%)
Unknown	102	(2.2%)
Total	4696	
Missing	21	

II. Clinical results of patients treated with endoscopy in 2006

Table 20 Clinical stage (UICC TNM 6th)

*** Excluding 277 treatment unknown, missing cases of treatment types**

cStage	Endoscopic treatment (%)		Chemotherapy and/or radiotherapy (%)		Surgery				Total (%)	
					Palliative surgery (%)		Esophagectomy (%)			
0	142	(20.4%)	1	(0.1%)	1	(0.6%)	12	(0.5%)	156	(3.3%)
I	478	(68.7%)	168	(12.8%)	42	(26.3%)	588	(23.3%)	1276	(27.2%)
IIA	6	(0.9%)	121	(9.2%)	28	(17.5%)	468	(18.5%)	623	(13.3%)
IIB	8	(1.1%)	89	(6.8%)	8	(5.0%)	333	(13.2%)	438	(9.3%)
III	14	(2.0%)	456	(34.7%)	48	(30.0%)	832	(32.9%)	1350	(28.8%)
IV	2	(0.3%)	127	(9.7%)	3	(1.9%)	28	(1.1%)	160	(3.4%)
IVA	1	(0.1%)	46	(3.5%)	3	(1.9%)	56	(2.2%)	106	(2.3%)
IVB	10	(1.4%)	216	(16.5%)	15	(9.4%)	125	(4.9%)	366	(7.8%)
Unknown	35	(5.0%)	89	(6.8%)	12	(7.5%)	84	(3.3%)	220	(4.7%)
Total	696		1313		160		2526		4695	
Missing	1		2		0		19		22	

Table 22 Treatment details in patients receiving endoscopy

Treatment details	Cases (%)	
EMR	288	(41.4%)
ESD	354	(50.9%)
EMR + PDT	2	(0.3%)
EMR + YAG laser / APC	6	(0.9%)
EMR + ESD	5	(0.7%)
EMR + other treatment	1	(0.1%)
ESD + other treatment	1	(0.1%)
PDT	2	(0.3%)
YAG laser / APC	1	(0.1%)
YAG laser / APC + ESD	1	(0.1%)
YAG laser / APC + Unknown	1	(0.1%)
Esophageal stent	28	(4.0%)
Esophageal stent + other treatment	2	(0.3%)
Tracheal stent	1	(0.1%)
Others	3	(0.4%)
Total	696	
Missing	1	

EMR: endoscopic mucosal resection, ESD: endoscopic submucosaldissection, PDT:photodynamic therapy, YAG: yttrium aluminum garnet, APC: Argon plasma coagulation, MCT: microwave coagulation theraphy

*** "Esophageal stenting + tracheal stenting + other (PEG)" case is included in "Esophageal stenting + tracheal stenting".**

Table 26 Complications of EMR/ESD

Complications of EMR/ESD	Cases (%)	
None	616	(93.6%)
Perforation	3	(0.5%)
Bleeding	5	(0.8%)
Mediastinitis	1	(0.2%)
Stenosis	23	(3.5%)
Stenosis+Others	1	(0.2%)
Perforation+Stenosis	1	(0.2%)
Perforation+Stenosis+Others	1	(0.2%)
Perforation+Bleeding	1	(0.2%)
Perforation+Others	1	(0.2%)
Others	5	(0.8%)
Unknown	0	(0.0%)
Total	658	
Missing	4	

Table 30 Depth of tumor invasion of EMR/ESD specimens

Pathological depth of tumor invasion (pT)	Cases (%)	
pTX	2	(0.3%)
pT0	14	(2.1%)
pTis	183	(27.9%)
pT1a	369	(56.2%)
pT1b	80	(12.2%)
pT2	3	(0.5%)
Unknown	6	(0.9%)
Total	657	
Missing	5	

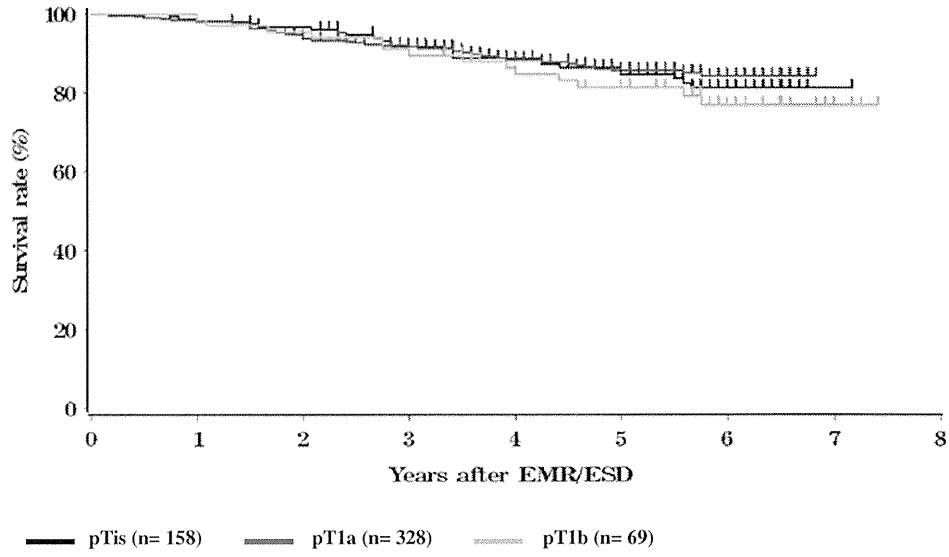

Fig. 3 Survival of patients treated by EMR/ESD in relation to the pathological depth of tumor invasion (pT)

	Years after EMR/ESD							
	1	2	3	4	5	6	7	8
pTis	98.0%	96.7%	91.7%	88.8%	84.6%	81.2%	81.2%	81.2%
pT1a	98.4%	94.3%	91.9%	88.2%	85.6%	84.2%	84.2%	-
pT1b	98.5%	95.5%	91.0%	86.4%	81.5%	76.9%	76.9%	76.9%

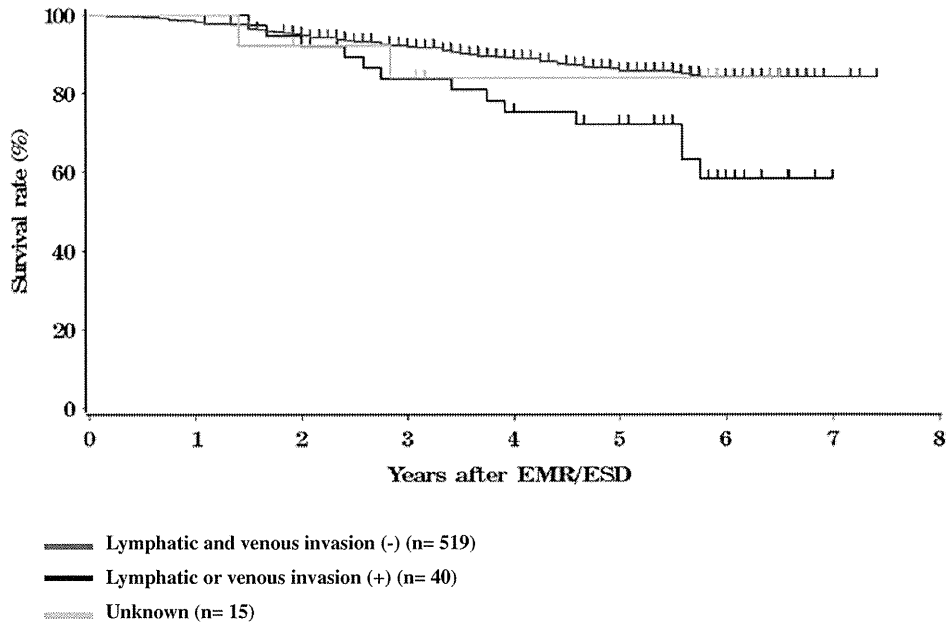

Fig. 4 Survival of patients treated by EMR/ESD in relation to the lymphatic or venous invasion

	Years after EMR/ESD							
	1	2	3	4	5	6	7	8
Lymphatic and venous invasion (-)	98.2%	95.2%	92.3%	89.1%	85.7%	84.3%	84.3%	84.3%
Lymphatic or venous invasion (+)	100.0%	92.1%	83.7%	75.4%	72.2%	58.3%	58.3%	58.3%
Unknown	100.0%	92.3%	83.9%	83.9%	83.9%	83.9%	83.9%	-