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A Retrospective Study of Clinical Outcomes for Patients with Esophageal Cancer Who Were Treated with Radiotherapy Alone

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Keywords
Esophageal cancer · Esophagus cancer · Radiotherapy · Radiation therapy · Radiotherapy alone

Abstract
Introduction: Patients with esophageal cancer who are in a poor general condition receive radiotherapy alone, but outcomes are often unsatisfactory. The aim of this study was to clarify recent outcomes of radiotherapy alone for esophageal cancer. ***Methods:*** Patients who underwent 50 Gy or more of radiotherapy without chemotherapy were retrospectively reviewed. Endpoints were overall survival (OS), disease-specific survival (DSS), local control (LC), and progression-free survival (PFS). Survival curves were drawn using the Kaplan-Meier method, and predictors were analyzed using the Cox proportional hazards model. ***Results:*** Sixty-nine patients were included. The median follow-up period was 17.9 months. The 5-year OS, DSS, LC, and PFS rates were 33.2%, 49.8%, 46.2%, and 16.8%, respectively. In the multivariate Cox proportional hazard model, clinical stage was a significant predictor for OS (hazard ratio [HR]: 4.42, 95% confidence interval [CI]: 1.80–11.17, $p = 0.001$), DSS (HR: 2.08, 95% CI: 1.43–3.12, $p = 0.0001$), LC (HR: 1.86, 95% CI: 1.28–2.74, $p = 0.001$), and PFS (HR: 1.65, 95% CI: 1.25–2.18, $p = 0.0004$). Radiation dose was a significant predictor for LC (HR: 0.87, 95% CI: 0.78–0.97, $p = 0.018$) and tumor location was a significant predictor for PFS (HR: 1.55, 95% CI: 1.10–2.19, $p = 0.018$). In subgroup analysis, the 5-year OS, DSS, LC, and PFS rates for stage I were 60.0%, 80.0%, 71.9%, and 46.1%, respectively. ***Conclusions:*** Stage, radiation dose, and tumor location are significant predictors for outcomes. Patients with stage I esophageal cancer can be cured by radiotherapy alone.

Introduction

Esophageal cancer is the 9th most newly diagnosed cancer worldwide [1]. Neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy followed by surgery is standard treatment for patients with esophageal cancer [2, 3]. Chemoradiotherapy is also a curative treatment for patients with esophageal cancer [4]. There have been many studies in which chemotherapy, radiotherapy, and surgery were combined in order to improve outcomes. The treatment burden has been gradually increasing, but treatment outcomes have also been improving. However, some patients cannot receive such a strong treatment strategy due to their poor

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general conditions. Such patients receive radiotherapy alone, but the outcomes of radiotherapy alone are not satisfactory. Cooper et al. [4] reported that the 5-year overall survival (OS) rate for patients who received radiotherapy alone was 0%.

On the other hand, radiotherapy techniques have been improving. Decades ago, a radiotherapy field was made on the basis of X-ray images, and doses for the field were normalized by the depth of the patient's body [5]. Radiation oncologists call it 2D planning. In recent years, three-dimensional computed tomography (CB)-based radiotherapy planning (3D planning) has become the mainstream. Mackley et al. [6] showed that the number of patients who had esophagitis was significantly smaller in patients for whom 3D planning was performed than in patients for whom 2D planning was performed. Moreover, the method of position matching for daily radiotherapy has been improving. Leong J published a method of image-guided radiotherapy (IGRT) using electronic portal imaging devices (EPID) [7]. This is the current mainstream method by using X-ray images and bones for daily setup verification for patients. IGRT by using EPID started in the early 90s [8]. In order to set up not only by bones but also soft tissue, a setup method using cone-beam computed tomography (CBCT) was developed, and the use of that method has been spreading [9].

Both radiotherapy techniques and treatment strategy for patients with esophageal cancer have been improving. Of course, multidisciplinary therapy is a standard treatment strategy for patients with esophageal cancer. However, there will continue to be patients who are treated with radiotherapy alone due to their poor general condition. The aim of this study was to clarify the recent outcomes and identify predictors for outcomes of radiotherapy alone.

Methods

Patient Population

This study had institutional review board approval. We retrospectively reviewed our clinical medical records. Patients with esophageal cancer who were treated with 50 Gy or more of radiotherapy without chemotherapy between January 2011 and May 2021 were included. Patients who had distant metastasis other than supraclavicular lymph node metastasis were excluded. The patients were staged according to International Union against Cancer TNM Classification of Malignant Tumors, 8th edition [10]. This study included some patients with T1aN0M0 who were treated with radiotherapy instead of endoscopic submucosal dissection due to extension of the tumor to the entire circumference of the esophagus or a large area.

Treatment

Radiation plans were made using a 3D planning system (Eclipse, Varian Medical Systems). Gross tumor volume was delineated using CT, 18F-fluorodeoxyglucose positron emission tomography/CT, and endoscopy. Patients received involved-field radiotherapy (IFRT) or elective nodal irradiation. IFRT was defined as the primary tumor and lymph node area receiving 40 Gy at 2 Gy per day and the primary and lymph node lesions receiving 20–30 Gy at 2 Gy per day. Elective nodal irradiation was defined as the primary and lymph node lesions receiving 50–70 Gy at 2 Gy per day. The radiation oncologist who was in charge checked the general condition of each patient. For patients with a poor general condition, the dose per fraction was decreased to 1.8 Gy per day. The area of IFRT covered the primary tumor and elective nodes including the area of supraclavicular, mediastinal, and celiac lymph nodes. The area of supraclavicular lymph nodes was sometimes omitted due to the patient's general condition [11].

Endpoints and Follow-Up

The primary endpoint was OS, and the secondary endpoints were disease-specific survival (DSS), local control (LC) period, and progression-free survival (PFS). The endpoints were calculated from the first day of radiotherapy. The OS period was the period until the day the patient died. The DSS period was the period until the day the patient died from esophageal cancer. The LC period was the period until the day the patient had local recurrence. The PFS period was the period until the day the patient had local recurrence or distant metastasis or died. Follow-up CT and endoscopy were performed within 8 weeks after the last day of radiotherapy. The patients underwent follow-up examination, endoscopy, and CT every 3–6 months.

Statistical Analysis

JMP® Pro v.15.2.0 (SAS Institute) was used for statistical analysis. OS, DSS, LC, and PFS were calculated using the Kaplan-Meier method. Gender, age, performance status, tumor location, clinical stage, total radiotherapy dose, and pretreatment blood albumin level were included in the Cox proportional hazards model for OS, DSS, LC, and PFS. Factors with $p < 0.05$ in univariate analyses were included in multivariate analysis. $p < 0.05$ was defined as significant.

Results

Sixty-nine patients were included in this study (Fig. 1). Patients' characteristics are summarized in Table 1.

Treatment Results

The median follow-up periods were 17.9 months for all patients and 22.2 months for survivors. The median OS period was 37.3 months, the 3-year OS rate was 52.8%, and the 5-year OS rate was 33.2%. The median DSS period was 43.2 months, the 3-year DSS rate was 60.9%, and the 5-year DSS rate was 49.8%. Twenty-nine patients died from esophageal cancer, and 13 patients died from other causes. The median LC period was 30.5 months, the

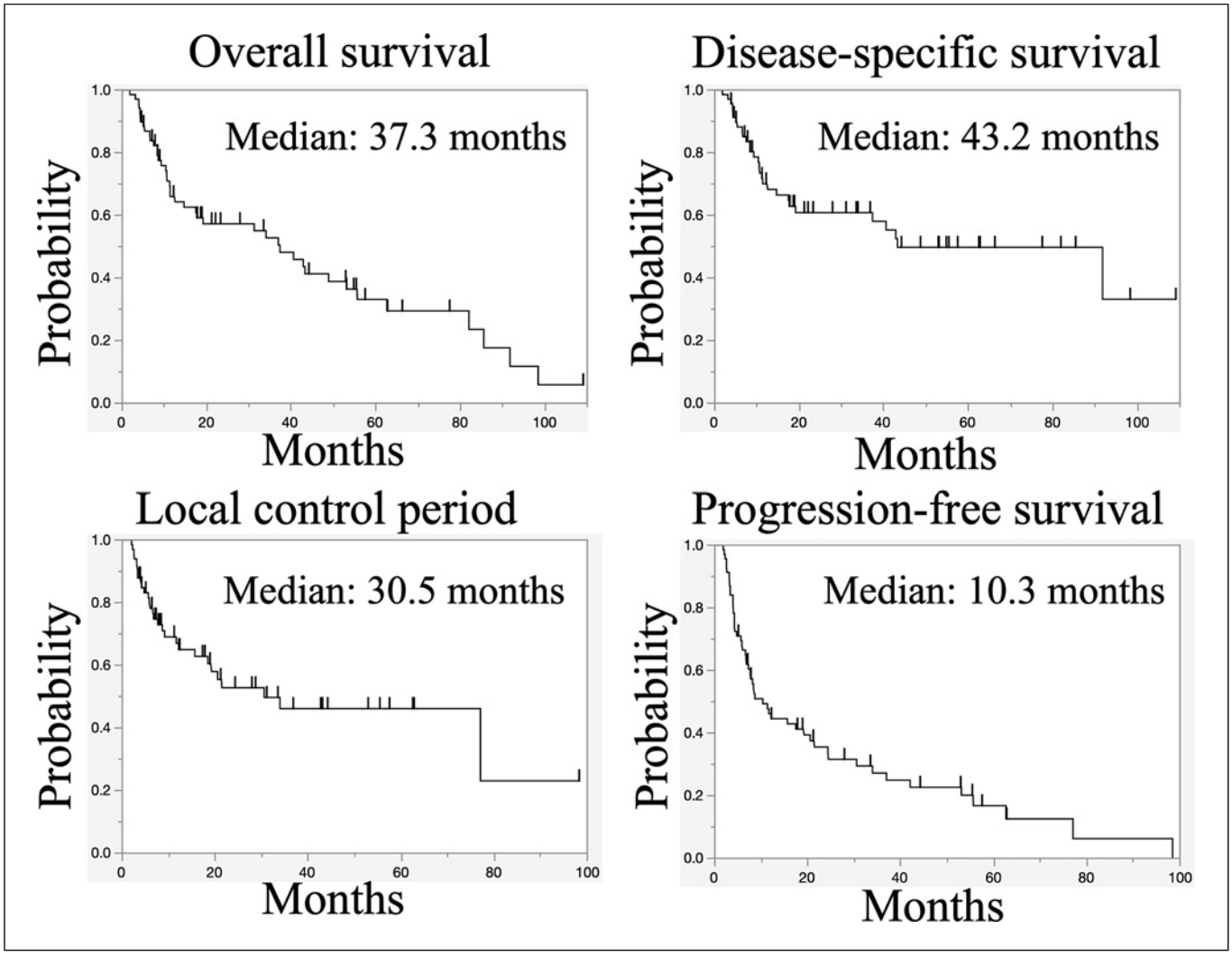

Fig. 1. Kaplan-Meier curves for OS, DSS, LC period, and PFS for all patients.

3-year LC rate was 46.2%, and the 5-year LC rate was 46.2%. The median PFS period was 10.3 months, the 3-year PFS rate was 27.2%, and the 5-year PFS rate was 16.8%. Twenty-nine patients had local recurrence, and 13 patients had distant metastasis (Fig. 1). There were 4 patients who had no outcome events and were lost to follow-up within 12 months.

Univariate and Multivariate Cox Proportional Hazards Models

In univariate analysis, performance status, T stage, and clinical stage were significant predictors for OS, DSS, LC, and PFS. N stage, M stage, and blood albumin level were significant predictors for OS, DSS, and PFS. Total radiation dose was a significant predictor for LC, and tumor location was a significant predictor for PFS. The results of univariate analysis are summarized in Table 2.

T stage, N stage, M stage, and clinical stage had correlations. Therefore, only clinical stage was included in multivariate analysis. Clinical stage was a significant predictor for OS (hazard ratio [HR]: 4.42, 95% confidence interval [CI]: 1.80–11.17, $p = 0.001$), DSS (HR: 2.08, 95% CI: 1.43–3.12, $p = 0.0001$), LC (HR: 1.86, 95% CI: 1.28–2.74, $p = 0.001$), and PFS (HR: 1.65, 95% CI: 1.25–2.18, $p = 0.0004$). Total radiation dose was a significant predictor for LC (HR: 0.87, 95% CI: 0.78–0.97, $p = 0.016$). Tumor location was a significant predictor for PFS (HR: 1.55, 95% CI: 1.10–2.19, $p = 0.012$), and patients with cervical esophageal cancer had the worst PFS. The results of multivariate analysis are summarized in Table 3.

Table 1. Patients' characteristics (n = 69)

	n	%
Age		
Median 81 years (range 53–94 years)		
Gender		
Female	14	20.3
Male	55	79.7
PS		
0	19	27.5
1	35	50.7
2	10	14.5
3	3	4.3
4	2	2.9
Tumor location		
Ut	9	13.0
Mt	33	47.8
Lt	23	33.3
Ae	1	1.4
Ce	3	4.3
Histology		
SCC	67	97.1
AC	1	1.4
Other	1	1.4
T stage		
T1	28	40.6
T2	4	5.8
T3	27	39.1
T4	10	14.5
N stage		
N0	29	42.0
N1	26	37.7
N2	13	18.8
N3	1	1.4
M stage		
M0	64	92.8
M1	5	7.2
Clinical stage		
I	27	39.1
II	9	13.0
III	22	31.9
IV	11	15.9
Albumin level		
Median 3.6 g/dL (range 2.5–4.9 g/dL)		
Total radiation dose		
Median 60 Gy (range 50–66 Gy)		

PS, performance status; Ut, upper thoracic; Mt middle thoracic; Lt, lower thoracic; Ae abdomen esophagus; Ce, cervical esophagus; SCC, squamous cell carcinoma; AC, adenocarcinoma.

Kaplan-Meier Curves for OS, DSS, LC, and PFS in Patients with Each Stage

Kaplan-Meier curves are shown in Figure 2. In patients with stage I, the median OS period was 62.6 months, the 3-year OS rate was 83.1%, and the 5-year OS rate was 60.0%. The median DSS period was not reached, the 3-year DSS rate was 92.3%, and the 5-year DSS rate was 80.0%. The median LC period was 59.7 months, the 3-year LC rate was 71.9%, and the 5-year LC rate was 71.9%. The median PFS period was 53.0 months, the 3-year PFS rate was 58.6%, and the 5-year PFS rate was 46.1%.

In patients with stage II, the median OS period was 17.6 months, the 3-year OS rate was 44.0%, and the 5-year OS rate was 44.0%. The median DSS period was 17.6 months, the 3-year DSS rate was 44.0%, and the 5-year DSS rate was 44.0%. The median LC period was 13.3 months, the 3-year LC rate was 0%, and the 5-year LC rate was 0%. The median PFS period was 7.6 months, the 3-year PFS rate was 0%, and the 5-year PFS rate was 0%.

In patients with stage III, the median OS period was 11.2 months, the 3-year OS rate was 33.0%, and the 5-year OS rate was 0%. The median DSS period was 14.6 months, the 3-year DSS rate was 46.0%, and the 5-year DSS rate was 15.0%. The median LC period was 7.3 months, the 3-year LC rate was 54.0%, and the 5-year LC rate was 54.0%. The median PFS period was 6.7 months, the 3-year PFS rate was 13.0%, and the 5-year PFS rate was 0%.

In patients with stage IV, the median OS period was 10.3 months, the 3-year OS rate was 13.0%, and the 5-year OS rate was 13.0%. The median DSS period was 10.3 months, the 3-year DSS rate was 13.0%, and the 5-year DSS rate was 13.0%. The median LC period was 12.1 months, the 3-year LC rate was 0%, and the 5-year LC rate was 0%. The median PFS period was 5.8 months, the 3-year PFS rate was 0%, and the 5-year PFS rate was 0%.

Kaplan-Meier Curves for Patients with Clinical Stage I

There were 6 clinical T1aN0M0 patients, 16 clinical T1bN0M0 patients, and 5 clinical T1N1M0 patients among the 27 clinical stage I patients. In T1aN0M0 patients, the median OS period was not reached, the 3-year OS rate was 100%, and the 5-year OS rate was 100%. The median DSS period was not reached, the 3-year DSS rate was 100%, and the 5-year DSS rate was 100%. The median LC period was 77.0 months, the 3-year LC rate was 100%, and the 5-year LC rate was 100%. The median

Table 2. Univariate analysis for OS, DSS, LC, and PFS

	OS			DSS			LC			PFS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender (male vs. female)	1.34	0.62–2.66	0.431	0.53	0.24–1.17	0.133	0.72	0.31–1.72	0.476	1.49	0.74–2.78	0.249
Age	1.03	0.99–1.08	0.090	1.03	0.98–1.09	0.200	0.97	0.93–1.01	0.155	1.00	0.96–1.03	0.856
PS	1.62	1.12–2.29	0.012	1.69	1.11–2.48	0.015	1.58	1.00–2.42	0.049	1.53	1.09–2.09	0.014
Tumor location (Ut vs. Mt vs. Lt-Ae vs. Ce)	1.48	0.98–2.24	0.065	1.63	0.99–2.68	0.053	1.31	0.80–2.14	0.287	1.46	1.01–2.09	0.042
T stage	1.95	1.47–2.62	<0.0001	2.43	1.70–3.56	<0.0001	1.92	1.36–2.78	0.0002	1.86	1.44–2.42	<0.0001
N stage	2.17	1.47–3.19	0.0002	2.43	1.54–3.81	0.0002	1.56	0.98–2.42	0.058	1.76	1.25–2.45	0.0002
M stage	3.56	1.04–9.29	0.044	4.12	1.20–10.96	0.028	1.68	0.27–5.80	0.515	2.76	0.82–6.99	0.093
Clinical stage	1.87	1.43–2.48	<0.0001	2.26	1.61–3.24	<0.0001	1.78	1.27–2.53	0.0008	1.75	1.36–2.25	<0.0001
Total radiation dose	0.96	0.87–1.06	0.429	0.92	0.82–1.03	0.152	0.87	0.76–0.98	0.023	0.91	0.83–1.00	0.052
Blood albumin level	0.36	0.19–0.68	0.002	0.39	0.18–0.81	0.013	0.54	0.04–1.38	0.108	0.50	0.29–0.86	0.013

OS, overall survival; DSS, disease-specific survival; LC, local control period; PFS, progression-free survival; PS, performance status; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Ae, abdomen esophagus; Ce, cervical esophagus.

Table 3. Multivariate analysis for OS, DSS, LC, and PFS

	OS			DSS			LC			PFS		
	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
PS	1.21	0.79–1.79	0.358	1.26	0.77–1.95	0.337	1.07	0.65–1.70	0.796	1.21	0.84–1.71	0.296
Tumor location (Ut vs. Mt vs. Lt-Ae vs. Ce)										1.55	1.10–2.19	0.012
Clinical stage	4.42	1.80–11.17	0.001	2.08	1.43–3.12	0.0001	1.86	1.28–2.74	0.001	1.65	1.25–2.18	0.0004
Total radiation dose							0.87	0.78–0.97	0.016			
Blood albumin level	0.58	0.27–1.27	0.166	0.80	0.32–2.11	0.648				0.69	0.36–1.35	0.276

T stage, N stage, M stage, clinical stage were significant predictors in univariate analysis. Only clinical stage was included in multivariate analysis because these factors had correlations. OS, overall survival; DSS, disease-specific survival; LC, local control period; PFS, progression-free survival; PS, performance status; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Ae, abdomen esophagus; Ce, cervical esophagus.

PFS period was 62.6 months, the 3-year PFS rate was 83.0%, and the 5-year PFS rate was 83.0%.

In T1bN0M0 patients, the median OS period was 53.0 months, the 3-year OS rate was 87.0%, and the 5-year OS rate was 45.0%. The median DSS period was not reached, the 3-year DSS rate was 94.0%, and the 5-year DSS rate was 82.0%. The median LC period was not reached, the 3-year LC rate was 57.0%, and the 5-year LC rate was 57.0%. The median PFS period was 21.4 months, the 3-year PFS rate was 50.0%, and the 5-year PFS rate was 37.0%.

In T1N1M0 patients, the median OS period was 43.2 months, the 3-year OS rate was 80.0%, and the 5-year OS rate was 50.0%. The median DSS period was not reached, the 3-year DSS rate was 94.0%, and the 5-year DSS rate was 82.0%. The median LC period was not reached, the 3-year LC rate was 57.0%, and the 5-year LC rate was 57.0%. The median PFS period was 21.4 months, the 3-year PFS rate was 50.0%, and the 5-year PFS rate was 37.0%. There were no significant differences between the types of stage I for OS, DSS, LC, and PFS (Fig. 3).

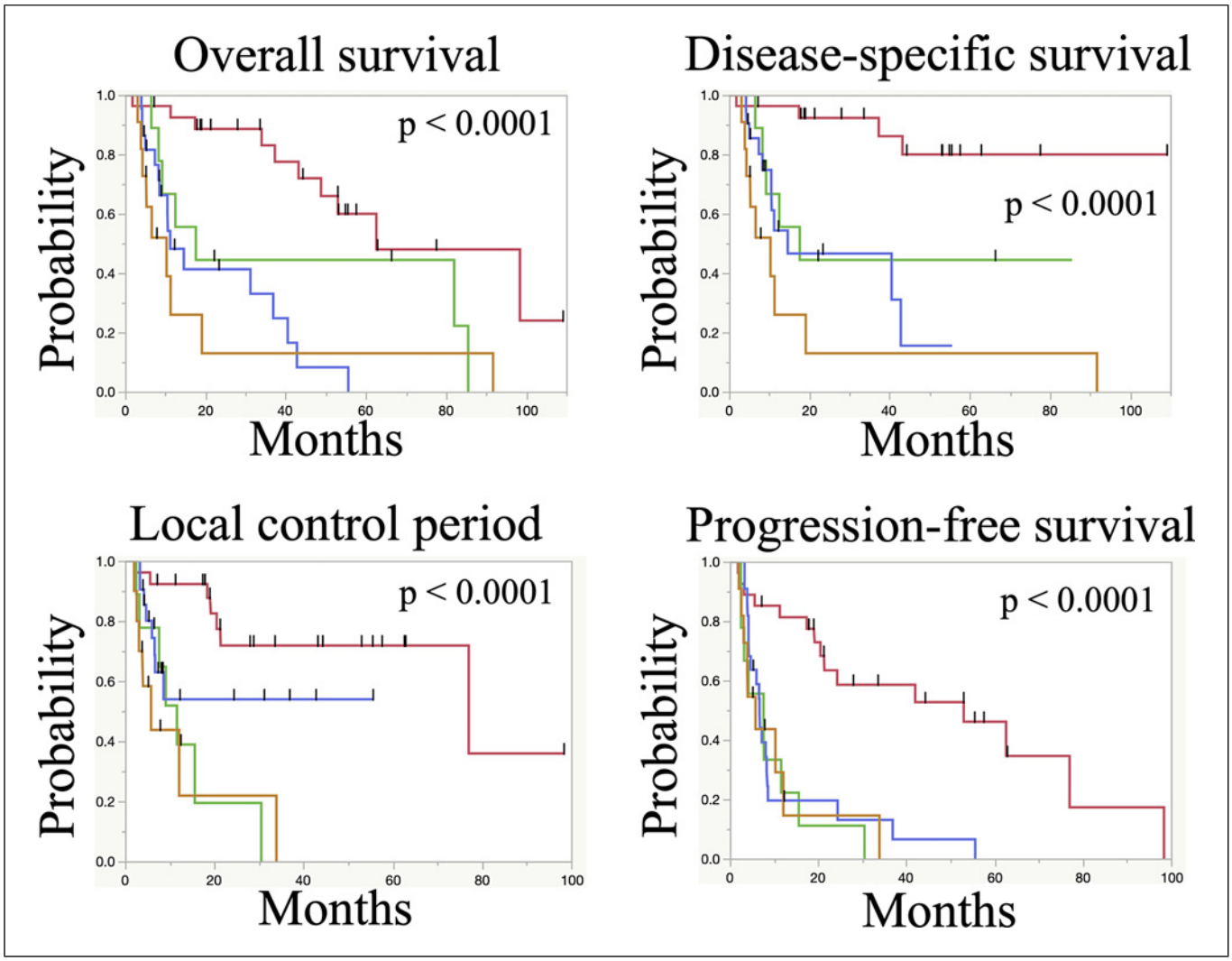

Fig. 2. Results of log-rank tests for Kaplan-Meier curves for OS, DSS, LC period, and PFS according to clinical stage. Stage I: red line, stage II: green line, stage III: blue line, stage IV: brown line.

Discussion

We showed that patients with stage I esophageal cancer were able to be cured by radiotherapy alone. The log-rank test showed that total radiation dose was a significant predictor for the LC period and that tumor location was a significant predictor for PFS. The results should be useful for deciding the treatment strategy for patients with a poor general condition.

Cooper et al. [4] reported that the 5-year OS rate for patients with esophageal cancer who were treated with radiotherapy alone was 0%. Their trial included patients with stage T1-3N0-1M0 esophageal cancer, and 62 patients were assigned to radiotherapy alone of 64 Gy in 32 fractions. The 5-year OS rate for patients in our study was 33.2%. The difference between the results of their study and our study was due to the prospective and retrospective study design and the difference in era. Their study included patients between 1986 and 1990, and the treatment planning was done using 2D planning. Our study included patients between 2011 and 2021, and all of the radiation plans were made using 3D planning. Not only the planning technique but also IGRT has improved over time [8]. All of the patients in our study received radiotherapy of IGRT by EPID or CBCT. On the other hand, the patients in the study by Cooper et al. [4] received radiotherapy before IGRT became the mainstream. Of course, not only radiotherapy techniques but

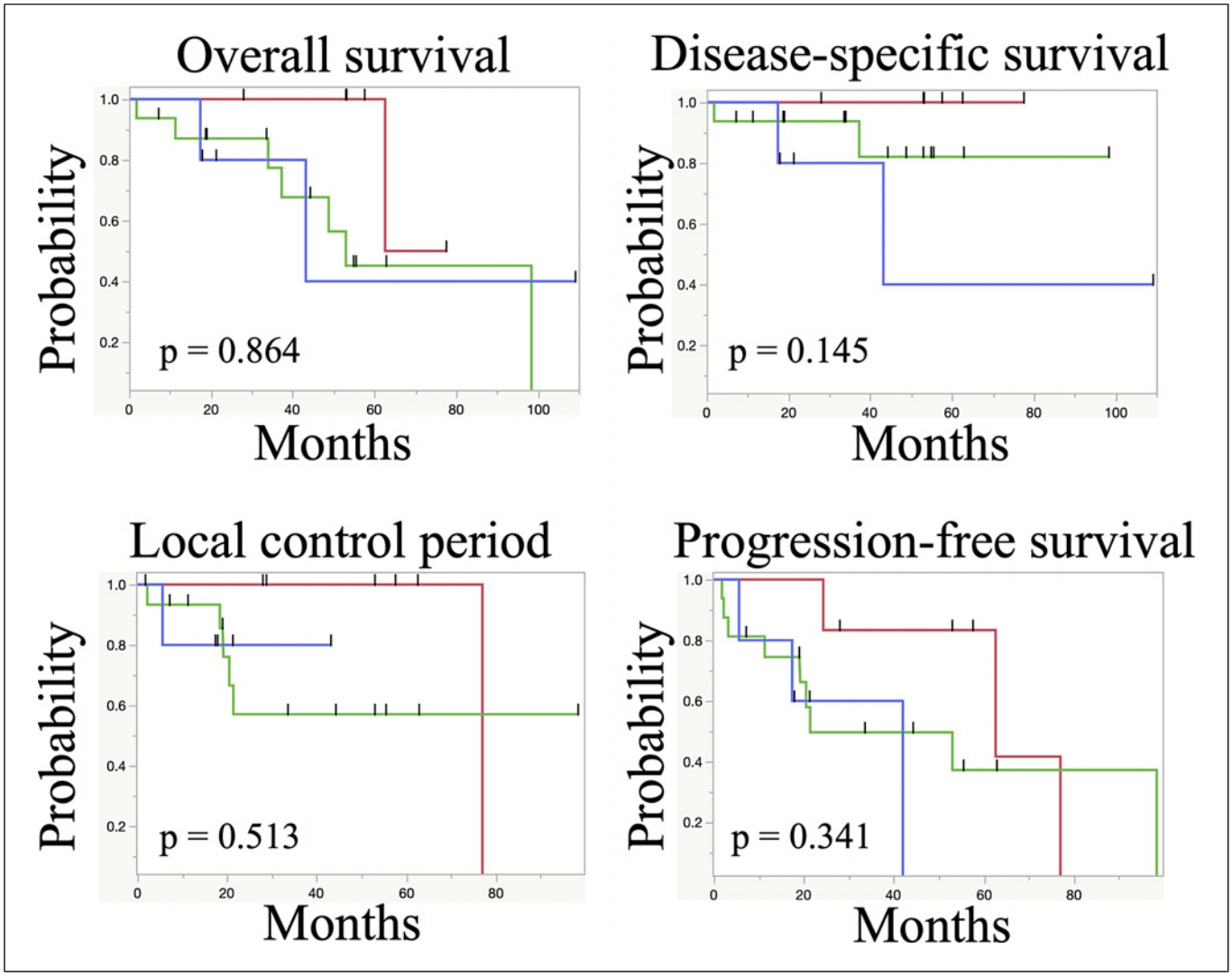

Fig. 3. Kaplan-Meier curves for OS, DSS, LC period, and PFS for patients with stage IT1aN0M0: red line, T1bN0M0: green line, T1N1M0: blue line.

also medical technologies have been improved. The OS rate for patients with esophageal cancer might have become higher due to those improvements.

Our study showed that total radiation dose was a significant predictor for the LC period and that tumor location was a significant predictor for PFS (Table 3). It was already discussed on the basis of the results of a past randomized trial whether radiation dose should be increased or not. Minsky et al. [12] showed that there was no difference in OS rate or local/regional control rate between patients who received chemoradiotherapy of 50.4 Gy in 28 fractions and patients who received 64.8 Gy in 36 fractions. Based on the results of that RCT, the standard radiotherapy dose for patients with esophageal cancer treated with chemoradiotherapy was set to 50.4 Gy in 28 fractions in Western countries. The difference between their study and our study was that patients received chemoradiotherapy or radiotherapy alone. When patients receive chemoradiotherapy, there might be few benefits for outcomes due to adverse events caused by increasing the radiotherapy dose. On the other hand, when patients receive radiotherapy alone, there might be a benefit for LC by increasing the radiation dose. However, total radiation dose was a significant predictor for LC but not a significant predictor for OS or DSS. These patients had to choose radiotherapy alone due to their poor general conditions. Even if the LC period improved, the survival period might not have been

affected because of their poor general conditions. It is controversial whether tumor location is associated with treatment outcomes for patients with thoracic esophageal cancer [13]. On the other hand, cervical esophageal cancer has rich lymphatic drainage [14]. Therefore, the PFS period for patients with cervical esophageal cancer might be shorter than that for patients with thoracic esophageal cancer.

Our results showed that patients with stage I esophageal cancer were curable by radiotherapy alone. Kato et al. [15] showed that chemoradiotherapy for patients with stage T1bN0M0 thoracic esophageal cancer was noninferior to surgery. The 5-year OS rate and PFS rate for patients who received chemoradiotherapy were 85.5% and 71.6%, respectively. Nemoto et al. [16] reported that the 5-year OS rate and LC rate for patients with stage T1N0M0 who received chemoradiotherapy or radiotherapy alone were 45% and 66%, respectively. Their study included 13 patients who received chemoradiotherapy and 65 patients who received radiotherapy alone. In our study, the 5-year OS, DSS, LC, and PFS rates for patients with stage I esophageal cancer were 60.0%, 82.0%, 71.9%, and 46.1%, respectively (Fig. 2). The 5-year OS and PFS rates in our study were lower than the results of the chemoradiotherapy study by Kato et al. [15], but the 5-year OS and LC rates in our study were higher than the results of the study by Nemoto et al. [16] that included both patients who received radiotherapy alone and patients who received chemoradiotherapy. From these results, even for patients with stage I esophageal cancer, chemotherapy concurrent to radiotherapy is important for the treatment strategy. Our study included patients with stage T1N1M0, and all of the patients received radiotherapy alone, but OS and LC rates were slightly higher than those in the study by Nemoto et al. [16] Developments in medicine and radiotherapy technology might have contributed to the results [7–9].

Conroy et al. [17] compared the OS and PFS rates for patients who were treated with FOLFOX and radiotherapy and those for patients who were treated with fluorouracil, cisplatin, and radiotherapy. There was no significant difference between the two groups. The median OS period in their study was shorter than that in our study. However, there were more patients with stage I in our study than in Conroy's study. That is the reason why the OS rates were different in their study and our study. FOLFOX can be used even in patients with poor general health, and it may therefore become a future treatment option.

Moreno et al. [18] reported that the 5-year OS rate for patients with T1-2N0M0 esophageal cancer who received only observation was 7%. They also reported that even elderly patients who are generally considered to be in a poor general condition benefited from receiving curative treatment. From the results of their study and our study, patients with early-stage esophageal cancer for whom surgery and chemoradiotherapy are difficult due to a poor general condition or comorbidities are able to have benefits of radiotherapy alone.

Ji et al. [19] showed that the 2-year OS rate for patients who received concurrent chemoradiotherapy with S-1 was higher than that for patients who received radiotherapy alone. They included patients with stage II–IV esophageal cancer and randomized them into two groups: a chemoradiotherapy group and a radiotherapy alone group. The 2-year OS rate was significantly higher in the chemoradiotherapy group (53.2%) than in the radiotherapy group (35.8%). The National Comprehensive Cancer Network (NCCN) suggested that concurrent chemoradiotherapy regimens for esophageal cancer should include paclitaxel and carboplatin, fluorouracil and oxaliplatin, and fluorouracil and cisplatin [20]. Combination therapy using two or more chemotherapy drugs with radiotherapy is effective for curing cancer, but it is also highly invasive. Jones et al. [21] showed that hypofractionated radiotherapy with 50 Gy in 16 fractions or 50–52.5 Gy in 20 fractions was not inferior to chemoradiotherapy. Chemoradiotherapy with S-1 or hypofractionated radiotherapy might be a better choice for patients with a poor general condition who are unable to tolerate the chemotherapy regimens recommended by NCCN.

Limitation

The limitation of this study was that our study was a single institutional retrospective study. Therefore, it is possible that there was a selection bias and a measurement bias. To make a generalization, a prospective and multi-institutional study is needed.

Conclusions

We present detailed outcomes of patients with esophageal cancer who were treated with radiotherapy alone. Patients with stage I esophageal cancer were successfully cured with radiotherapy alone. However, the outcomes for patients with stage II–IV esophageal cancer were unsatisfactory. While multidisciplinary therapy is crucial for treatment of esophageal cancer, not all patients are able to receive such an aggressive treatment strategy

due to their poor general condition. We hope that the results of our study will aid in decision-making for patients who undergo radiotherapy alone.

Acknowledgments

We would like to express our gratitude to all colleagues and patients.

Statement of Ethics

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. This study protocol was reviewed and approved by the Ethics Committee Tohoku University Graduate School of Medicine, approval number 2021-1-558. Patient consent was not required in accordance with Ethics Committee Tohoku University Graduate School of Medicine.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was obtained for this project.

Author Contributions

Noriyoshi Takahashi designed the analysis, reviewed the clinical data, performed statistical analysis, and drafted the manuscript. Yu Suzuki, Keita Kishida, So Omata, Yuta Sato, Hinako Harada, and Yasuhiro Seki treated patients and collected the clinical data. Rei Umezawa, Takaya Yamamoto, Kazuya Takeda, and Keiichi Jingu treated patients and revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author, Noriyoshi Takahashi, upon reasonable request after approval from the Ethical Committee of the Tohoku University.

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