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Correlation between Overall Survival and Quality of Life in Patients with Esophageal Cancer: A Comparison between Radiation and Chemoradiation

Murakawa Y*[1], Ootsuka K[1], Oikawa T[2], Iwai W[2], Kubozono M[3] and Fukui K[3]

[1]Department of Cancer Chemotherapy, Miyagi Cancer Center, Natori, Japan

[2]Department of Gastroenterology, Miyagi Cancer Center, Natori, Japan

[3]Department of Radiation Oncology, Miyagi Cancer Center, Natori, Japan

***Corresponding author:** Murakawa Y, PhD, Department of Cancer Chemotherapy, Miyagi Cancer Center, Nodayama 47-1, Medeshima, Natori, Miyagi 981-1293, Japan, Fax: +81 22381 1174, Tel: +81 22384 3151, E-mail: murakawa-ya995@miyagi-pho.jp

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Abstract

Desirable treatment options for inoperable esophageal cancer considering not only overall survival (OS) but also quality of life (QOL) during the entire clinical course remain unclear. We evaluated OS and QOL during the clinical course of patients with inoperable esophageal cancer undergoing chemoradiation or radiation. Forty-four patients with inoperable esophageal cancer between 2015 and 2020 were included in this retrospective study. Treatments included palliative radiation (p-rad ≤40 Gy), definitive radiation (d-rad ≥50 Gy), palliative chemoradiation (p-CRT), and definitive chemoradiation (d-CRT). Endpoints included OS and QOL (length of hospitalization [LOH] and outpatient consultation times [OCT]). Hospital-free survival (HFS) was defined as the period without hospitalization or outpatient consultation. The chi-square test, multivariate Cox regression analysis, Kaplan–Meier method, and scatter plot analysis were used to analyze the correlation between OS and QOL. Second primary cancer was found in 30% of the patients. Patients who received p-rad had the worst OS and HFS (OS: p-rad 2.2 months vs. d-rad 20.5 months, $p<0.005$; p-rad 2.2 months vs. p-CRT 8.8 months, $p<0.05$; p-rad 2.2 months vs. d-CRT 20.7 months, $p<0.001$; HFS: p-rad 0.4 months vs. d-CRT 10.9 months, $p<0.005$). Patients undergoing p-CRT and d-CRT showed longer LOH with respect to OS than patients undergoing p-rad and d-rad. We observed a significant positive correlation between OS and OCT and between OS and HFS, regardless of the treatment type. Patients undergoing d-rad may have the same OS and HFS as those undergoing d-CRT. Patients attributed approximately 8% of their OS to hospitalization and outpatient consultation, regardless of the treatment type. There is presently no objective QOL index that can be adapted to the entire clinical course of cancer patients, and our results suggest that HFS may potentially be used to evaluate QOL during this time.

Keywords: Esophageal Cancer; Chemotherapy; Radiotherapy; Survival; Quality of Life

List of abbreviations: OS: Overall survival; QOL: Quality of life; CRT: Chemoradiation; Rad: Radiation; d-CRT: Definitive chemoradiation; p-CRT: Palliative chemoradiation; d-rad: Definitive radiation; p-rad: Palliative radiation; LOH: Length of hospitalization; OCT: Outpatient consultation times; HFS: Hospital-free survival; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; cStage: Clinical stage; COD: Coefficient of determination

Introduction

Advanced and inoperable esophageal cancer is a fatal malignancy with a poor prognosis. The occurrence of esophageal cancer, similar to other malignancies, increases with age. The most frequent histological type is squamous cell carcinoma. Moreover, the development of esophageal cancer is frequently triggered by alcohol, smoking, and chronic exposure to irritants. Recent data ranked esophageal cancer sixth in the world and ninth in Japan for estimated deaths among all cancer-related deaths [1,2].

The main treatment strategies for patients with inoperable esophageal cancer are chemoradiation (CRT) or radiation (rad). In the National Comprehensive Cancer Network Guidelines Version 4.2021, definitive-CRT(d-CRT) is recommended for patients with inoperable esophageal cancer, while palliative-rad (p-rad) is recommended for patients not indicated for d-CRT. This guideline defines definitive-rad (d-rad) as 50–50.4 Gy (1.8–2.0 Gy/day) and p-rad as a reduced dose according to the patient's condition. The guidelines recommend adequate enteral and/or IV hydration throughout d-CRT and recovery due to dysphagia [3]. In the Japanese esophageal cancer practice guidelines, the dose of d-rad is 60 Gy (2.0 Gy/day) [4]. The reported toxicities of radiation are radiation esophagitis in the early period and recurrent dysphagia, perforation of esophagus, and bleeding in the late period.

Esophageal carcinoma has several prominent characteristics. Among them, dysphagia, which is observed in many patients with esophageal cancer, leads to a deterioration in the quality of life (QOL) [5,6]. Esophageal cancer is characterized by relatively frequent occurrences of second primary cancers that affect the treatment of esophageal cancer [7].

In advanced cancer, the therapeutic goal of oncologists and radiologists is not to achieve a cure but rather to control symptoms, prevent complications, prolong survival, and maintain a high QOL. Psychological interventions may be a valid strategy for influencing patient satisfaction, which greatly affects QOL [8]. Several types of questionnaires that depend on patient subjectivity are used for evaluating QOL. However, it is challenging to consecutively administer to patients with incurable cancer self-rating evaluations from the beginning of treatment until death.

On the other hand, long hospitalization and frequent outpatient visits have a negative impact on QOL [9,10]. We have studied the correlation between overall survival (OS), length of hospitalization (LOH), outpatient consult times (OCT), and hospital-free survival (HFS), which is defined as the period without hospitalization or outpatient consultation, as objective indicators of QOL in patients with cancer and noted a strong correlation between OS and HFS and the difference in the ratio of OCT to OS, depending on cancer and chemotherapy regimens [11,12].

At present, there is no study on the desirable treatment options for inoperable esophageal cancer considering not only OS but also QOL during the entire clinical course. The aim of this study was to compare OS, LOH, OCT, and HFS with four treatments: p-rad, d-rad, d-CRT, and palliative-CRT (p-CRT).

Materials and Methods

In this study, we retrospectively evaluated 44 patients with esophageal cancer who attended the Miyagi Cancer Center (Natori, Japan) between October 1, 2015, and October 31, 2020. All patients were histologically confirmed as having squamous cell carcinoma, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2. The patients were diagnosed with incurable esophageal cancer of cStage II to IV due to distant metastases or locally advanced tumor by computed tomography. The exclusion criteria were a refusal to undergo radiation therapy and the discontinuation of radiation.

Patients underwent radiotherapy or chemoradiotherapy. The dose of radiation was determined by considering the site of esophageal cancer and the general condition of the patient. The P-rad doses were 30 Gy (3.0 Gy/day, n=7) and 40 Gy (2.0 Gy/day, n=1). The d-rad doses were 50 Gy (2.0 Gy/day, n=1), 50.4 Gy (1.8 Gy/day, n=2), 60 Gy (3.0 Gy/day, n=28), and 66 Gy (3.0 Gy/day, n=5). First-line chemotherapy included fluorouracil and cisplatin or nedaplatin (fluorouracil (700 mg/m$^{2)}$ for four days with continuous

infusion and cisplatin (70 mg/m2) or nedaplatin (90 mg/m^2) on day 1 for two cycles, followed by two cycles of fluorouracil (800 mg/m^2) (for five days) and cisplatin or nedaplatin. Second-line chemotherapy included paclitaxel (100 mg/m^2) with an anticancer agent administered on days 1, 8, and 15 or docetaxel (60 mg/m^2) every four weeks. Third-line chemotherapy included nivolumab (240 mg/body) every other week. Radiotherapy was performed in all the patients.

We collected data on sex, age, ECOG PS, tumor location, and cStage between October 1, 2015, and October 31, 2020, and on the OS, LOH, OCT, and second primary cancer between October 1, 2015, and November 31, 2021, from electric medical records. Second primary cancer was defined as active advanced malignancies that existed at the time of diagnosis of esophageal cancer or were diagnosed at the same time or during treatment for esophageal cancer. Cases who received home health care after radiation or chemoradiation, and died at home were considered data loss cases.

Statistical Analyses

We used the chi-square test to compare the clinicopathological characteristics (e.g., sex, age, ECOG PS, tumor location, cStage, second primary cancer, and missing data on LOH or OCT due to transfer to another hospital or receiving home health care after rad or CRT) during the clinical course. OS and HFS curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox regression analysis was performed to adjust for confounding factors of OS and HFS. A two-tailed *P* value of <0.05 was considered significant.

The correlations between OS and LOH, OS and OCT, and OS and HFS were examined by scatter plot analysis and compared using treatment for 36 patients with complete data for LOH and OCT. A coefficient of determination (COD) $r^2 \geq 0.5$ was considered a strong correlation, while $0.5>r2\geq0.1$ was considered a moderate correlation. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (software version 23; SPSS Inc., Chicago, IL, USA).

The international review board of the Miyagi Cancer Center approved this study (approval no. 3). All procedures were performed according to the ethical standards of the institutional and national research committees and the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. Informed consent, with an opt-out option, was obtained from all patients according to the local ethics policy on the retrospective analysis of our own anonymized clinical data.

Results

As shown in Table 1, 44 patients with esophageal cancer were enrolled in the study. The majority of patients were male (female/male: 7/37). Patients with ECOG PS 1 accounted for 50% of the total cohort (PS 0/ PS 1/ PS 2: 8/23/13). The percentage of patients with cStage IV disease was 50% (cStage II/III/IV: 8/14/22). Second primary cancer was found in 30% of the patients (n=13). Sex, ECOG PS, cStage, second primary cancer, and data loss of LOH and/or OCT were not statistically different among the four treatment groups. Patients who received p-rad and d-rad were older than those who received chemoradiation (≤70/>70 years: p-rad 1/3; d-rad 1/8; p-CRT 4/0; d-CRT 18/9; p<0.01). Most patients in all treatment groups had thoracic esophageal cancer, except for those in the p-rad group (cervical/thorax/abdominal: p-rad 1/2/1; d-rad 0/9/0; p-CRT 0/4/0; d-CRT 0/26/1; p<0.05).

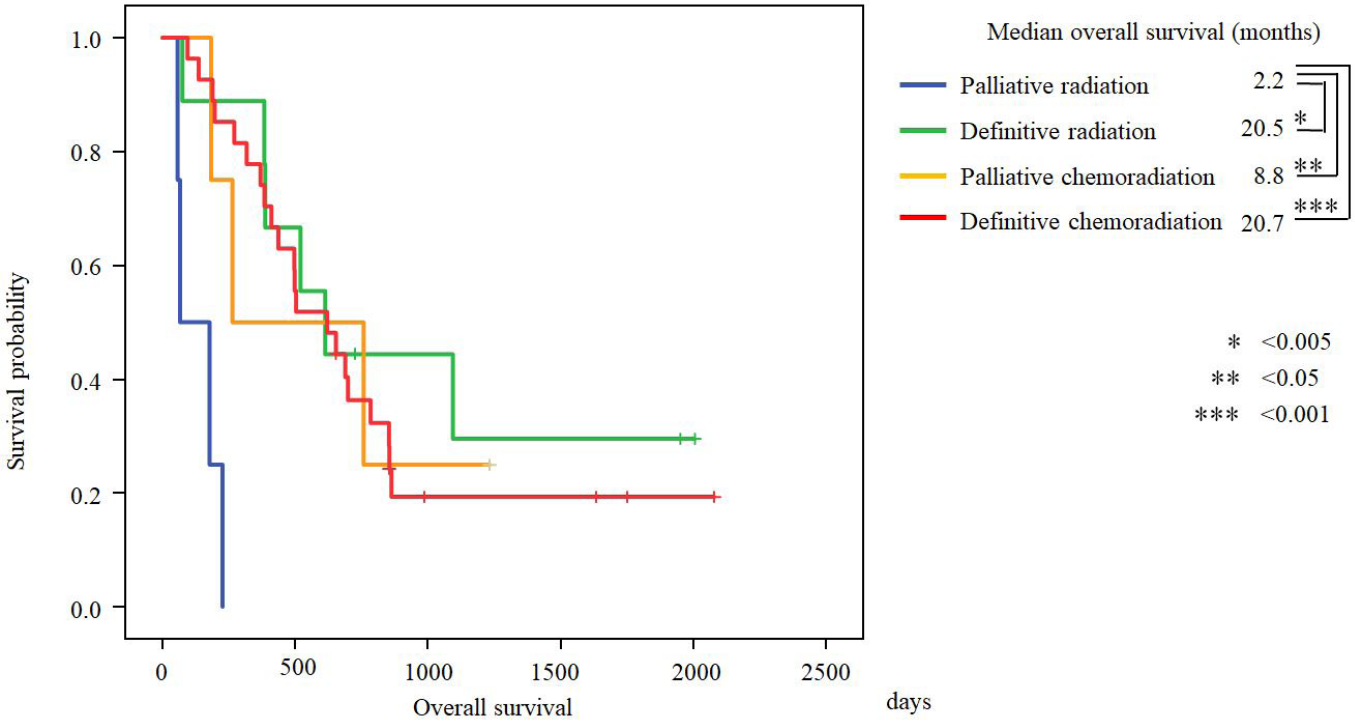
Second primary cancers included laryngeal cancer (n=4), lung cancer (n=1), malignant melanoma of the nasal cavity (n=1), neuroendocrine carcinoma of the esophagus (n=1), gastric cancer (n=2), pancreatic cancer (n=1), gallbladder cancer (n=1), hepatoma (n=1), and kidney cancer (n=1). By the end of November 2021, 34 patients had died, and the cause of death in two patients was malignancies other than esophageal cancer.

In this study, the main adverse effect of radiation was radiation esophagitis, which was observed in almost all patients in varying degrees during the early period. The main adverse effects of radiation in the late period were the perforation of the esophagus and

pleural effusion. Six patients with perforation of the esophagus died of pneumonia or mediastinitis. The adverse effect of chemotherapy was temporary myelosuppression, which was not serious.

Patients who received p-rad had a worse median OS than those who received other treatments (p-rad 2.2 months vs. d-rad 20.5 months, $p<0.005$; p-rad 2.2 months vs. p-CRT 8.8 months, $p<0.05$; p-rad 2.2 months vs. d-CRT 20.7 months, $p<0.001$). However, there was no significant difference in the median OS between patients in the d-rad and d-CRT groups (Figure 1).

Patients who received p-rad had a worse median HFS than those who received d-CRT (p-rad 0.4 months vs. d-CRT 10.9 months, $p<0.005$) However, we found no significant difference in the median HFS between patients in the d-rad and d-CRT groups (Figure 2).



Patients at risk

Palliative radiation	4	0				
Definitive radiation	9	6	3	3	1	0
Palliative chemoradiation	4	2	1	0		
Definitive chemoradiation	27	15	3	3	1	0

Figure 1: Kaplan–Meier curves for overall survival

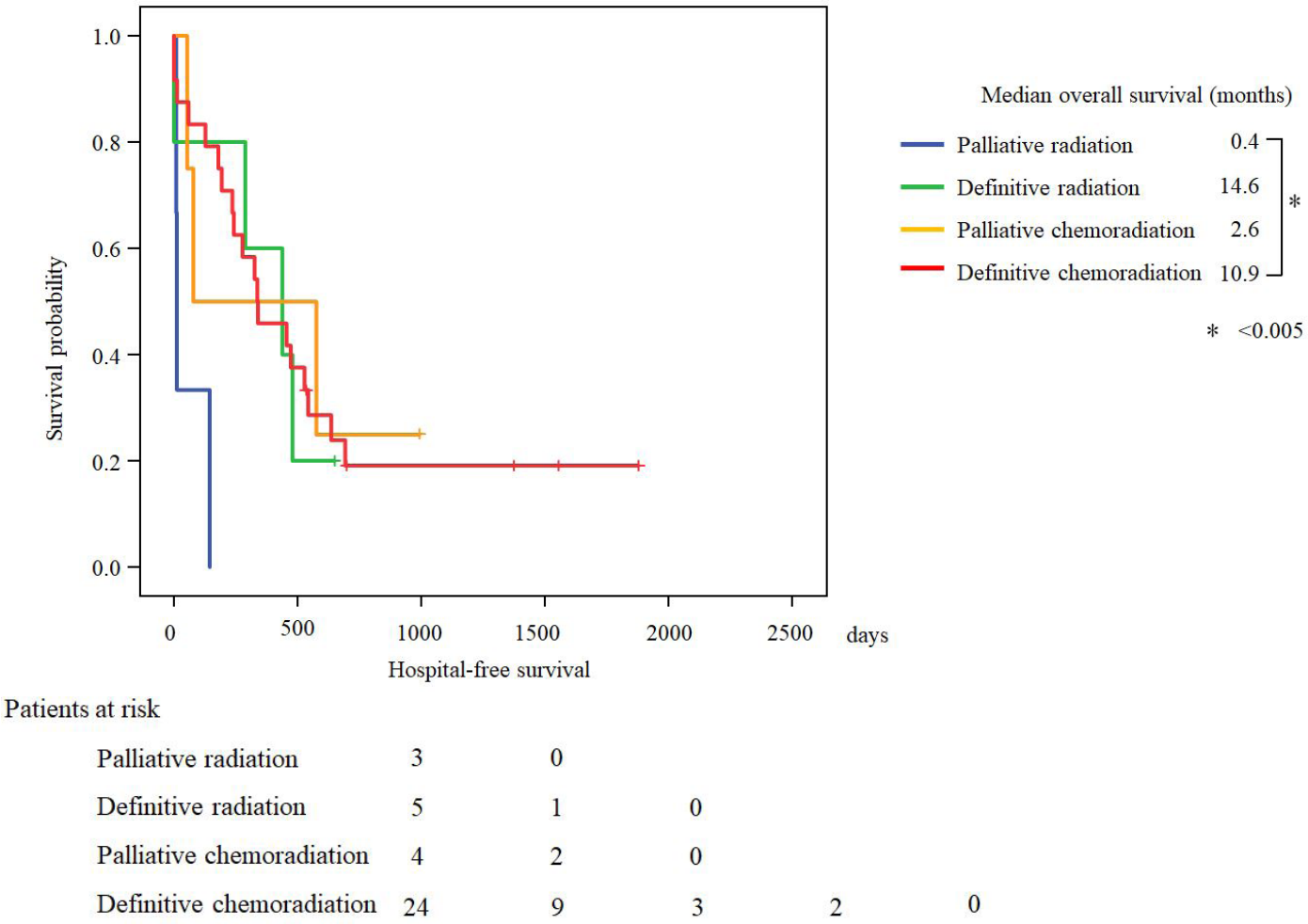


Figure 2: Kaplan–Meier curves for hospital-free survival

Of the four treatments, d-CRT was significantly and independently associated with a longer OS compared to p-rad (hazard ratio [HR]: 17.21, 95% confidence interval [CI]: 3.06-96.84, $p<0.005$). Sex, age, ECOG PS, tumor location, cStage, and double cancer were not associated with longer OS. None of the variables were associated with a longer HFS (Supplemental Table 1).

The correlations between OS and LOH, OS and OCT, and OS and HFS were examined using a scatter plot analysis. In the correlation between OS and LOH, patients treated with p-CRT and d-CRT showed longer hospital stays with respect to OS than those treated with p-rad and d-rad (Figure 3). In the correlation between OS and OCT, we observed a significant positive correlation between OS (x-axis) and OCT (y-axis) among patients, regardless of the type of treatment (COD: $r^2=0.736$, y=1.34+0.06*X) (Figure 4). In the correlation between OS and HFS, we observed a significant positive correlation between OS (x-axis) and HFS (y-axis) among all patients, regardless of the type of treatment (COD: $r^2=0.988$, y=1.07E2+0.92*X). We also found that 92% of the patients' OS period had no hospitalization or outpatient visits (Figure 5).

			Palliative-rad.		Definitive-rad.		Palliative-CRT		Definitive-CRT		*p*
Variable	**n**	**(%)**	**n**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Sex											0.730
Female	7	(15.9)	0	(0.0)	2	(22.2)	1	(25.0)	4	(14.8)	
Male	37	(84.1)	4	(100)	7	(77.8)	3	(75.0)	23	(85.2)	
Age (years)											<0.01[#]
≦70	24	(54.5)	1	(25.0)	1	(11.1)	4	(100)	18	(66.7)	
>70	20	(45.5)	3	(75.0)	8	(88.9)	0	(0)	9	(33.3)	
ECOG PS											0.478
0	8	(18.2)	1	(25.0)	1	(11.1)	0	(0)	6	(22.2)	
1	23	(52.3)	1	(25.0)	5	(55.6)	4	(100)	13	(48.1)	
2	13	(29.5)	2	(50.0)	3	(33.3)	0	(0)	8	(29.6)	
Location											<0.05[#]
Cervical	1	(2.3)	1	(25.0)	0	(0)	0	(0)	0	(0)	
Thorax	41	(93.2)	2	(50.0)	9	(100)	4	(100)	26	(96.3)	
Abdominal	2	(4.5)	1	(25.0)	0	(0)	0	(0)	1	(3.7)	
cStage											0.069
II	8	(18.2)	0	(0)	3	(33.3)	0	(0)	5	(18.5)	
III	14	(31.8)	0	(0)	2	(22.2)	0	(0)	12	(44.4)	
IV	22	(50.0)	4	(100)	4	(44.4)	4	(100)	10	(37.0)	
Second primary cancer											0.580
(-)	31	(70.5)	3	(75.0)	6	(66.7)	4	(100)	18	(66.7)	
(+)	13	(29.5)	1	(25.0)	3	(33.3)	0	(0)	9	(33.3)	
Data loss[##]											0.107
(-)	36	(81.8)	3	(75.0)	5	(55.6)	4	(100)	24	(88.9)	
(+)	8	(18.2)	1	(25.0)	4	(44.4)	0	(0)	3	(11.1)	
Total	44	(100)	4	(100)	9	(100)	4	(100)	27	(100)	

Abbreviation: CRT: Chemoradiation; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; rad: Radiation

[#]<0.05

[##]Data loss of length of hospitalization [LOH] or/and outpatient consultation times [OCT]

Table 1: Patient clinical characteristics

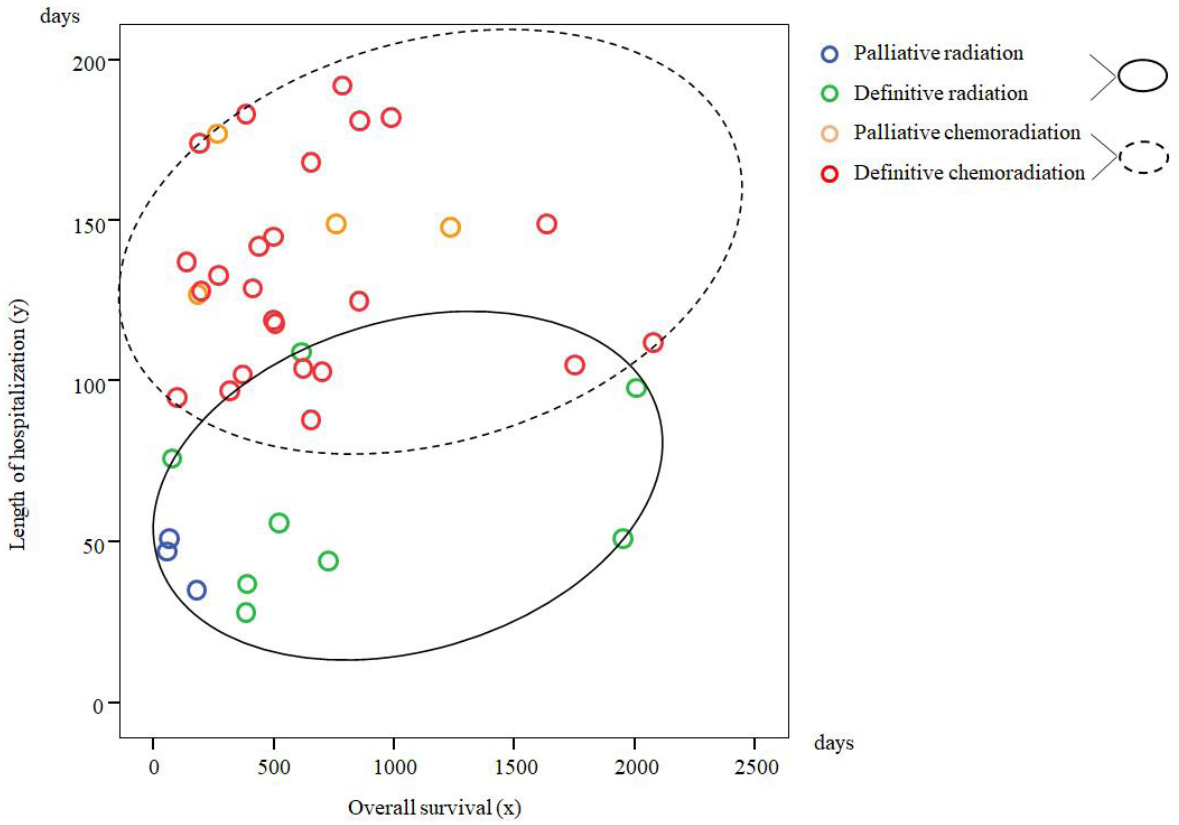


Figure 3: Correlation between overall survival and length of hospitalization

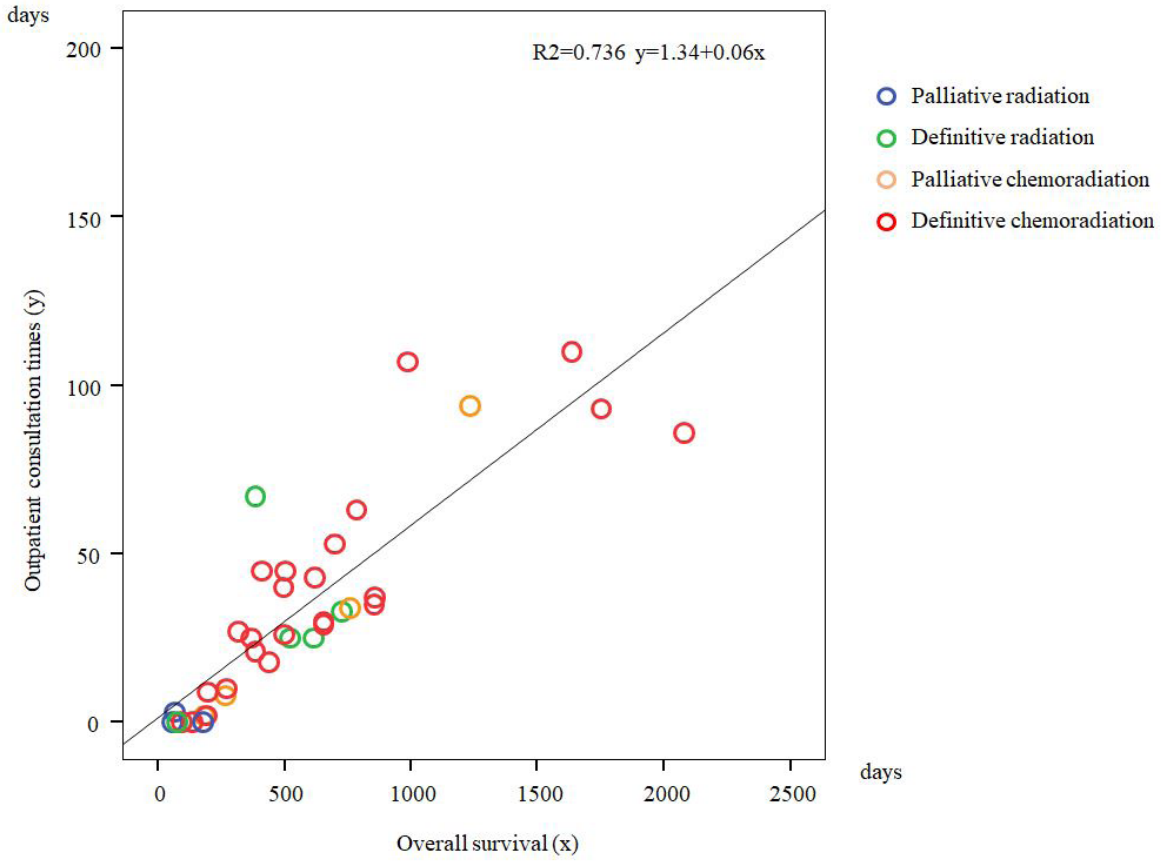


Figure 4: Correlation between overall survival and outpatient consultation times

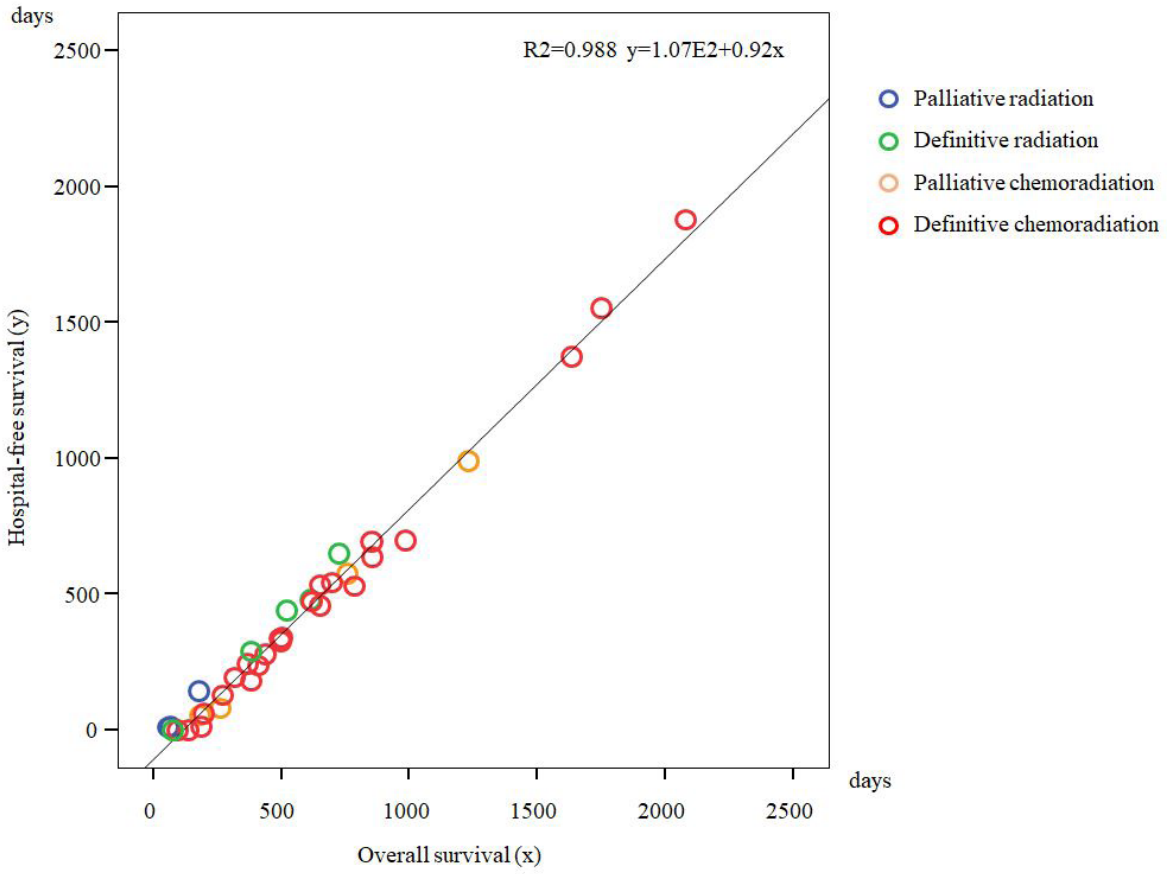


Figure 5: Correlation between overall survival and hospital-free survival

Discussion

D-rad and d-CRT showed no significant differences in OS and HFS. All treatments showed a significant positive correlation between the HFS and OS. Patients attributed approximately 8% of their OS to hospitalization and OCTs, regardless of the type of treatment.

A phase III randomized study and meta-analysis demonstrated that CRT is more effective than rad alone for the treatment of esophageal cancer [13,14]. In esophageal cancer treatment in Japan, d-CRT is also recommended for patients with inoperable esophageal cancer, despite it being associated with more than 10% fatal complications [4]. One study showed that the long-term outcomes of rad, with or without chemotherapy, for esophageal carcinoma without distant metastases were not statistically significant [15]. The complications of rad, including persistent stricture, ulceration, and radiation pneumonitis, should not be underestimated [16].

Studies reported that some treatments had better prognosis than no treatment for elderly patients with esophageal cancer; however, a considerable number of patients were untreated in clinical practice [17,18]. Another study reported that CRT had a better prognosis than radiation in elderly patients with esophageal cancer [19]. In this study, most patients undergoing d-rad were over 70 years old; however, d-rad showed no inferiority to d-CRT in OS and HFS.

In a meta-analysis on radiation dose of d-CRT, high-dose radiation (≥60 Gy) was reported to improve OS compared to standard-dose radiation (50.4 Gy) in patients with esophageal cancer [20]. However, one report showed that high-dose radiation (64.8 Gy) does not significantly improve QOL compared to standard-dose radiation (50.4 Gy) in d-CRT [21]. In this study, good OS was obtained without chemotherapy at doses of 50 Gy and above in some cases.

Chemotherapy and radiation tend to be performed as outpatient procedures [22,23]. In actual clinical practice, inpatient treatment is unavoidable in many cases. Outpatient radiation and long-term chemotherapy increase the number of outpatient consultations.

We should not underestimate the risk of secondary primary cancers. Primary esophageal cancers are reported to be associated with secondary primary squamous cell carcinoma of the aerodigestive tract [7]. This association has been described as the concept of "field cancerization" [24]. According to the Comprehensive Registry of Esophageal Cancer in Japan, 2013, death due to other cancers is reported to be around 7.8% [25]. In this study, 32% of patients with a second malignancy had squamous carcinoma of the digestive tract, and death due to other cancers was 5.8%.

WHO advocates four domains for QOL: physical health, psychological state, social relationships, and the environment [26]. Commonly used QOL questionnaires for cancer patients are the European Organization for Research and Treatment of Cancer QLQ-C30 and Functional Assessment of Cancer Therapy-General [27,28]. However, the low feasibility of a longitudinal QOL survey using a questionnaire has been reported [29]. One study reported that QOL evaluation is often difficult to analyze due to missing data in the questionnaire [30]. One of the problems with applying the current questionnaires to patients with esophageal cancer is the lack of a scale for dysphagia [6].

Hospitalization has been reported to exacerbate circadian rhythms and impair QOL [31]. Waiting time during outpatient consultation is generally identified as a factor that impacts a patient's satisfaction, thus affecting QOL [32]. In this study, the main reasons for hospitalization were to receive radiation and/or first-line chemotherapy and help control symptoms that are difficult to manage with OCT. The outpatient consultations were conducted for (1) subsequent chemotherapy cycles; (2) evaluating outcomes of the treatment using techniques such as endoscopy and computed tomography; and (3) identifying ways to manage the exacerbation of cancer and the adverse effects of chemotherapy.

At present, there is no objective QOL index that can be adapted to the entire clinical course of cancer patients. Compared to QOL questionnaires, which are challenging to consecutively administer for self-rating evaluation, use of HFS may be potentially feasible.

This study had several limitations. We conducted a retrospective study of only 44 patients from a single facility. Therefore, as the number of cases in the p-rad and p-CRT groups was small, we were unable to draw a definitive conclusion from this study. Variations in chemotherapy and rad, such as reduced drug dosage, extended treatment interval for chemotherapy, and several rad schedules, could have also impacted the results. This study also included patients with short survival periods (< three months), who died before the therapeutic effect appeared. In addition, there was age and tumor location bias in the treatment groups. HFS is insufficient for evaluating QOL during the entire clinical course because it is not a QOL indicator based on the patient's own evaluation.

Conclusions

The findings of this study suggest that a good OS and HFS similar to d-CRT were obtained with d-rad in some cases. Patients attributed approximately 8% of their OS period to hospitalization and outpatient consultation, regardless of the type of treatment. Future studies on factors that predict cases in which a good HFS can be obtained with d-rad are warranted. When conducting a randomized controlled trial on the treatment of cancer, it may be necessary to examine HFS for evaluation of QOL during the entire clinical course.

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Supplementary Information

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