Prognostic value of liver metastasis in patients with esophageal squamous cell carcinoma treated with nivolumab

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Abstract. Nivolumab has been approved for unresectable recurrent advanced esophageal cancer. The present study aimed to provide real-world data on diverse patient profiles, including the elderly and those with poor performance status, while exploring therapeutic efficacy biomarkers. This retrospective study included 42 patients with esophageal cancer who received nivolumab after second- or later-line treatment at Kyoto Prefectural University of Medicine (Kyoto, Japan) from February 2020 to December 2021. The study evaluated real-world patient data for the outcomes, safety and clinical characteristics impacting efficacy. The median patient age was 70 years (range, 52-80), and 36 patients (85%) were male. A total of 22 patients (52%) were ≥70 years of age, and three (7%) had an Eastern Clinical Oncology Group Performance Status of 2, which was not included in the clinical trial. The response and disease control rates were 26 and 78%, respectively. With a median follow-up period of 7.9 months, the median progression-free survival and overall survival were 3.5 (95% CI, 2.0-6.0) and 19 (95% CI, 6.4-not reached) months, respectively. Patients with liver metastases had significantly worse progression-free survival and overall survival, while lung and lymph node metastases did not clearly impact nivolumab efficacy. Multivariate analysis revealed that liver metastases may predict both worse progression-free survival [hazard ratio (HR) 2.37; 95% CI, 1.07-5.24; P=0.03) and overall survival (HR, 2.75; 95% CI, 1.00-7.53; P=0.04). This study provided real-world evidence of nivolumab's favorable efficacy across diverse profiles, including the elderly and those with impaired performance status. No serious immune-related adverse events occurred and liver metastasis emerged as a predictive biomarker for nivolumab efficacy in esophageal squamous cell cancer.

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Introduction

Esophageal cancer is the eighth most common cancer and sixth leading cause of mortality worldwide (1). Unresectable advanced or recurrent esophageal cancer remains an intractable malignant disease, and >10,000 people die annually from esophageal cancer in Japan (2). In Japan, fluoropyrimidines plus platinum-based chemotherapy was used as the first-line therapy, followed by taxanes as the second-line therapy for advanced esophageal cancer until the launch of immune checkpoint inhibitors (ICIs). Nivolumab, an anti-programmed cell death protein 1 (PD-1) antibody that reverts the ability of T cells to recognize and kill tumor cells, showed a survival benefit over taxane for esophageal squamous cell cancer (ESCC) patients who were refractory to fluoropyrimidines- and platinum-based chemotherapy in the phase III ATTRACTION-3 trial (3). Based on these results, nivolumab has been approved in Japan since February 2020 for ESCC patients who have progressed after chemotherapy.

The ATTRACTION-3 trial showed a promising efficacy with acceptable toxicity profiles for nivolumab; however, this study excluded patients with a poor Eastern Cooperative Oncology Group performance status (ECOG-PS≥2) and consequently did not include patients >70 years of age in the nivolumab group. A small number of real-world data on nivolumab as second- or further-line therapy has been reported (4); however, data on patients with conditions that were excluded from the phase III ATTRACTION-3 trial are still required. Thus, its efficacy and safety in these patients are still unknown and worthy of further exploration in real-world settings. Although ICIs, including nivolumab, demonstrate marked and durable responses in some patients, they can

occasionally cause immune-related adverse events (irAEs), including fatalities. Therefore, it is imperative to predict the efficacy of ICI therapy before treatment initiation. Several reports suggest the usefulness of biomarkers, such as PD-L1 expression with CD8+ tumor-infiltrating lymphocytes (5) and inflammatory markers (CRP/albumin ratios (CAR)) (6), in predicting nivolumab efficacy in ESCC; nonetheless, this information remains limited and lacking, with no established biomarkers as of yet. Accumulating evidence has shown that liver metastasis reduces the efficacy of ICI (7-11). However, the potential value of liver metastasis as a predictor of ICI efficacy for ESCC remains unclear. The identification of a convenient and reliable biomarker for the ICI treatment of ESCC remains a challenge.

Herein, we present the efficacy and safety of nivolumab monotherapy as second or further-line therapy for ESCC patients from a real-world data, with an analysis of the predictive factors for treatment efficacy.

Patients and methods

Study design and patients. We conducted a retrospective analysis of consecutive patients with unresectable advanced or recurrent esophageal cancer treated with nivolumab as a second- or later-line treatment at the Kyoto Prefectural University of Medicine between February 2020 and December 2021. The data used in this study were extracted in January 2022. All patients were pathologically confirmed to have esophageal squamous or adenosquamous cell carcinoma and were refractory or intolerant to at least one line of fluoropyrimidine-, platinum-, or taxane-based chemotherapy. This study was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine (approval no. ERB-E-42). All procedures were performed in accordance with the ethical standards of the Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine and the Declaration of Helsinki. An opt-out approach was employed to obtain informed consent from patients, and personal information was protected during data collection.

Treatment and evaluation. Intravenous nivolumab was administered at a dose of 240 mg every 2 weeks or 480 mg every 4 weeks. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Information was collected from the electronic medical records of the hospital. The data collected for this study included sex, age, height, weight, ECOG PS, number and duration of nivolumab administration, smoking and alcohol consumption, histopathology, TNM at diagnosis, metastatic organ at diagnosis, best response to primary therapy, overall survival (OS), progression-free survival (PFS), blood test data (albumin, CRP, neutrophils, lymphocytes), presence of surgery, presence of radiation therapy, presence of treatment-related adverse events, severity of treatment-related adverse events, and time to onset of treatment-related adverse events. The overall response was evaluated based on the Response Evaluation Criteria in Solid Tumors version 1.1. The severity of adverse events was graded according to CTCAE 4.0 criteria.

Statistical analysis. OS was defined as the time from the initiation of nivolumab therapy until death by any cause or final follow-up. PFS was defined as the time from the administration of the first dose of nivolumab to disease progression or death. OS and PFS were estimated using the Kaplan-Meier method. The log-rank test was used to compare groups, and Cox regression models were used to calculate hazard ratios (HR) and 95% confidence interval (95% CI). The effects of liver metastases and possible factors, such as PS, smoking status, and inflammatory markers (CAR, neutrophil/lymphocyte ratio (NLR), and prognostic nutritional index (PNI)), on PFS and OS were analyzed using COX regression models. The cutoff values for NLR and PNI were determined based on previous reports (12,13), and median value was employed for the others.

PFS and OS were estimated with a 95% confidence interval (CI) using the Kaplan–Meier method and compared using the log-rank test. Cox regression models were used to calculate the hazard ratio (HR) and 95% CI. Significant variables in the univariate analysis, $P<0.05$ for PFS and $P\leq0.01$ for OS, were included in the multivariate analysis. All statistical tests were two-sided, and $P<0.05$ was set as the level of significance. Statistical analyses were performed using the JMP Pro 17 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. The characteristics of the 42 enrolled patients are summarized in Table I. The median age was 70 years old, with 22 patients (52%) aged 70 years or older, a demographic not represented in the ATTRACTION-3 trial. The proportion of males was 85%. The patients had ECOG-PS scores of 0 (n=21), 1 (n=18), or 2 (n=3). Histopathological findings included squamous cell carcinoma in 41 patients (97%) and adenosquamous cell carcinoma in one patient (3%). Nivolumab was used in 16 (38%) second-line cases and 26 (61%) third-line or later cases. All the patients received at least one regimen of fluoropyrimidine-, platinum-, or taxane-based chemotherapy. Twenty-eight (66%) and 19 (45%) patients underwent surgery and radiation therapy, respectively, prior to treatment. Twenty-five patients (40%) had metastases in more than two organs, with the most prevalent metastatic organs being the lymph nodes (88%), lungs (35%), and liver (28%), followed by the bone (11%). Except for two patients (5%) who were non-smokers, 40 patients (95%) had a history of smoking (at least once).

Efficacy of nivolumab. The median observation period after nivolumab therapy was 7.9 months (0.6-23.8), and the median number of doses was nine (1-53). As shown in Table II, two patients (4%) had a complete response; nine (21%), a partial response; 22 (52%), stable disease; and nine (21%), progressive disease. Response and disease control rates were 26 and 78%, respectively. Four patients (9%) responded to nivolumab and continued treatment. The median PFS and OS were 3.5 (95% CI 2.0-6.0, Fig. 1A) and 19 (95% CI 6.4-not reached, Fig. 1B) months, respectively. In a comparison of PFS and OS based on liver metastatic status, PFS and OS in patients without liver metastases were significantly better than those with liver metastases (median PFS 5.3 vs. 1.5 months, P=0.01, Fig. 1C;

Table I. Characteristics of patients (n=42).

Characteristics	n (%)
Age[a], years	
<65	12 (28)
≥65	30 (71)
of which ≥70	22 (52)
Sex	
Male	36 (85)
Female	6 (14)
ECOG Performance status	
0	21 (50)
1	18 (42)
2	3 (7)
Pathological tissue	
Squamous cell carcinoma	41 (97)
Adenosquamous cell carcinoma	1 (3)
Treatment lines	
2nd	16 (38)
3rd or lator	26 (61)
Previous therapies	
Surgery	28 (66)
Radiotherapy	19 (45)
Systemic anticancer therapy	42 (100)
Number of organs with metastases	
<2	17 (59)
≥2	25 (40)
Site of metastases	
Lymph node	37 (88)
Liver	12 (28)
Lung	15 (35)
Bone	5 (11)
History of smoking	
Never	2 (5)
Not never	40 (95)

[a]Mean age, 70 (range, 52-80) years.

Table II. Treatment outcome (n=42).

Outcome	N
Doses of nivolumab administered, n (range)	9 (1-53)
Best overall response, n (%)	
Complete response	2 (4)
Partial response	9 (21)
Stable disease	22 (52)
Progressive disease	9 (21)
Not evaluated	0
Disease control, n (%)	33 (78)
Response, n (%)	11 (26)

median OS not reached vs. 6.5 months, P<0.01, Fig. 1D). In contrast, a comparison based on lymph node and lung metastasis status showed no significant differences in PFS and OS depending on the metastatic status, although there was a trend toward longer OS in patients without lymph node metastasis (Fig. 2).

Predictive role of liver metastasis and the other possible predictive factors. Factors, including liver metastatic status and inflammatory markers, that may contribute to the PFS and OS of nivolumab were analyzed. The following factors were included in the analysis: age, ECOG-PS, smoking history, alcohol consumption, NLR, CAR, hemoglobin level, PNI, and metastatic status. As shown in Table III, the PFS was significantly worse in patients with PS≥2 (HR 7.23, 95%CI 1.87-27.95, P=0.004), history of no smoking (HR 7.20, 95%CI 1.54-33.48, P=0.01), NLR≥4 (HR 3.33, 95%CI 1.65-6.73, P=0.0008), bone metastasis (HR 3.63, 95%CI 1.29-10.2, P=0.01), and liver metastasis (HR 2.64, 95%CI 1.28-5.43, P=0.008) in the univariate analyses. In the multivariate analyses, liver metastasis (HR 2.37, 95%CI 1.07-5.24, P=0.03), history of no smoking (HR 5.81, 95%CI 1.07-31.35, P=0.04), and NLR≥4 (HR 2.53, 95%CI 1.21-5.76, P=0.02) were shown to be possible worse predictive factors for PFS. Table IV shows the univariate and multivariate analyses of OS. In the univariate analyses, PS, NLR, PNI, and liver metastasis were predictive factors. Because of the small number of events occurring in the analysis of OS, fewer than two explanatory variables in the multivariate analysis was considered desirable; however, given the importance of liver metastasis in previous reports (7-11), a multivariate analysis was performed using three explanatory variables including liver metastasis. Multivariate analysis revealed that liver metastasis (HR 2.75, 95%CI 1.00-7.53, P=0.04) and NLR≥4 (HR 3.15, 95%CI 1.17-8.49, P=0.02) were statistically associated with worse OS.

Frequency of immune-related adverse events. IrAEs occurred in 12 of 42 patients (28%) of all grades, with three (7%) patients experiencing grade 3 or higher irAEs. Treatment discontinuation was required in three patients (7%) who developed grade 3 pneumonitis (n=2) and thyroiditis (n=1). No adverse events resulted in mortality. The most common irAEs were thyroiditis and rash in four patients (9%), followed by diarrhea, pneumonia, adrenal insufficiency, and pituitaryitis (Table V).

Discussion

In the present study, the clinical efficacy and safety of nivolumab as second- or third-line treatments for ESCC were confirmed using real-world data. Notably, both treatment efficacy and safety profiles were comparable to or better than those of the phase 3 ATTRACTION-3 trial, despite the fact that our study included a relatively large number of patients with poor PS and aged >70 years, a demographic not included in the ATTRACTION-3 trial. Furthermore, analysis of the predictors of PFS and OS demonstrated that the presence of liver metastases is a possible predictor of worse PFS and OS. Although there have been several reports on the possibility

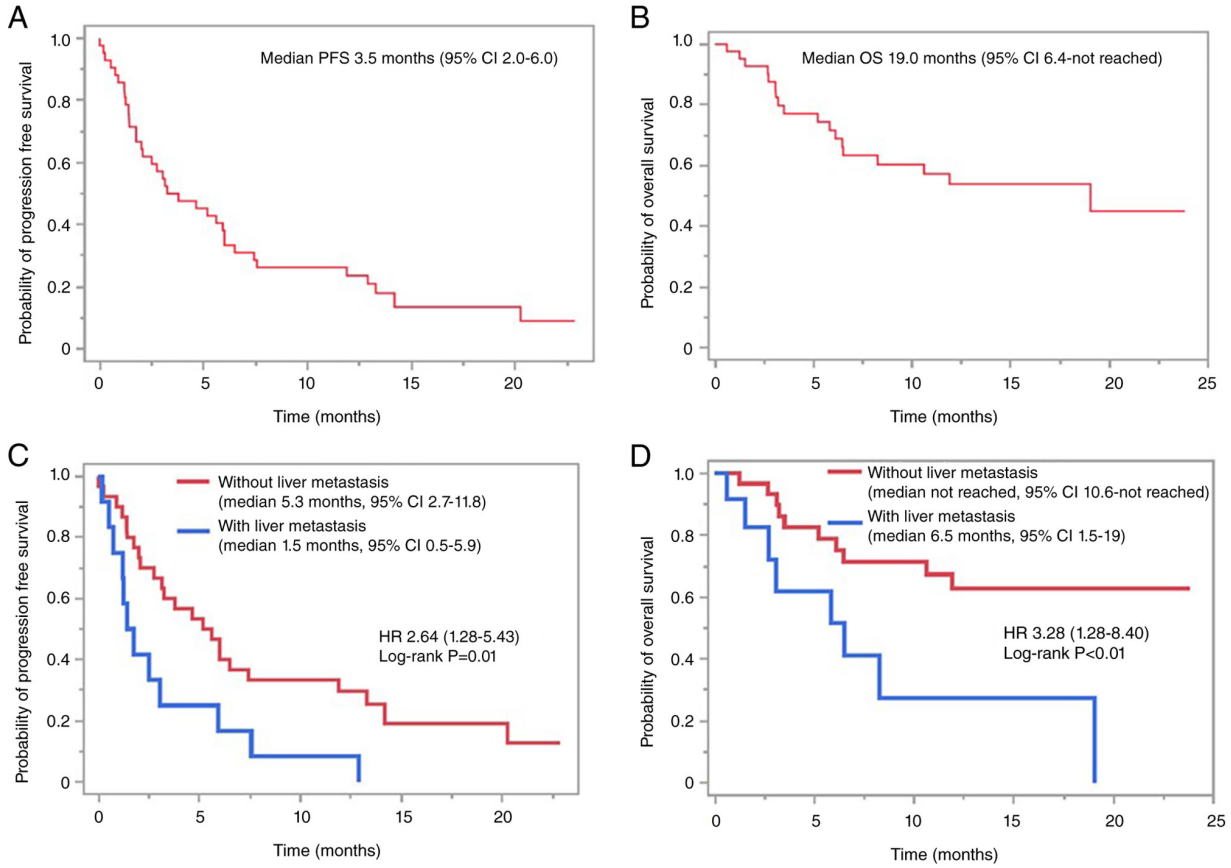

Figure 1. Survival curves for PFS and OS. Kaplan-Meier analysis of (A) PFS and (B) OS for all patients; and (C) PFS and (D) OS of patients stratified by the presence and absence of liver metastasis. PFS, progression-free survival; OS, overall survival; HR, hazard ratio.

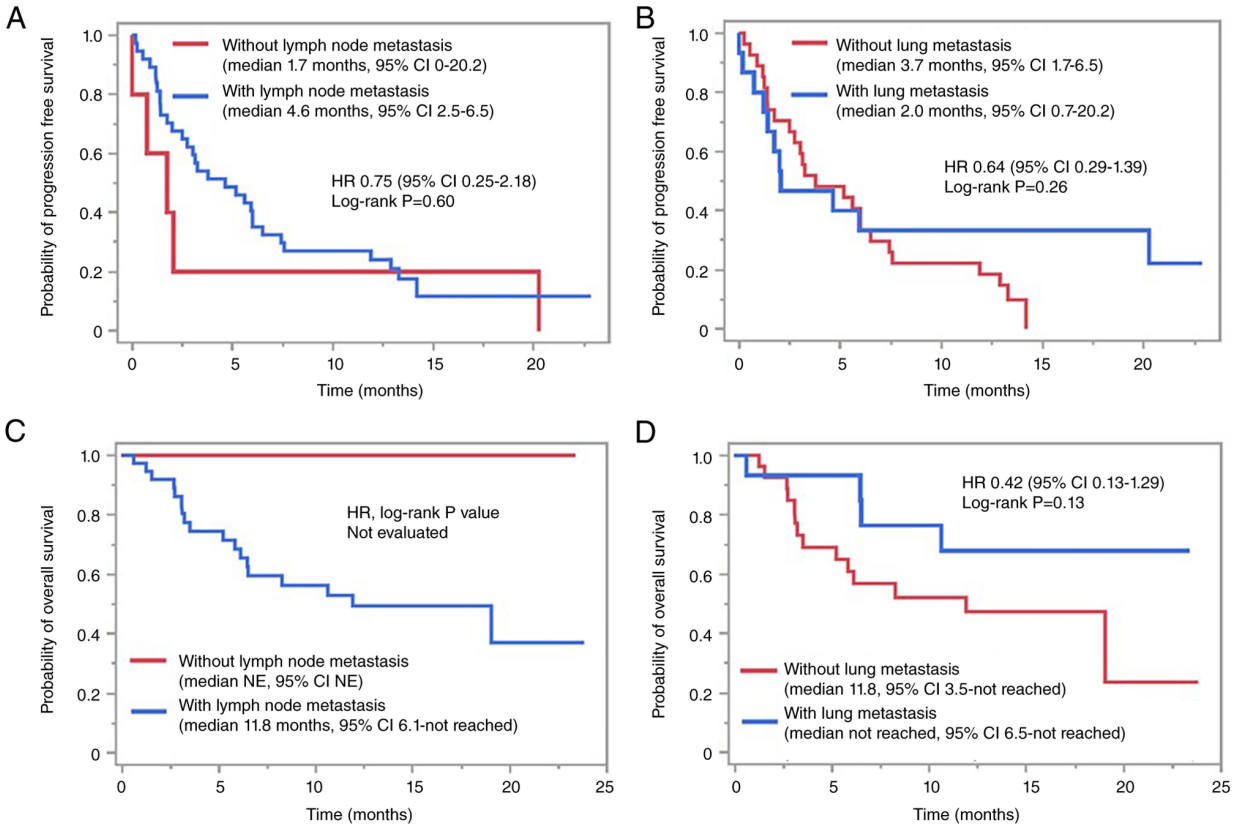

Figure 2. Survival curves for PFS and OS by metastatic organs. Kaplan-Meier analysis of (A) PFS and (C) OS for patients with or without lymph node metastasis; and (B) PFS and (D) OS of patients with or without lung metastasis. PFS, progression-free survival; OS, overall survival; HR, hazard ratio.

Table III. Univariate and multivariate analysis for PFS.

		Univariate analysis		Multivariate analysis	
Variables	Categories	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	≥65 vs. <65	1.22 (0.58-2.58)	0.59		
ECOG PS	≥2 vs. <2	7.23 (1.87-27.95)	<0.01	2.62 (0.42-16.03)	0.29
Smoking	Never vs. Current or past	7.20 (1.54-33.48)	0.01	5.81 (1.07-31.35)	0.04
Alcohol drinking	Yes vs. No	0.55 (0.07-4.15)	0.56		
NLR	≥4 vs. <4	3.33 (1.65-6.73)	<0.01	2.53 (1.21-5.76)	0.02
PNI[a]	≥40 vs. <40	0.58 (0.30-1.15)	0.12		
CAR	≥0.30 vs. <0.30	1.19 (0.48-2.93)	0.70		
Lung metastasis	Yes vs. No	0.64 (0.29-1.39)	0.26		
Lymph node metastasis	Yes vs. No	0.75 (0.25-2.18)	0.60		
Bone metastasis	Yes vs. No	3.63 (1.29-10.2)	0.01	1.27 (0.28-5.65)	0.75
Liver metastasis	Yes vs. No	2.64 (1.28-5.43)	<0.01	2.37 (1.07-5.24)	0.03

[a]PNI=10 x Albumin + 0.005 x Lymphocyte. NLR, neutrophil-lymphocyte ratio; CAR, CRP-albumin ratio; PNI, Prognostic nutritional index; PFS, progression-free survival.

Table IV. Univariate and multivariate analysis for OS.

		Univariate analysis		Multivariate analysis	
Variables	Categories	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	≥65 vs. <65	1.57 (0.51-4.79)	0.42		
ECOG PS	≥2 vs. <2	12.68 (2.07-77.42)	<0.01	5.39 (0.82-35.34)	0.07
Smoking	Never vs. Current or past	3.88 (0.87-17.15)	0.07		
Alcohol drinking	Yes vs. No	0.13 (0.01-1.17)	0.06		
NLR	≥4 vs. <4	3.56 (1.38-9.13)	<0.01	3.15 (1.17-8.49)	0.02
PNI[a]	≥40 vs. <40	0.36 (0.13-0.94)	0.03		
CAR	≥0.30 vs. <0.30	0.82 (0.32-2.11)	0.68		
Lung metastasis	Yes vs. No	0.42 (0.13-1.29)	0.13		
Lymphnode metastasis	Yes vs. No	Unreached	-		
Bone metastasis	Yes vs. No	3.90 (0.77-19.77)	0.09		
Liver metastasis	Yes vs. No	3.28 (1.28-8.40)	0.01	2.75 (1.00-7.53)	0.04

[a]PNI=10 x Albumin + 0.005 x Lymphocyte. NLR, neutrophil-lymphocyte ratio; CAR, CRP-albumin ratio; PNI, Prognostic nutritional index; PFS, progression-free survival.

that liver metastases may attenuate the effects of ICIs (7-11), this is the first report on ESCC to clearly demonstrate this fact.

This study included patients over 70 years of age (22 cases, 52%) and patients with PS2 (3 cases, 7%), both of which were not included in the ATTRACTION-3 trial; however, the treatment efficacy was rather favorable compared to that of the ATTRACTION-3 trial (overall response rate (ORR), 26% vs. 19%; disease control rate (DCR) 78% vs. 37%; median PFS 3.5 vs. 1.7 months; median OS 19.0 vs. 10.9 months). Comparing the patient profile to that of the ATTRACTION-3 trial, this study included fewer non-smokers (5% vs. 14%) and more patients over 65 years of age (71% vs. 47%). There were no marked differences in the proportion of male patients, number of metastatic organs, sites of metastasis, or prior treatment. Smoking history has been reported to affect the efficacy of ICI in non-small cell lung carcinoma (14-16), and it is possible that the small number of non-smokers in this study contributed to this favorable result. Since this was a retrospective study with a small number of patients, coupled with unknown PD-L1 status in most cases, discussing the reasons for more favorable results than in the ATTRACTION-3 trial is constrained by these limitations. Notably, the findings of this study, drawn from real-world data that included a larger proportion of patients in relatively poor condition, were comparable to or better than those of the ATTRACTION-3 trial. Due to the small number of cases in this study, we did not explore the

Table V. Characteristics of immuno-related adverse events (n=42).

Characteristics	All Grade, n (%)	Grade 3/4, n (%)
All events	12 (28)	3 (7)
Events leading to discontinuation	3 (7)	3 (7)
Events leading to death	0	0
Event details		
Rash	4 (9)	0
Diarrhea	2 (4)	0
Fatigue	0	0
Thyroiditis	4 (9)	1 (2)
Pituitaryitis	1 (2)	0
Interstitial pneumonia	2 (4)	2 (4)
Adrenal insufficiency	1 (2)	0

difference in efficacy of nivolumab by the treatment line (2nd vs. 3rd line or later), which should be explored in future studies with larger sample sizes.

IrAEs were observed in 12 cases (28%), most of which were mild. Grade 3 or higher irAEs were observed in 7% of patients, and there were no treatment-related deaths. In patients aged >70, five cases (22.7%) had irAEs of any grade, indicating no increase in irAEs compared to younger patients. Only one case had a grade 3 or higher adverse event (AE) (4%, interstitial pneumonia). Although the retrospective nature of the study may have resulted in an underestimation in assessing AEs, especially the mild ones, we believe that this study provided evidence of the safety of this treatment in real-world clinical practice.

We also examined the predictors of nivolumab monotherapy. In the present study, no smoking history, liver metastasis and high NLR (≥4) were independent poor predictive factors for PFS and NLR and liver metastasis were the same for OS. The confidence of the results for OS, however, needs to be evaluated with caution due to the relatively small number of events in this study. In addition to our results, numerous reports in non-small cell lung have suggested that smokers treated with ICIs have a better prognosis because of their stronger immunogenicity and activated immune microenvironment (14-16). NLR has the advantage of being easily derived from routine blood tests and has proven to be useful as an indicator of systemic immune status (17). Consistent with our findings, several reports have shown that NLR has the potential to be a predictive indicator for patients receiving ICIs for various cancers (18-20). Patients with liver metastases had significantly worse PFS and OS, whereas lung and lymph node metastases showed no clear impact on the efficacy of nivolumab. Furthermore, univariate and multivariate analyses revealed that liver metastasis was an independent predictor of nivolumab monotherapy. Consistent with our findings, Yu *et al*. reported that liver metastases diminished immunotherapy efficacy in patients and preclinical models (7). They demonstrated that the effectiveness of ICIs was attenuated in melanoma and lung cancer patients with liver metastases, contrasting with molecularly targeted therapy or cytotoxic chemotherapy. They also demonstrated that, in a preclinical model, liver metastases induced systemic tumor-specific CD8+ T cell loss through apoptosis following their interaction with activated monocyte-derived macrophages, thereby reducing ICI efficacy. There have been several other reports on the mechanisms of liver metastasis-induced reduction in the efficacy of ICI. Liver metastases cause the loss of tumor-specific effector T cells and loss of function in activated Treg cells and/or liver macrophages (10,11). Recently, it was reported that in the 1st line treatment for ESCC, liver metastases patients tended to develop progression disease early after the initiation of nivolumab plus ipilimumab combination therapy (21). In gastric cancer, hyper progression after ICI therapy is reported to be significantly more common in cases with liver metastasis (8). Therefore, the risk of early disease progression should be also considered when using nivolumab in esophageal cancer patients with liver metastases. Taken together, liver metastasis is a potential biomarker for nivolumab treatment in ESCC. These results should be confirmed in future prospective studies owing to the inherent potential biases of our analyses.

This study had several limitations. The main limitation was that this was a retrospective study with a relatively small sample size and was conducted at a single center. Approximately six (14%) patients were currently undergoing treatment, and 17 (40%) patients were being followed up in the event of death; therefore, the OS data may be immature. Furthermore, most cases in this study could not be evaluated for PD-L1 expression because nivolumab was approved for use regardless of PD-L1 expression.

In conclusion, this study provided real-world data on patients with diverse profiles, such as elderly patients and those with poor PS, unlike the phase 3 ATTRACTION-3 trial, in which nivolumab provided favorable efficacy with no increase in serious irAEs. In this study, liver metastases and NLR were identified as potential predictive biomarkers of nivolumab efficacy in ESCC. Further studies with larger numbers of patients are warranted to validate these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RM and TI confirm the authenticity of all the raw data. RM, TI, TD, JI, DS, NI, KI, HirK, OD, NY, AS, KU, TT, HF, HidK and YI contributed to the study conception and design. RM, TI and TD designed this study. RM contributed to data collection. RM and TI analyzed the data. TD, JI, DS, NI, KI, HirK, OD,

NY, AS, KU, TT, HF, HidK and YI supervised the study. RM and TI wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of Kyoto Prefectural University of Medicine (approval no. ERB-E-42) and conducted following the declaration of Helsinki principles and its amendment. All authors read the final manuscript and approved it for publication. An opt-out approach was employed to obtain informed consent from patients, and personal information was protected during data collection.

Patient consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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