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Long-Term Prognostic Predictors of Esophageal Squamous Cell Carcinoma Potentially Indicated for Endoscopic Submucosal Dissection

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Keywords
Esophageal squamous cell carcinoma · Endoscopic submucosal dissection · Comorbidity

Abstract
Introduction: Patients with esophageal squamous cell carcinoma (ESCC) have various comorbidities. Thus, it is necessary to determine the appropriateness of performing treatment based on the patient's general condition. ***Aim:*** This study aimed to clarify the prognostic predictors of ESCC indicated for endoscopic submucosal dissection (ESD). ***Methods:*** This retrospective study enrolled 241 patients with superficial ESCC endoscopically diagnosed as ESD-indicated lesions at the Nagoya University Hospital between January 2007 and December 2017. We evaluated the 3- and 5-year overall survival (OS) rates and prognostic predictors, such as the Prognostic Nutritional Index (PNI), Charlson Comorbidity Index (CCI), Psoas Muscle Index, and Controlling Nutritional Status score. Furthermore, we created a score-based classification using the prognostic predictors identified by multivariate analysis, and the 3- and 5-year OS rates were compared among the calculated scores. ***Results:*** In the multivariate analysis, PNI < 45 (hazard ratio [HR]: 2.39; 95% confidence interval [CI]: 1.28–4.46; $p = 0.006$) and CCI ≥ 3 (HR: 4.42; 95% CI: 2.40–8.12; $p < 0.001$) were significantly associated with the OS. Based on the HR, 0 and 1 were assigned to PNI and 0, 2, and 4 were assigned to CCI, and the score classification of 0–5 points was created. The 3- and 5-year OS rates in patients with a score 3 were significantly higher than in those with scores 4 and 5. As a result of scoring, the prognosis was stratified; the 3- and 5-year OS rates in patients with scores 4 and 5, that is, CCI ≥ 6, were clearly low, at approximately 10%. ***Conclusions:*** CCI and PNI can be prognostic predictors of patients with superficial ESCC indicated for ESD. Observation without ESD might be an acceptable strategy among patients with CCI ≥ 6.

Introduction

In recent years, studies have attempted to predict prognosis based on the nutritional status and comorbidities of patients with gastrointestinal cancers. As typical prognostic predictors, Prognostic Nutritional Index (PNI), Controlling Nutritional Status (CONUT) score, Psoas Muscle Index (PMI), and Charlson Comorbidity

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Index (CCI) have been reported. The PNI is the nutritional index originally proposed to evaluate the surgical risks of patients with gastrointestinal cancer [1]. Recently, the PNI has been identified as prognostic predictors in patients with gastric cancer, pancreatic cancer, and hepatocellular carcinoma [2–4]. The CONUT score, which was calculated by scoring serum albumin level, lymphocyte count, and total cholesterol level, has also been reported to be associated with prognosis in gastrointestinal cancers [5–7]. PMI, which is calculated by iliopsoas muscle area at the third lumbar vertebrae level and body height, is an index used originally for a sarcopenia criterion in cirrhosis patients [8]. Recent studies revealed that PMI was associated with the long-term results of patients with CKD and pancreatic cancer [9, 10]. CCI, which stratifies the risk of death from comorbidities, has been commonly used to evaluate the clinical outcomes, including prognosis and complications [11–13]. CCI is calculated as the total scores assigned to several comorbidities (e.g., congestive heart failure, myocardial infarction, cerebrovascular disease, diabetes mellitus, CKD, liver disease, solid tumor, leukemia, and AIDS) [14].

Endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma (ESCC) can be performed safely with recent technological advances [15]. Short-term results were reported as 5.0–5.2% for perforation, 0–2.1% for bleeding, and 7.2–11.6% for stenosis [16, 17]. As a long-term prognosis, the 5-year overall survival (OS) rate after ESD has been reported to be >85% [18–20]. However, it is necessary to determine the appropriateness of performing treatment based on the general condition, comorbidity, and nutritional condition, because it is reported that patients with ESCC are likely to have simultaneous and metachronous cancers in other organs as well as the esophagus [21–23]. Although there have been reports on the prognostic predictors of patients with advanced esophageal cancer and additional resection after esophageal ESD, there are no reports on the prognostic predictors of patients with ESCC potentially indicated for ESD [24, 25]. To fill this research gap, this study aimed to clarify the prognostic predictors of ESCC indicated for ESD.

Materials and Methods

Patients and Study Design

In this single-center retrospective study, a total of 243 patients with superficial ESCC diagnosed as invasion depth of mucosa or shallow submucosa (<200 μm) endoscopically and no metastasis by CT scan, for which ESD was potentially indicated, at the Nagoya University Hospital between January 2007 and December 2017 were enrolled [26, 27]. In this study, follow-up for 1 year or longer was defined as long-term follow-up. Two patients whose follow-up periods were within 1 year because of dropout were excluded from this study. In detail, 226 were ESD cases, 10 were observation cases, and 5 were chemoradiotherapy (CRT) cases. Depth of invasion was determined by white light endoscopy and magnifying endoscopy with narrow-band imaging or blue light imaging according to Inoue classification (before 2011) or Japanese Esophageal Society Classification (after 2012) [28, 29]. In patients who were treated multiple times at the Nagoya University Hospital, we chose the first lesion considered to be an index lesion. In our hospital, patients with all-round lesions were indicated for surgery during the study period; thus, they were excluded from the study population. Metastasis was determined using chest and abdominal CT in principle.

Age, sex, preference history (drinking, smoking), pathological results, treatment option, general condition (Eastern Cooperative Oncology Group performance status [ECOG PS], BMI), nutritional status (PNI, CONUT score, and PMI), and comorbidity (CCI) were divided into 2 or more groups, and their association with prognosis was examined. BMI was calculated as weight (kg) divided by height (m) squared. The PNI was calculated as 10 × serum albumin level (g/dL) + 0.005 × lymphocyte count (/mm^3). ECOG PS was classified as PS 0–1 and PS ≥ 2. PNI was classified into 2 groups, namely, PNI <45 and PNI ≥ 45. The CONUT score was classified into 2 groups: normal CONUT 0–1 and malnutrition CONUT ≥ 2. Preference history, BMI, PMI, and CCI were classified into 2 groups using receiver operating characteristic (ROC) curve analysis. Furthermore, score classification was based on items extracted as prognostic predictors, which were identified by multivariate analysis, and the 3- and 5-year OS rates were compared among calculated scores.

This study complied with the Declaration of Helsinki and was approved by the Nagoya University Research Ethics Committee. The choice of treatment option was determined with sufficient informed consent.

Data Collection

Survival information of the enrolled patients was principally obtained from their medical records. In patients who had not been consulted since 2019, their survival or death was confirmed by sending a letter to their referral or home. The follow-up period was defined as the time between the date of the initial ESD of the index lesion and the date of final visit to our hospital, the date of survival confirmed by the letter, or the date of death. In cases without ESD, the follow-up period was started from the date of the initial diagnosis of ESCC. Physical information, comorbidities, blood test data, and CT images within 6 months before the start of the follow-up period were evaluated as valid information. PMI was calculated by measuring the L3 level iliopsoas muscle area on CT images by the manual trace method.

Post-Treatment Evaluation

Curative resection was defined as epithelium (EP) and lamina propria mucosa (LPM) lesions with negative lymphovascular invasion and negative horizontal and vertical margins. Patients with curative resection, EP/LPM lesions with only positive horizontal margin, and muscularis mucosa (MM) lesions with negative lymphovascular invasion and negative horizontal/vertical margin among non-curative resections were categorized into the low-risk group of residual or recurrent cancer. Others were categorized into the high-risk group. The curative resection group was monitored

Table 1. Characteristics of the patients and lesions

	N = 241
Age, median (range), years	69.0 (45–89)
Sex, *n* (%)	
Male	204 (84.6)
Female	37 (15.4)
Follow-up period, median (range), months	56 (4–143)
Location, *n* (%)	
Upper (Ce, Ut)	38 (15.8)
Middle (Mt)	105 (43.6)
Lower (Lt, Ae)	98 (40.7)
Macroscopic type, *n* (%)	
Protruded	6 (2.5)
Flat and depressed	235 (97.5)
Treatment, *n* (%)	
ESD	226 (93.8)
CRT	5 (2.1)
Observation	10 (4.1)
PMI, median (range), cm^2/mm^2	
Male	5.56 (1.69–9.40)
Female	3.56 (2.01–5.89)
PNI, median (range)	48.50 (32.5–67.0)
CONUT score, *n* (%)	
0–1	121 (50.2)
≥2	120 (49.8)
ECOG performance status, *n* (%)	
0–1	226 (93.8)
≥2	15 (6.2)
BMI, median (range)	21.4 (13.4–37.4)
Charlson Comorbidity Index, *n* (%)	
0	58 (24.1)
1	28 (11.6)
2	81 (33.6)
3	45 (18.7)
4	13 (5.4)
5	5 (2.1)
≥6	11 (4.6)
Alcohol intake, median (range), g/day	29 (0–524)
Brinkman index, median (range)	740 (0–3,000)

Ae, abdominal esophagus; Ce, cervical esophagus; CONUT, Controlling Nutritional Status; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; ESD, endoscopic submucosal dissection; Lt, lower thoracic esophagus; Mt, middle thoracic esophagus; PMI, Psoas Muscle Index; PNI, Prognostic Nutritional Index; Ut, upper thoracic esophagus.

Table 2. Pathological characteristics

	N = 226
Tumor size, median (range), mm	20.0 (5–80)
Invasion depth, *n* (%)	
EP	68 (30.1)
LPM	121 (53.5)
MM	25 (11.1)
SM1[a]	6 (2.7)
SM2[b]	6 (2.7)
Horizontal margin, *n* (%)	
Positive	4 (1.8)
Vertical margin, *n* (%)	
Positive	6 (2.7)
Lymphatic invasion, *n* (%)	
Positive	12 (5.3)
Vascular invasion, *n* (%)	
Positive	2 (0.9)
Curative resection, *n* (%)	183 (81.0)
Non-curative resection, *n* (%)	43 (19.0)
	additional therapy 15/43
Low risk, *n* (%)	206 (91.2)
High risk, *n* (%)	20 (8.8)

EP, epithelium; LPM, lamina propria mucosae; MM, muscularis mucosae; SM, submucosal layer. [a] SM1 ≤ 200 μm from MM. [b] SM2 > 200 μm from MM.

by esophagogastroduodenoscopy (EGD) every 6 months. Cases other than curative resection, including the CRT cases, were evaluated for recurrence by EGD at least twice a year and by CT scan at least once a year. Observation cases underwent EGD and CT scan as needed, such as when symptomatic.

Statistical Analysis

Quantitative data are expressed as median (range). OS was defined as the time from the starting date of follow-up to the date of death from any cause or the date of the last survival confirmation. All survival data are shown with 95% confidence intervals (95% CIs). The Kaplan-Meier method was used to evaluate OS rates, and the log-rank test was used to ascertain significance levels. ROC curve analysis was used to define the cutoff value for preference history, BMI, PMI, and CCI. The correlation between age and prognosis was evaluated using Spearman's correlation coefficient. The Cox proportional hazards model was used to calculate hazard ratios (HR). The items that were significant in the univariate analysis were used in the multivariate analysis. $p < 0.05$ was considered statistically significant. The missing data were analyzed using pairwise deletion. All statistical analyses were performed with IBM SPSS version 25.0 (IBM Japan Ltd., Tokyo, Japan).

Results

Patient and Lesion Characteristics

A total of 241 patients were finally enrolled and analyzed. The patient and lesion characteristics are shown in Table 1. The median age of the population was 69.0 years. The median follow-up period was 56 months. The follow-up rates after 1, 2, and 3 years were 96.7% (233/241), 86.7% (209/241), and 68.5% (165/241), respectively. The male-to-female sex ratio was 6:1. The median PMI was

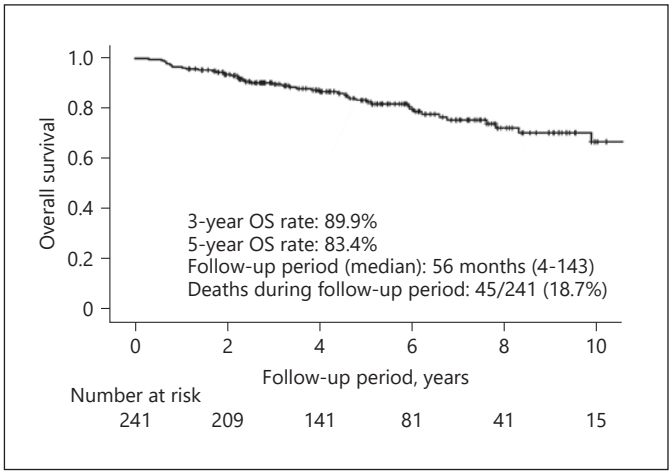

Fig. 1. The 3- and 5-year overall survival (OS) rates of all patients were 89.9 and 83.4%, respectively. Deaths during the follow-up period were observed in 45/241 (18.7%) cases, with 10 deaths from esophageal cancer and 35 deaths from other causes.

Table 3. Causes of death in enrolled patients

	N = 45
Deaths from esophageal cancer, *n* (%)	10 (22.2)
Deaths from other causes, *n* (%)	35 (77.8)
Other organ malignancy, *n* (%)	27 (60.0)
Pharyngeal cancer, *n* (%)	9 (20.0)
Lung cancer, *n* (%)	6 (13.3)
Hepatocellular carcinoma, *n* (%)	4 (8.9)
Gastric cancer, *n* (%)	2 (4.4)
Cholangiocarcinoma, *n* (%)	2 (4.4)
Pancreatic cancer, *n* (%)	1 (2.2)
Tongue cancer, *n* (%)	1 (2.2)
Malignant lymphoma, *n* (%)	1 (2.2)
Cancer of unknown primary, *n* (%)	1 (2.2)
Pneumonia	3 (6.7)
Urinary tract infection, *n* (%)	1 (2.2)
Cerebral infarction, *n* (%)	1 (2.2)
Aortic dissection, *n* (%)	1 (2.2)
Gastrointestinal bleeding, *n* (%)	1 (2.2)
Decrepitude, *n* (%)	1 (2.2)

5.53 for men and 3.56 for women, and the median BMI was 21.4, indicating a lean tendency.

Pathological Result of ESD

The pathological results obtained from ESD specimens are shown in Table 2. The rate of EP/LPM lesions was 83.6%. The rates of positive horizontal margin, positive vertical margin, lymphatic invasion, and vascular invasion were 1.8, 2.7, 5.3, and 0.9%, respectively. There were 183 curative resections and 43 non-curative resections. Of the 43 non-curative resections, 15 patients received additional treatment, surgery, or CRT. Of the 226 ESD cases, 206 cases belonged to the low-risk group and the remaining 20 cases belonged to the high-risk group.

Survival

In all patients, the 3- and 5-year OS rates were 89.9 and 83.4%, respectively. Deaths during the follow-up period were observed in 45/241 (18.7%) cases, with 10 deaths from ESCC and 35 deaths from other causes (Fig. 1). Causes of death in the enrolled patients are shown in Table 3. Of the deaths from other causes, 27 cases were death from other organ malignancy, and 3 cases were death from pneumonia. In the observation and CRT cases, no one died of esophageal cancer.

The optimal CCI cutoff value for predicting prognosis was defined as CCI ≤ 2 and CCI ≥ 3 using ROC curve analysis. The 3- and 5-year OS rates in patients with CCI ≤ 2 (96.2 and 91.5%, respectively) were significantly higher than in those with CCI ≥ 3 (75.4 and 64.8%, respectively, $p < 0.001$). ECOG PS was classified as PS 0–1 and PS ≥ 2. The 3- and 5-year OS rates in patients with PS 0–1 (91.9 and 85.1%, respectively) were significantly higher than in those with PS ≥ 2 (57.8 and 57.8%, respectively, $p < 0.001$). PNI was classified into 2 groups, namely, PNI <45 and PNI ≥ 45. The 3- and 5-year OS rates in patients with PNI ≥ 45 (92.5 and 87.0%, respectively) were significantly higher than in those with PNI < 45 (78.3 and 67.5%, respectively, $p = 0.001$). The CONUT score was classified into 2 groups: normal CONUT 0–1 and malnutrition CONUT ≥ 2. The 3- and 5-year OS rates in patients with CONUT 0–1 (95.0 and 88.9%, respectively) were significantly higher than in those with CONUT ≥ 2 (84.2 and 77.4%, respectively, $p = 0.026$). Treatment options were classified into 3 groups: ESD group, CRT group, and observation group. The 3- and 5-year OS rates in patients in ESD group (95.1 and 89.0%, respectively) were significantly higher than in those in CRT group (40.0 and 20.0%, respectively, $p < 0.001$) and observation group (0 and 0%, respectively, $p < 0.001$) (Fig. 2a–e). No significant differences in prognosis rates were found among other study items.

Prognostic Predictors for OS

The prognostic predictors for OS are shown in Table 4. In the univariate analysis with the Cox proportional hazards model, ECOG PS ≥ 2 (HR: 4.36; 95% CI: 1.82–9.84; $p = 0.001$), PNI < 45 (HR: 2.81; 95% CI: 1.52–5.19; $p = 0.001$), CONUT ≥ 2 (HR: 1.96; 95% CI: 1.07–3.57; $p = 0.028$), and CCI ≥ 3 (HR: 4.74; 95% CI: 2.59–8.66; $p <$

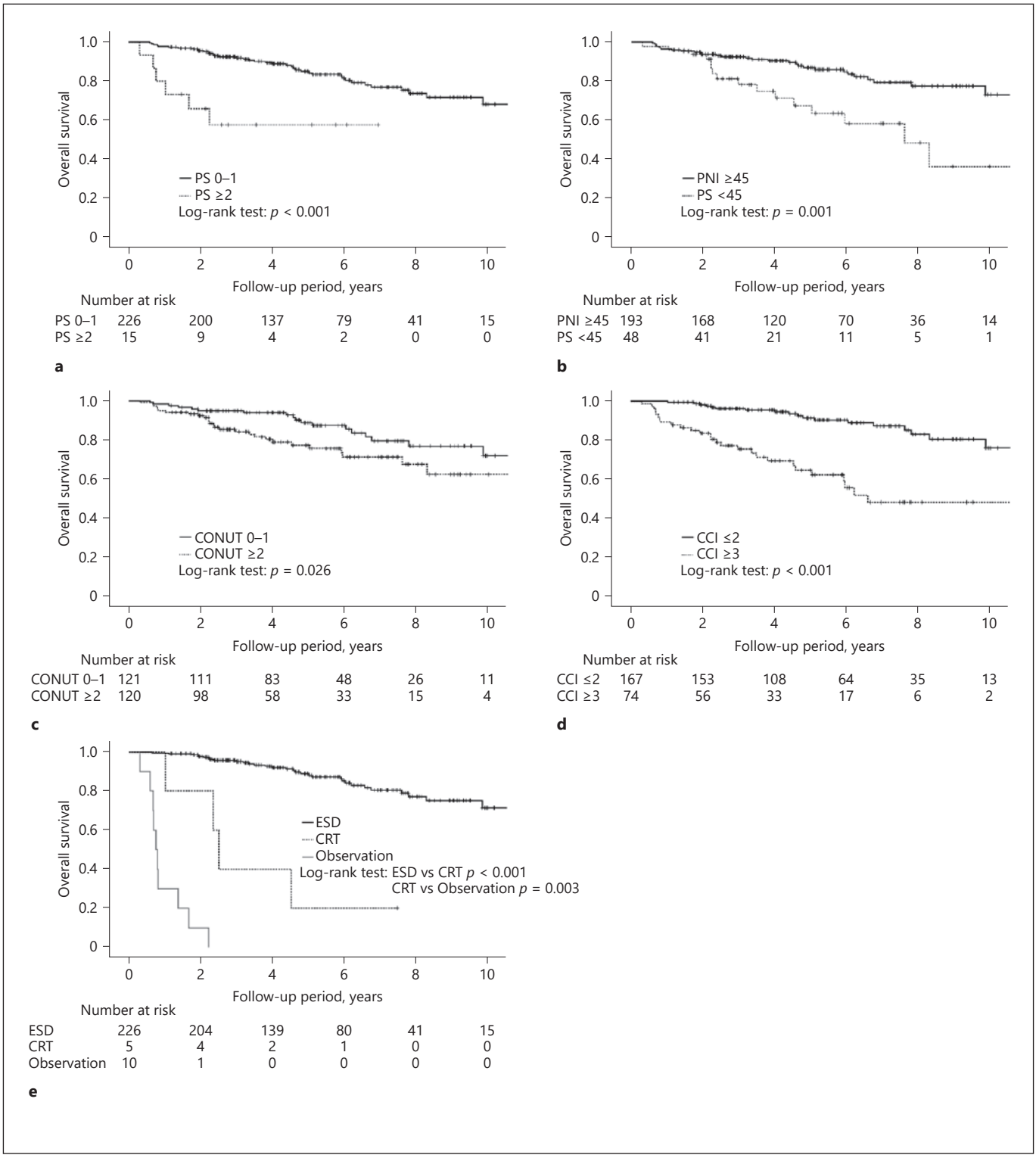

Fig. 2. a Overall survival (OS) rates comparing patients with Performance Status (PS) 0–1 and PS ≥ 2. **b** OS rates comparing patients with Prognostic Nutritional Index (PNI) ≥ 45 and PNI < 45. **c** OS rates comparing patients with Controlling Nutritional Status (CONUT) score 0–1 and CONUT score ≥2. **d** OS rates comparing patients with Charlson Comorbidity Index (CCI) ≤ 2 and CCI ≥ 3. **e** OS rates comparing patients with each treatment option: endoscopic submucosal dissection (ESD), chemoradiotherapy (CRT), and observation.

Table 4. Prognostic predictors for overall survival

	Patients, *n*	Deaths, *n*	Univariate analysis			Multivariate analysis		
			HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years								
Continuous variable	241	45	1.01	0.97–1.05	0.676			
Sex								
Female	37	6	0.76	0.32–1.80	0.531			
Male	204	39	1					
Alcohol intake, g/day								
≥23	130	28	1.58	0.82–3.05	0.176			
<23	91	13	1					
Brinkman index								
≥890	85	19	1.25	0.68–2.26	0.473			
<890	140	25	1					
Curability								
High risk	20	2	0.96	0.23–4.06	0.959			
Low risk	206	29	1					
ECOG PS								
≥2	15	6	4.36	1.82–9.84	0.001	2.09	0.81–5.39	0.126
0–1	226	39	1			1		
BMI								
≥21.8	110	21	1.09	0.61–1.96	0.775			
<21.8	131	24	1					
PNI								
<45	48	16	2.81	1.52–5.19	0.001	2.39	1.28–4.46	0.006
≥45	193	29	1			1		
CONUT score								
≥2	120	27	1.96	1.07–3.57	0.028	1.05	0.52–2.12	0.90
0–1	121	18	1			1		
PMI								
<Male: 5.68, Female: 4.16	132	23	0.99	0.53–1.81	0.964			
≥Male: 5.68, Female: 4.16	102	19	1					
CCI								
≥3	74	27	4.74	2.59–8.66	<0.001	4.42	2.40–8.12	<0.001
≤2	167	18	1			1		

The *p* value was calculated by Cox hazards regression analysis. CCI, Charlson Comorbidity Index; CI, confidence interval; CONUT, Controlling Nutritional Status; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; PMI, Psoas Muscle Index; PNI, Prognostic Nutritional Index.

0.001) were significantly associated with OS. In the multivariate analysis, PNI < 45 (HR: 2.39; 95% CI: 1.28–4.46; $p = 0.006$) and CCI ≥ 3 (HR, 4.42; 95% CI, 2.40–8.12; $p < 0.001$) were significantly associated with OS. There was little correlation between age and prognosis.

We performed another analysis based on the results of the multivariate analysis. CCI was further divided into 3 groups: CCI 0–2, low CCI group; CCI 3–5, moderate CCI group; and CCI ≥ 6, high CCI group. Based on the HR, PNI ≥ 45 was assigned 0 points, PNI < 45 was 1 point, and the low, moderate, and high CCI groups scored 0, 2, and 4 points, respectively. A score-based classification of 0–5 points was created. The 3- and 5-year OS rates in patients with a score 0 (97.7 and 93.3%, respectively) were significantly higher than in those with a score 1 (88.0 and 81.7%, respectively, $p = 0.016$) and a score 2 (90.7 and 80.5%, respectively, $p = 0.005$). The 3- and 5-year OS rates in patients with a score 3 (77.9 and 58.4%, respectively) were significantly higher than in those with a score 4 (12.5 and 12.5%, respectively, $p < 0.001$) and a score 5 (0 and 0%, respectively, $p < 0.001$) (Fig. 3).

Discussion/Conclusion

To the best of our knowledge, this is the first report to examine prognostic predictors including PNI, PMI, and CCI for superficial ESCC for which ESD was potentially

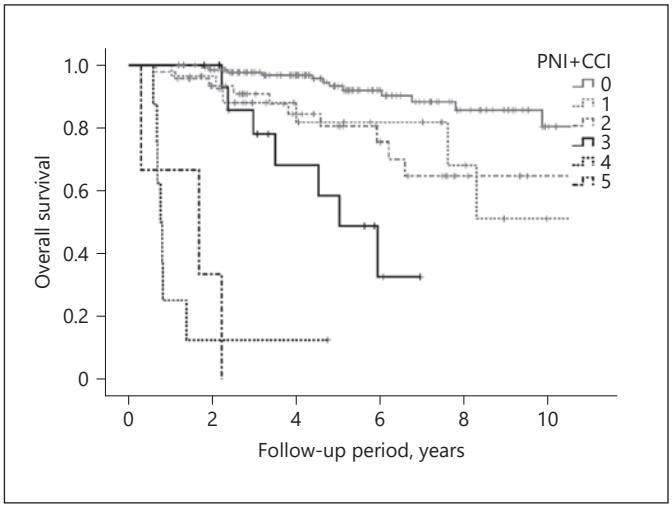

Fig. 3. Based on the hazard ratio, Prognostic Nutritional Index (PNI) ≥ 45 was assigned 0 points, PNI < 45 was 1 point, and the low, moderate, and high Charlson Comorbidity Index (CCI) groups scored 0, 2, and 4 points, respectively. A score classification of 0–5 points was created. The 3- and 5-year overall survival (OS) rates in patients with a score 0 (97.7 and 93.3%, respectively) were significantly higher than in those with a score 1 (88.0 and 81.7%, respectively, $p = 0.016$) and a score 2 (90.7 and 80.5%, respectively, $p = 0.005$). The 3- and 5-year OS rates in patients with a score 3 (77.9 and 58.4%, respectively) were significantly higher than in those with a score 4 (12.5 and 12.5%, respectively, $p < 0.001$) and a score 5 (0 and 0%, respectively, $p < 0.001$).

indicated. Studies on the prognostic predictors of ESD include reports that PNI, CCI, and PS were extracted as prognostic predictors for ESD of early gastric cancer for elderly patients [30]. In this study, PNI and CCI were finally extracted as prognostic predictors in the multivariate analysis. Therefore, we clarified that PNI and CCI are important prognostic predictors before ESD for ESCC. The Registration Committee for Esophageal Cancer of the Japan Esophageal Society reported that the 3- and 5-year OS rates after ESD treatment were 91.0 and 86.0%, respectively [18]. Because no difference was found from the OS results of this study, our findings would be generally applicable to the whole Japanese cohort.

In this study, based on the HR, PNI ≥ 45 was assigned 0 points, PNI < 45 was 1 point, and the low, moderate, and high CCI groups scored 0, 2, and 4 points, respectively. A score classification of 0–5 points was created. In the high-risk group with scores 4 and 5, that is, CCI ≥ 6, the 3- and 5-year OS rates were clearly low, at approximately 10%. Most cases with CCI ≥ 6 have comorbidities across multiple organs or solid cancer with distant metastasis. CCI is an index proposed in 1987 [14]. Medical progress has improved treatment outcomes for each disease, and an increase in controllable comorbidities and prognosis extension of solid cancer with distant metastasis have been achieved. Although the reconstruction of CCI may be necessary in the future, this study clarifies that the current CCI can be a sufficient prognostic predictor.

Guanrei et al. [31] reported that superficial ESCC progresses to advanced cancer in 4–5 years in the natural history. Until an esophageal tumor becomes advanced cancer, stenosis is unlikely to occur, with little influence on the patient's quality of life [32]. Observation without esophageal ESD is considered an accepted treatment strategy for patients at a high risk of death from other diseases within 3–4 years. Because the 3- and 5-year OS rates in the high-risk group with CCI ≥ 6 were clearly low at approximately 10%, observation strategy without ESD for superficial ESCC might be an acceptable option among patients with CCI ≥ 6.

The PNI was originally designed to evaluate the nutritional and immunological status of patients undergoing surgical treatment for gastrointestinal diseases [33]. However, the original PNI required various parameters and was complicated to calculate. Therefore, Onodera et al. [1] proposed the modified PNI, which was calculated using the serum albumin level and lymphocyte count in the peripheral blood. They reported that the incidence of postoperative complications was higher in patients with a low PNI than in those with a high PNI [1]. Recently, studies have reported the importance of the PNI in the long-term outcomes of several malignancies [2–4]. The cutoff value is usually specified at 45, since PNI < 45 is defined as moderate to severe malnutrition. In this study, the cutoff value of PNI was set to 45, as previously reported, and was extracted as a significant prognostic predictor.

In this study, not only ESD cases but also lesions that were technically possible to undergo ESD including observation and CRT cases were included in the population. The clinical issue was the appropriateness of performing ESD at the time of diagnosis of superficial ESCC. Therefore, we aimed to evaluate the prognostic factors at the time of diagnosis of superficial ESCC potentially indicated for ESD: before selecting treatment option. Examining the comparison among the treatment options, the 3- and 5-year OS rates in patients in ESD group were significantly higher than in those in CRT group and observation group. However, treatment options were not included in the examination items of the multivariate analysis in this study, because a strong selection bias was considered to have occurred during the selection of treatment method. In other words, CRT and observation were selected be-

cause we considered that the prognosis would be clinically poor from the beginning at the time of selecting treatment method. In fact, all patients in CRT group had advanced pharyngeal cancer, and all in observation group had severe comorbidities. The prognosis of the group selected for observation was still poor; thus, this result might support the fact that the empirically established clinical selection was not significantly inappropriate.

In this study, we found little correlation between age and prognosis. The reported incidence of multiple primary cancers in patients with ESCC was 10–30%, suggesting that even young patients have limited survival time due to comorbidities [21–23]. BMI and PMI were also examined, but they were not associated with prognosis. Patients with ESCC tend to be originally leaner, and some studies reported that increasing BMI can reduce the risk of ESCC [34, 35]. Average value −2 SD in PMI (male 6.36, female 3.92) for healthy subjects aged <50 years has been proposed as the standard of low skeletal muscle mass in Japanese [8]. The median PMI in this study was 5.53 for men and 3.56 for women, and more than half of the subjects were judged to have low skeletal muscle mass. In other diseases, PMI has been reported to be useful as a prognostic predictor. Since sarcopenia was a fundamental factor for patients with ESCC, we considered that there was no association between PMI and prognosis.

This study had some limitations. First, this was a single-center retrospective study, and the number of cases was relatively small. In particular, there were few CRT cases and observation cases. Second, the treatment strategy for esophageal cancer was determined at the discretion of the attending physician and the patient. These facts may cause selection bias. However, in the observation cases and CRT cases, all the causes of death were the diseases other than esophageal cancer, so it appears that there was little association between treatment choice and prognosis. Therefore, PNI and CCI remain important prognostic predictors, and our study supports the importance of pre-treatment status. Third, since we have not examined physiological function tests including respiratory function tests in this study, there could be hidden prognostic factors.

In conclusion, CCI and PNI can be used as prognostic predictors of patients with superficial ESCC for which ESD is recommended. Moreover, observation strategy without ESD for superficial ESCC might be an acceptable option among patients with CCI ≥ 6, because this population is at a high risk of mortality from other causes prior to the appearance of symptoms associated with the progression of esophageal cancer.

Statement of Ethics

All study participants provided informed consent, and the study design was approved by the appropriate ethics review board of the Nagoya University Hospital (IRB No. 2015-0485).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.S. drafted and wrote the manuscript. The acquisition of the data was performed by K.F., E.I., T.S., K.M., T.Y., T.I., E.O., M.N., and H.K. T.S. analyzed the data. K.F. and M.F. revised the manuscript. M.F. gave the final approval of the manuscript.

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