

# Prognostic value of pre-treatment maximum standardized uptake value and CRP in radiotherapy of esophageal cancer

HARUKA JINNOUCHI, HIDEOMI YAMASHITA, TOMOKI KIRITOSHI, YOSUKE MIKI,  
ATSUTO KATANO, KEIICHI NAKAGAWA and OSAMU ABE

Department of Radiology, University of Tokyo Hospital, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

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**Abstract.** The aim of the present study was to evaluate the prognostic value of the pre-treatment maximum standardized uptake value ( $SUV_{max}$ ) and CRP in patients who underwent chemoradiotherapy for esophageal squamous cell carcinoma. A retrospective review of 69 consecutive patients with esophageal cancer who underwent concurrent chemoradiotherapy between 2013 and 2016 was performed. The total radiotherapy doses were 50, 50.4 or 60 Gy. The endpoints of the present study were overall survival (OS) and disease-free survival (DFS). The median follow-up for censored cases was 45.7 months. In 56 patients,  $^{18}F$ -fluorodeoxyglucose positron emission tomography was performed within 1 month prior to chemoradiotherapy. Data on CRP within 1 month prior to chemoradiotherapy were available for all patients. In the group of  $SUV_{max} > 12.85$ , the rates of 2-year OS and DFS were 49.0 and 35.7%, respectively. In the group of  $SUV_{max} \leq 12.85$ , these values were 72.4 and 67.1%, respectively ( $P=0.048$  and  $P=0.057$ , respectively). In the group of  $CRP \geq 1$  mg/dl, these percentages were 38.5 and 25.0%, respectively. In the group of  $CRP < 1$  mg/dl, these rates were 71.2 and 59.7%, respectively ( $P=0.013$  and  $P<0.001$ , respectively). A multivariate analysis revealed that pre-treatment serum CRP levels remained an independent prognostic factor for both OS and DFS [OS: hazard ratio (HR), 0.25,  $P=0.001$ ; DFS: HR, 0.28,  $P=0.005$ ]. In conclusion, high  $SUV_{max}$  was associated with lower OS, while high CRP was associated with lower OS and DFS.

## Introduction

Esophageal cancer is associated with poor prognosis and has a 5-year survival rate of 17-34% (1). Therefore, obtaining information on the expected prognosis is important to ensure that more intensive treatment can be provided to patients with poor

prognoses. For example, a phase III trial (NEOCRTEC5010) compared the safety and survival outcomes of surgery alone with those of neoadjuvant chemoradiotherapy (CRT) followed by surgery. The results showed improved overall survival (OS) and disease-free survival (DFS) in patients who underwent the combined treatment (2). Nevertheless, esophagectomy after CRT has been linked to a high risk of complications and treatment-related mortality (3,4). Therefore, the availability of additional information regarding the prediction of patient prognosis would allow the provision of more suitable treatments.

The maximum standardized uptake value ( $SUV_{max}$ ) is broadly used for the semiquantitative measurement of the maximum  $^{18}F$ -2-fluorodeoxyglucose ( $^{18}F$ -FDG) uptake. This value is determined using positron emission tomography (PET) with computed tomography (CT). Since the  $^{18}F$ -FDG reflects tumor glucose metabolism, the SUV is used as a surrogate marker for tumor metabolism (5). Several studies have documented the value of a PET scan for assessing the prognosis of esophageal, head and neck, and non-small-cell lung cancer (1,6-8).

It is established that chronic inflammation induces carcinogenesis and progression of cancer (9). C-reactive protein (CRP) belongs to a family of acute-phase proteins whose plasma concentrations increase in response to inflammation. Following the occurrence of inflammation in tissue cells, CRP is secreted from the liver into the blood (10). Notably, it is upregulated by pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-8, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (11). Several studies have shown that the elevation of pre-treatment CRP levels is a significant prognostic indicator in patients with esophageal cancer and tends to correlate with TNM staging (12,13). Jurisic *et al* (14) have shown that TNF- $\alpha$  is also increased in certain types of tumors. Although other markers, such as IL-1 $\beta$ , IL-6, IL-8, IL-10, and monocyte chemoattractant protein-1 (MCP-1), are used in the diagnosis of cancer (15), CRP appears to be a rapid, simple, and cost-effective predictor in clinical practice.

Moreover, Chen *et al* (16) revealed that elevated levels of CRP are associated with a high metabolic rate and proliferative activity (measured according to the  $SUV_{max}$ ) in head and neck carcinoma.

In this study, we aimed to retrospectively evaluate the prognostic values of pre-treatment  $SUV_{max}$  of  $^{18}F$ -FDG-PET and CRP in radiotherapy (RT) of esophageal cancer.

**Correspondence to:** Dr Hideomi Yamashita, Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan  
E-mail: yamachan07291973@yahoo.co.jp

**Key words:** esophageal cancer, radiotherapy, maximum standardized uptake value, CRP, prognostic factor

## Materials and methods

**Study participants.** We retrospectively (March 2013-December 2016) researched patients with esophageal squamous cell cancer, which was detected with CT scans at the University of Tokyo Hospital. The clinical TNM stage was determined according to the 7th edition of the American Joint Committee on Cancer staging in esophageal cancer. All patients underwent RT with or without chemotherapy.

**Treatment.** RT was performed using 6-10 MV photon linear accelerators at doses of 50-60 Gy. The irradiation method was either three-dimensional conformal RT or intensity-modulated RT. The gross tumor volume was defined based on the results of the CT scan, endoscopy, and PET scan, if available. The treatment fields encompassed the tumor bed with 3-5 cm proximal and distal margins and 2 cm lateral margins. Involved-field RT (IFRT) was conducted.

**Measurement of CRP.** Serum CRP levels were measured in peripheral venous blood samples using a latex turbidimetric immunoassay on day 1 of RT.

**Measurement of  $SUV_{max}$ .** PET-CT was conducted within 2 weeks prior to the initiation of RT using Aquiduo PCA-7000B (Toshiba Medical Systems Corp.). This system consists of a 16-detector row CT scanner and a lutetium oxyorthosilicate-based PET scanner. Patients, fasted for  $\geq 5$  h, received 4.5 MBq/kg (minimum: 180 MBq; maximum: 405 MBq) of  $^{18}F$ -FDG. Data were acquired 60 min after injection. The PET images were captured in the three-dimensional acquisition mode at eight bed positions from the knee to the skull. Transmission imaging was performed using CT (120 kV, 50 mA, 0.5 sec, helical scan) with an axial field of view of 50 cm and matrix size of 512x512. The CT images were reconstructed using true cone-beam tomography. The PET images were iteratively reconstructed using Fourier rebinning and ordered subset expectation maximization for 14 subsets and four iterations.

Regions of interests, representing the areas in the lesions showing the highest accumulation of  $^{18}F$ -FDG, were drawn on the fused PET/CT image. The  $SUV_{max}$  was measured in the regions of interest. The  $SUV_{max}$  was calculated using the following formula:

$$SUV_{max} = \frac{\text{maximum tissue concentration (MBq/g)}}{\text{injected activity (MBq)/body weight (g)}}$$

**Statistical analysis.** OS and DFS were set as clinical outcomes. Statistical analysis was performed using the EZR version 1.38 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). The  $\chi^2$  test and Fisher's exact probability test were used to compare data between the two groups. The Receiver Operating Characteristic (PPV) and negative predictive value (NPV) in patients who had OS event. Univariate analysis was conducted using the Kaplan-Meier method. The statistical significance of differences between survival curves was examined using the log-rank test. Multivariate analysis was performed using the

Cox proportional hazards regression model. Carriable selection of step-wise method with Bayesian information criterion was conducted. Univariate and multivariate analyses were considered significant at  $P < 0.05$ .

## Results

**Patient characteristics.** A total of 69 consecutive patients were included in this analysis. Patient characteristics are shown in Table I. The median age of patients was 65 years (range: 44-95 years); 53 and 16 patients were males (76.8%) and females (23.2%), respectively. Concurrent chemotherapy consisted mainly of nedaplatin (NDP) and tegafur/gimeracil/oteracil (TS-1); another regimen included cisplatin (CDDP) and 5-fluorouracil (5-FU). Two patients (2.9%) underwent only RT. A total of 62 patients (89.8%) received radiation doses of 50.4 Gy/28 Fr or 50 Gy/25 Fr, and seven patients (10.1%) received doses of 60 Gy/30 Fr. The majority of patients ( $N=58$ ; 84%) had clinical T stage 3 or 4 disease. The most common primary site was the middle thoracic esophagus in 39 patients (56.5%).

According to the  $\chi^2$  test and Fisher's exact probability test, patients with advanced T stage showed higher CRP ( $P=0.03$ ) and  $SUV_{max}$  ( $P < 0.01$ ) (Table II).

**Cut-off levels.** Data on the pre-therapeutic  $SUV_{max}$  were available in 56 patients (81.2%). The median  $SUV_{max}$  was 12.85 (0-31). Therefore, the patients were divided into two groups:  $SUV_{max} > 12.85$  (28 patients, 50%) and  $SUV_{max} \leq 12.85$  (28 patients, 50%). Data on the pre-therapeutic levels of CRP were available for all patients. The median CRP was 0.18 mg/dl ( $< 0.02$ -31 mg/dl). According to the ROC curve (Fig. 1), 0.790 mg/dl would be suitable cut-off with sensitivity of 67%, specificity of 78%, PPV of 52% and NPV of 87%. But we classified patients into two groups: CRP  $\geq 1$  mg/dl (20 patients, 29%) and CRP  $< 1$  mg/dl (49 patients, 71%). The reason we chose CRP level of 1 mg/dl as cut-off level of CRP, which is close to 0.790 mg/dl, is to make it easier for clinical use.

**Survival.** The median follow-up for censored cases was 45.7 months (3.1-68.9 months). The 2-year OS and DFS rates for all enrolled patients were 61.6% [95% confidence interval (CI): 48.6-72.3%] and 49.5% (95% CI: 37.1-60.8%), respectively. According to the comparison of the Kaplan-Meier curves using a log-rank test ( $P=0.05$ ), the OS was significantly worse in the  $SUV_{max} > 12.85$  group than in the  $SUV_{max} \leq 12.85$  group, with median survivals of not applicable versus 14.3 months, respectively. The DFS was worse in the elevated  $SUV_{max}$  group; however, the difference was not statistically significant ( $P=0.06$ ) (Fig. 2A). The OS and DFS were significantly worse in the CRP  $\geq 1$  mg/dl group than in the CRP  $< 1$  mg/dl group ( $P=0.01$  and  $P < 0.001$ , respectively) (Fig. 2B). Similarly, the OS and DFS were significantly worse in the elevated CRP and  $SUV_{max}$  groups ( $P=0.01$  and 0.003, respectively) (Fig. 2C).

**Correlation between CRP levels/ $SUV_{max}$  levels and survival.** In a univariate analysis, age, CRP,  $SUV_{max}$ , and CRP+ $SUV_{max}$  were prognostic factors for OS (Table III). Age, CRP, and

Table I. Patient characteristics.

Characteristic	Value
Age, years	
Range	44-95
Median	65
<75, n (%)	58 (84.1)
≥75, n (%)	11 (15.9)
Sex, n (%)	
Male	53 (76.8)
Female	16 (23.2)
Chemotherapy, n (%)	
NDP/TS1	62 (89.8)
CDDP/5-FU	5 (7.2)
None	2 (2.9)
RT dose, n (%)	
60 Gy	7 (10.1)
50.4 Gy	53 (76.8)
50 Gy	9 (13.0)
cStage, n (%)	
I	7 (10.1)
II	4 (5.8)
III	41 (59.4)
IV	17 (24.6)
Primary site, n (%)	
Ce	10 (14.5)
Ut	9 (13.0)
Mt	39 (56.5)
Lt	8 (11.6)
EGJ	3 (4.3)

NDP, nedaplatin; TS1, tegafur/gimeracil/oteracil; CDDP, cisplatin; 5-FU, 5-fluorouracil; Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; EGJ, esophagogastric junction.

Table II.  $\chi^2$  test and Fisher's exact probability test.

Variable	CRP ≥1 mg/dl, n	CRP <1 mg/dl, n	P-value
Age, years			0.28 <sup>a</sup>
<75	15	43	
≥75	5	6	
Sex			0.39 <sup>b</sup>
Male	14	39	
Female	6	10	
Stage			0.03 <sup>a</sup>
I-II	0	11	
III-IV	20	38	
Primary site			0.77 <sup>b</sup>
Ce-Ut	6	13	
Mt-EGJ	14	36	

<sup>a</sup>Fisher's exact test. <sup>b</sup> $\chi^2$  test. Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; EGJ, esophagogastric junction.

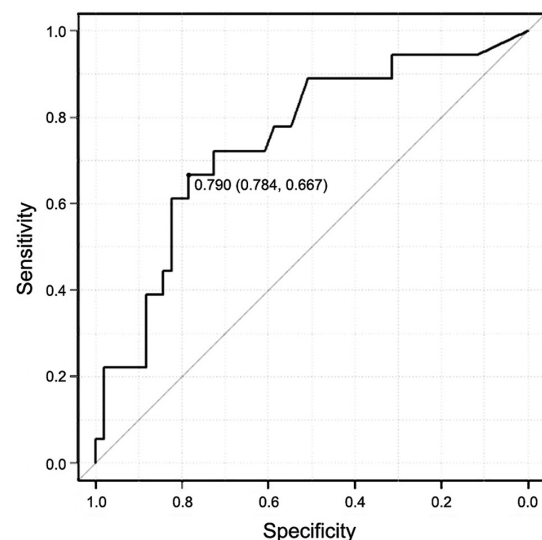


Figure 1. ROC curve of CRP. The area under the curve was 0.747 (95% confidence interval, 0.611-0.883). The cut-off level was 0.790 (sensitivity, 66.7%; specificity, 78.4%). ROC, receiver operating characteristic.

CRP+SUV<sub>max</sub> were also prognostic factors for DFS (Table IV). A multivariate analysis revealed that the pre-treatment serum CRP levels remained an independent prognostic factor for both OS and DFS (Table V). CRP levels also remained in the final model employing carriage selection of step-wise method with Bayesian information criterion for both OS and DFS (OS: Hazard ratio [HR]; 0.25, 95% CI; 0.08-0.76, P=0.01, DFS: HR; 0.28, 95% CI; 0.12-0.69, P<0.01).

## Discussion

In this study, a univariate analysis revealed that pre-treatment CRP is a prognostic factor for OS/DFS, while SUV<sub>max</sub> is a prognostic factor for OS.

The CRP may be a prognostic factor due to following mechanism. IL-6 is thought to correlate with CRP (11), and it has been confirmed that an IL-6 signaling pathway stimulates cancer progression through the IL-6 receptor on the surface of prostate cancer cells (17). It is possible that a similar process

occurs in esophageal cancer. However, further investigation is warranted to confirm this hypothesis. It has been demonstrated that the SUV<sub>max</sub> correlates with tumor aggressiveness in patients with head and neck cancer (18). This may explain its prognostic value in esophageal cancer.

Although a few studies have shown a correlation between the serum CRP levels/SUV<sub>max</sub> and OS/DFS in esophageal cancer, esophagectomy was performed in most of them (Table VI) (6,12,13,19,20). This is one of a few studies showing the prognostic value of the pre-treatment SUV<sub>max</sub> of <sup>18</sup>F-FDG-PET and serum CRP levels in RT of esophageal cancer.

Accurate prediction of prognosis before treatment would permit the provision of more intensive care. This would

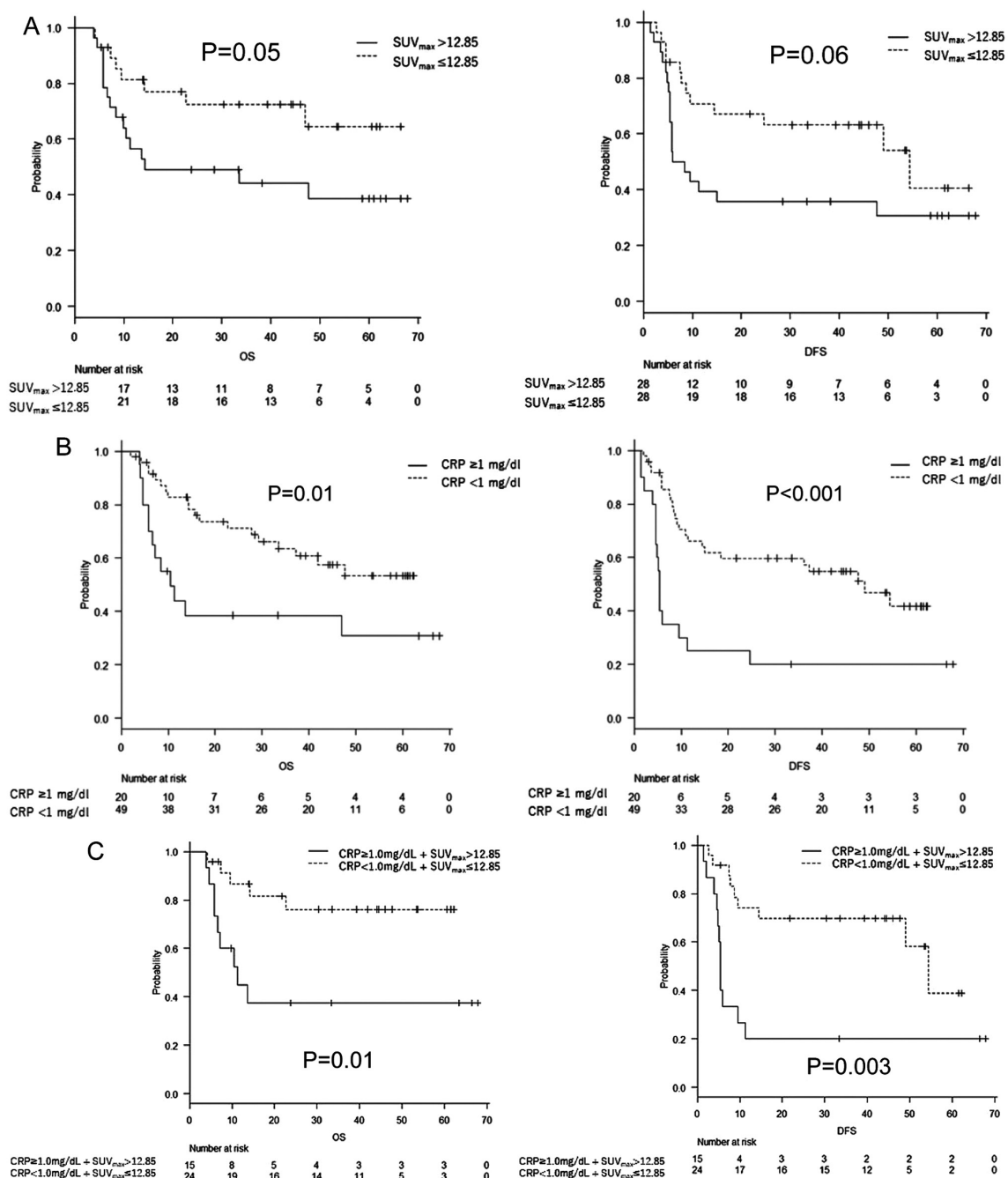


Figure 2. Survival. (A) OS and DFS according to  $SUV_{max}$ . The OS was significantly worse in the  $SUV_{max} >12.85$  group than in the  $SUV_{max} \leq 12.85$  group. (B) OS and DFS according to CRP. The OS and DFS were significantly worse in the  $CRP \geq 1$  mg/dl group than in the  $CRP < 1$  mg/dl group ( $P=0.01$  and  $P<0.001$ , respectively). (C) OS and DFS according to CRP and  $SUV_{max}$ . The OS and DFS were significantly worse in the elevated CRP and  $SUV_{max}$  groups ( $P=0.01$  and  $P=0.003$ , respectively). DFS, disease-free survival; OS, overall survival;  $SUV_{max}$ , maximum standardized uptake value.

include the addition of more cycles of chemotherapy as adjuvant treatment, use of more intensive concurrent chemotherapy regimens (e.g., docetaxel/CDDP/5-FU [DCF]), more careful observation after CRT (e.g., monthly endoscopy or CT), and consideration of salvage esophagectomy.

Higuchi *et al* (21) reported high effectiveness of concurrent CRT using DCF (DCF-R) in a phase II study. This study showed a favorable response, with a clinical response rate of 52.4% (37.3-67.5%) and a partial response rate of 33.3%. The investigators concluded that DCF-R frequently caused myelosuppression and esophagitis. However, it was highly efficacious and suggested to be a promising regimen in the

treatment of advanced esophageal cancer. Another retrospective study revealed improved OS and complete response in a DCF-R group compared with a CDDP/5-FU-R group (22). The researchers also reported that the incidence of grade 3/4 leukopenia was significantly higher in the DCF-R group. Notably, there were no significant intergroup differences in neutropenia, anemia, thrombocytopenia, radiation-induced dermatitis, radiation esophagitis, or late adverse events.

Based on the study conducted by Yamashita *et al* (23), we used NDP/S-1 in combination with RT in 89.8% of patients. In that study, the investigators reported that a complete response was achieved in 85% of patients who received CRT with



Table III. Univariate analysis of OS.

Variable	2-year OS, % (95% CI)	P-value (log-rank)
Age, years		<0.001
<75	69.3 (55.3-79.7)	
≥75	20.0 (3.1-47.5)	
CRP, mg/dl		0.013
<1	71.2 (55.4-82.2)	
≥1	38.5 (17.7-59.0)	
SUV <sub>max</sub>		0.048
≤12.85	72.4 (50.5-85.9)	
>12.85	49.0 (29.5-65.9)	
CRP/SUV <sub>max</sub>		0.008
CRP <1 mg/dl/SUV <sub>max</sub> ≤12.85	76.2 (51.6-89.4)	
CRP ≥1 mg/dl/SUV <sub>max</sub> >12.85	37.5 (14.1-61.2)	
Stage		0.298
I-II	67.5 (29.1-88.2)	
III-IV	45.1 (32.1-57.3)	
Primary site		0.579
Ce-Ut	62.6 (36.3-79.8)	
Mt-EGJ	61.6 (46.1-73.9)	

Ce, cervical esophagus; CI, confidence interval; EGJ, esophagogastric junction; Mt, middle thoracic esophagus; OS, overall survival; SUV<sub>max</sub>, maximum standardized uptake value; Ut, upper thoracic esophagus.

Table IV. Univariate analysis of DFS.

Variable	2-year DFS, % (95% CI)	P-value (log-rank)
Age, years		0.019
<75	54.6 (40.9-66.4)	
≥75 years	20.5 (3.2-48.2)	
CRP, mg/dl		<0.001
<1	59.7 (44.4-72.1)	
≥1	25.0 (9.1-44.9)	
SUV <sub>max</sub>		0.057
≤12.85	67.1 (46.2-81.3)	
>12.85	35.7 (18.9-53.0)	
CRP/SUV <sub>max</sub>		0.003
CRP <1 mg/dl/SUV <sub>max</sub> ≤12.85	69.8 (46.9-84.3)	
CRP ≥1 mg/dl/SUV <sub>max</sub> >12.85	20.0 (4.9-42.4)	
Stage		0.186
I-II	65.6 (26.0-87.6)	
III-IV	45.1 (32.1-57.3)	
Primary site		0.365
Ce-Ut	57.9 (33.2-76.3)	
Mt-EGJ	46.2 (31.8-59.5)	

Ce, cervical esophagus; CI, confidence interval; DFS, disease-free survival; EGJ, esophagogastric junction; Mt, middle thoracic esophagus; SUV<sub>max</sub>, maximum standardized uptake value; Ut, upper thoracic esophagus.

NDP/S-1. The 3-year OS rate in those who received definitive CRT or salvage CRT was 54.4 and 39.8%, respectively; 70% received treatment as outpatients.

In this study, we conducted IFRT based on PET. A phase II study reported that, of 63 patients who were treated with IFRT based on PET, only two patients experienced out-of-field loco-regional nodal recurrence (24). The same investigators have retrospectively reported that tendencies toward improved loco-regional progression-free survival and a significantly increased OS rate favored the IFRT arm over the elective nodal irradiation arm (25).

In the Radiation Therapy Oncology Group 9405 study, Minsky *et al* (26) revealed that high-dose RT does not improve local/regional control or survival. Furthermore, other studies have shown that doses >55 or >60 Gy are associated with higher rates of morbidity after salvage surgery (27,28). Therefore, we suggest that 60 Gy is not necessary even in patients with high CRP/SUV<sub>max</sub>.

Regarding the cut-off levels of SUV<sub>max</sub>, Huang *et al* (1) used ROC analysis, Shum *et al* (20) used MTV 2.5 and MTV 20% (volume higher than a fixed threshold of 20% of the maximum intra-tumoral activity), and Van Westreenen *et al* (19) used the median SUV<sub>max</sub>. We performed an ROC analysis; we found that 10.4 would be the most appropriate threshold, and the area under the curve was 0.64 (95% CI: 0.49-0.8). On the other hand, the median SUV<sub>max</sub> was 12.85. We thought that the median SUV<sub>max</sub> would be more reliable, and decided to use a SUV<sub>max</sub> of 12.85 as the threshold.

Concerning the cut-off levels of CRP, although this study used a latex turbidimetric immunoassay, most published studies have used the immunonephelometry method. The median CRP was 0.18 mg/dl, which did not seem to have any clinical significance. Hence, we decided to use the ROC curve. Since survival in the present study was comparable to that reported in other published studies, we think that the thresholds used in this study are reasonable.

The clinical stage did not remain significant in either the univariate or multivariate analysis. This may be attributed to the inclusion of only CT-visible tumors; patients with disease at an earlier stage may also have poor prognoses.

There were a few limitations in this study. Firstly, we included only CT-visible tumors. Otherwise, the SUV<sub>max</sub> would not be precise, and we would have been unable to distinguish whether the levels of CRP were elevated because of the tumor or other infectious causes. Thus, it is uncertain whether these prognostic factors are meaningful in CT-invisible tumors. Furthermore, the CT-visible tumors evaluated in this study included primary sites and metastatic lymph nodes. However, we are unsure whether primary sites and metastatic lymph nodes share similar characteristics. We did not search for adverse effects since we aimed to determine the correlation between SUV<sub>max</sub>/CRP and survival. Other limitations of this study are the various types of prescribed doses (we mainly prescribed 60 Gy before 2014); various types of adjuvant chemotherapy (we are currently planning to compare CDDP/5-FU versus NDP/TS-1); the retrospective design; and limited number of patients included.

Table V. Multivariate analysis.

Cox proportional hazards model	OS			DFS		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (<75 vs. $\geq 75$ years)	0.24	0.08-0.69	0.01	0.33	0.12-0.93	0.04
CRP (<1 vs. $\geq 1$ mg/dl)	0.54	0.21-1.37	0.20	0.43	0.19-0.96	0.04
$SUV_{max}$ ( $\leq 12.85$ vs. $> 12.85$ )	0.50	0.18-1.39	0.18	0.64	0.27-1.51	0.31
cStage (I-II vs. III-IV)	1.15	0.22-5.94	0.87	0.95	0.24-3.68	0.94

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival;  $SUV_{max}$ , maximum standardized uptake value.

Table VI. Previous studies showing the association between serum CRP levels/ $SUV_{max}$  and overall survival/disease-free survival in esophageal cancer.

A,  $SUV_{max}$

First author, year	No. of patients	Treatment modality	Threshold	MST, months		P-value	(Refs.)
				High	Low		
Van Westreenen <i>et al</i> , 2005	40	Esophagectomy or BSC	6.7	8.7	20.4	0.016	(19)
Shum <i>et al</i> , 2012	26	Esophagectomy with or without RT	16 ml <sup>a</sup>	15	NA	0.018	(20)
Brown <i>et al</i> , 2012	46	Esophagectomy	5.5	14	39	0.72	(6)
Present study	56	Radiotherapy with or without chemotherapy	12.85	14	NA	0.048	-

B, CRP

First author, year	No. of patients	Treatment modality	Threshold	MST, months		P-value	(Refs.)
				High	Low		
Wang <i>et al</i> , 2009	123	CRT with or without esophagectomy	5 mg/dl <sup>b</sup>	11	NA	<0.001	(12)
Huang <i>et al</i> , 2019	552	Esophagectomy	5 mg/dl <sup>b</sup>	40	NA	0.044	(13)
Present study	69	Radiotherapy with or without chemotherapy	1 mg/dl	10	NA	0.013	-

<sup>a</sup>MTV 2.5 (volume with  $^{18}F$ -FDG uptake  $SUV > 2.5$ ); <sup>b</sup>immunonephelometry method. BSC, best supportive care; CRT, chemoradiotherapy; FDG, fluorodeoxyglucose; MST, median survival time; MTV, metabolic tumor volume; NA, not applicable;  $SUV_{max}$ , maximum standardized uptake value.

In conclusion, prognostic prediction based on pre-treatment  $SUV_{max}$  of  $^{18}F$ -FDG-PET and serum CRP levels is possible in RT of esophageal cancer. It is important to consider the provision of more intensive treatment to patients with poor prognoses for better treatment outcome.

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#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

HJ designed the study, analyzed data and wrote the initial draft of the manuscript. TK, YM and AK recruited the patients and collected their clinical data. HY also made substantial contributions to conception of the study and revised the manuscript critically for important intellectual content. KN and OA made substantial contributions to analysis and interpretation of data,

were involved in revising the manuscript critically and gave final approval of the version to be published. All the raw data have been assessed by HJ and HY to ensure their legitimacy. All authors read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### Ethics approval and consent to participate

Written informed consent was provided by all individuals included in the study at the time of initial data collection. The study was approved by the Institutional Review Board of the University of Tokyo Hospital (Tokyo, Japan) and performed in accordance with the ethical guidelines of the institution and Declaration of Helsinki.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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