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Combining Preoperative Immunoinflammatory Scores and ^{18}F-Fluorodeoxyglucose Positron-emission Tomography Predicts Beneficiaries of Salvage Esophagectomy

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Abstract. *Background: This study evaluated the prognostic value of preoperative immunoinflammatory scores and ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) for patients undergoing salvage esophagectomy to identify suitable candidates for surgery. Patients and Methods: Twenty-five patients undergoing salvage esophagectomy were included. The prognostic value of the preoperative C-reactive protein-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and maximum standardized FDG uptake value (SUVmax) were investigated. Results: Multivariate analysis demonstrated high CAR to be an independent prognostic factor for overall survival (p=0.013). CAR had no association with clinicopathological variables, whereas the SUVmax was significantly positively associated with tumor aggressiveness. Multivariate analysis using residual tumor and the combination of CAR and SUVmax revealed both residual tumor (p=0.009) and high CAR/high SUVmax (p=0.016) to be independent prognostic factors for overall survival. Conclusion: Preoperative evaluation of CAR as an immunoinflammatory indicator and SUVmax as a marker of tumor aggressiveness will be useful to identify suitable candidates for this high-risk surgery.*

Salvage esophagectomy is the only established therapeutic strategy that provides any chance of long-term survival after local failure for patients with esophageal cancer (EC) receiving definitive chemoradiotherapy (CRT) (1, 2). However, previous studies reported that salvage esophagectomy is associated with high morbidity and mortality rates (1, 3). The long-term outcome of salvage esophagectomy also remains poor, with a 5-year survival rate of 0-33% (4). Clarification of factors that predict which candidates will benefit from this procedure remains a clinical challenge.

Systemic inflammation has received much attention in recent years in many malignancies because it is associated with tumor aggressiveness and prognosis. Several immunoinflammatory factors have been reported to be useful prognostic indicators for EC. The C-reactive protein-to-albumin ratio (CAR) has been associated with tumor progression and poor overall survival (OS) in patients with EC (5, 6). The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were also reported to be associated with poor OS in patients with EC (7, 8). An increased NLR during chemoradiation independently reflects a higher probability of disease relapse, metastasis, and mortality in these (9). However, the associations between these immunoinflammatory scores and postoperative survival in patients undergoing salvage esophagectomy for EC remain unclear.

In recent years, the use of ^{18}F-fluorodeoxyglucose positron-emission tomography (FDG-PET) has widely spread for the evaluation of malignancies. FDG-PET provides physiological information that facilitates a cancer diagnosis by detecting altered tissue glucose metabolism. FDG-PET is often described as an effective noninvasive imaging modality in EC for tumor staging, evaluating tumor response after treatment, and detecting tumor recurrence (10). FDG-PET can distinguish viable tumor tissues from treatment-related inflammation or fibrosis by functional evaluation based on

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metabolic information (11). However, FDG uptake is also influenced by inflammation (12). The significance of preoperative FDG uptake in patients undergoing salvage esophagectomy has not been fully assessed.

In this study, we hypothesized that preoperative inflammation-related factors of patients undergoing salvage surgery might provide helpful insight into predicting prognosis and in patient selection. Therefore, we investigated the prognostic value of preoperative immunoinflammatory scores and FDG uptake in patients undergoing salvage esophagectomy to investigate this hypothesis.

Patients and Methods

Patients. This retrospective study was approved by the Ethics Committee of the Graduate School of Medicine, Gunma University (Protocol number HS2019-025). Informed consent was received in the form of an opt-out on a web-site. We examined 25 patients with thoracic EC undergoing salvage esophagectomy between 1998 and 2018 at our Institute. Patients were excluded from this study if they had no data for serum albumin or lymphocyte count in peripheral blood, or FDG-PET within 1 month before surgery. Tumor characteristics and patient outcomes were collected from hospital patient records. The tumor stage and disease grade was classified according to the seventh edition of the TNM classification of the International Union Against Cancer (13). The preoperative diagnosis and tumor staging were confirmed by endoscopy, esophagography, endoscopic ultrasonography, and computed tomography.

Chemoradiation and salvage surgery. Patients received concurrent radiotherapy and chemotherapy for 6 weeks after the diagnostic procedures. Standard clinical measurements and radiological examinations were used to determine the tumor response according to RECIST. The treatment response of the primary lesion was evaluated according to the 11th edition of the Japanese Classification of Esophageal Cancer (14). One month after completing treatment, the first evaluation of the initial tumor response was performed. The second evaluation was performed after more than four weeks from the first evaluation. Endoscopy was repeated to confirm primary complete response (CR) and progressive disease. Patients were evaluated every three months after treatment completion for the first two years and six months thereafter. The details of chemoradiation and the definition of salvage esophagectomy were previously described (15). Postoperative complications were classified according to the Clavien-Dindo classification (16), and events classified as grade 3 or higher were documented as complications.

Measurement of immunoinflammatory scores and FDG uptake. CAR, NLR, and PLR were calculated as previously described (5). The maximum standardized FDG uptake value (SUVmax) of primary tumors was calculated in a routine clinical manner.

Statistical analysis. Patient characteristics were compared using chi-squared tests for categorical variables and Student's *t*-test for continuous variables. In the present study, OS was defined as the time from salvage esophagectomy to the date of the last follow-up or death from any cause. Receiver operating characteristics (ROC) curves were generated, and areas under the curve (AUC) were used to evaluate the discriminatory ability of the CAR, NLR, PLR, and SUVmax to predict OS. A correlation analysis was performed using Spearman's rank correlation coefficients. Kaplan-Meier curves were generated for OS, and significance was assessed using the log-rank test. Univariate and multivariate survival analyses were carried out using the Cox proportional hazards regression model. Variables selected using a stepwise selection to minimize the Akaike information criterion (17) were included in a multivariate Cox proportional model. A probability value of less than 0.05 was considered significant. All statistical analyses were performed using EZR (18)

Table I. *Patient characteristics*.

Characteristics		Value
Age, years	Mean±SD	70.12±7.57
Gender, n (%)	Male	23 (92.0)
	Female	2 (8.0)
Location of tumor, n (%)	Upper	4 (16.0)
	Middle	12 (48.0)
	Lower	9 (36.0)
Clinical response, n (%)	Non-CR	10 (40.0)
	CR	15 (60.0)
cT*, n (%)	T1	4 (16.0)
	T2	2 (8.0)
	T3	9 (36.0)
	T4	10 (40.0)
cN*, n (%)	Negative	8 (32.0)
	Positive	17 (68.0)
pT, n (%)	T0-1	8 (32.0)
	T2	2 (8.0)
	T3	9 (36.0)
	T4	6 (24.0)
pN, n (%)	Negative	18 (72.0)
	Positive	7 (28.0)
Residual tumor, n (%)	Negative	18 (72.0)
	Positive	7 (28.0)
Postoperative complications, n (%)	Negative	19 (76.0)
	Positive	6 (24.0)
SUVmax	Mean±SD	4.63±2.97
CAR	Mean±SD	0.27±0.52
NLR	Mean±SD	4.99±3.55
PLR	Mean±SD	249.7±120.73

CAR: C-Reactive protein-to-albumin ratio; CR: complete response; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SD: standard deviation; SUVmax: maximum standardized fluorodeoxyglucose uptake value. *Diagnosed before initial chemoradiotherapy/radiotherapy.

Results

Patient characteristics. The baseline patient characteristics are summarized in Table I. The histological diagnosis was squamous cell carcinoma in 23 patients (92%), carcinosarcoma in one (4.0%), and adenocarcinoma in one (4.0%). The best cut-off values of the CAR, NLR, PLR, and SUVmax for OS based on ROC curves were 0.075 (AUC=0.687, 95% CI=0.437-0.937), 4.84 (AUC=0.613, 95% CI=0.365-0.862),

Table II. *Univariate and multivariate analyses of preoperative factors for overall survival.*

		Univariate analysis		Multivariate analysis	
Characteristic	Subgroup	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, years	Per-year increase	0.96 (0.89-1.03)	0.29		
Sex	Male *vs*. female	0.07 (0.01-0.49)	**0.008**	0.16 (0.02-1.19)	0.073
SUVmax	High *vs*. low	2.99 (0.93-9.57)	0.065	3.31 (0.99-11.10)	0.052
cT*	3-4 *vs*. 1-2	2.78 (0.63-12.35)	0.18		
cN*	Positive *vs*. negative	2.38 (0.67-8.44)	0.18		
CAR	High *vs*. low	4.97 (1.39-17.81)	**0.014**	5.23 (1.42-19.34)	**0.013**
NLR	High *vs*. low	3.76 (1.27-11.14)	**0.017**		
PLR	High *vs*. low	5.16 (1.69-15.75)	**0.004**		

CAR: C-Reactive protein-to-albumin ratio; CI: confidence intervaI; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SUVmax: maximum standardized fluorodeoxyglucose uptake value. *Diagnosed before initial chemoradiotherapy/radiotherapy. *Diagnosed before initial chemoradiotherapy/radiotherapy. Statistically significant *p*-values are shown in bold.

236 (AUC=0.667, 95% CI=0.432-0.901), and 3.5 (AUC=0.612, 95% CI=0.357 to 0.866), respectively. The correlation analysis revealed no significant correlation between the SUVmax and CAR (Spearman's r=0.297, p=0.168), NLR (Spearman's r=0.286, p=0.185), or PLR (Spearman's r=0.355, p=0.096).

Survival analysis. Univariate analysis of preoperative factors revealed sex, CAR, NLR, and PLR to be significant prognostic factors for OS. Multivariate analysis demonstrated CAR to be an independent prognostic factor for OS (Table II). There were no significant differences in clinicopathological variables between groups with low and high CAR (Table III). The OS rate was significantly lower in patients with a high CAR than in those with a low CAR (p=0.007; Figure 1).

Prognostic value of the combination of preoperative CAR and SUVmax. Multivariate analysis revealed SUVmax to be a borderline significantly independent prognostic factor (p=0.052). SUVmax was significantly positively associated with tumor depth before initial treatment (p=0.018), pathological tumor depth (p=0.001), pathological lymph node metastasis (p=0.027), and residual tumor (p=0.027) (Table III). The OS rate was slightly lower in patients with a high SUVmax than in those with a low SUVmax but the difference was not significant (p=0.054; Figure 2). As the SUVmax was significantly associated with tumor aggressiveness, whereas CAR had no association with clinicopathological variables, we hypothesized that the combination of these preoperative tumor-related and non-related factors would provide a good prognostic indicator. We divided patients into three groups as follows: group A: low values for both CAR and SUVmax, group B: high CAR or SUVmax, and group C: high values for both CAR and SUVmax, and investigated the prognostic value. The OS rate was significantly different among the three groups (p<0.001; Figure 3). Multivariate analysis including residual tumor revealed having high values for both CAR and SUVmax to be an independent factor indicating significantly poorer OS (Table IV).

Discussion

The most important finding of the present study was that the combination of preoperative CAR and SUVmax was an independent prognostic factor for OS of EC patients undergoing salvage esophagectomy. To our knowledge, this was the first study to investigate the prognostic significance of the combination of preoperative CAR and SUVmax in salvage esophagectomy.

CAR was an independent preoperative prognostic factor for OS (p=0.013) of patients undergoing salvage surgery for EC. The prognostic significance of CAR for the OS was consistent with previous reports (5, 6, 19). C-Reactive protein is mainly produced by hepatocytes and regulated by interleukin-6 (20). Albumin is widely used as a reliable marker for nutritional status. CAR thus reflects both the inflammatory and nutritional status. It was also reported to be significantly associated with malignant tumor behavior and progression (5, 6, 19). Of note in the present study, CAR had no significant association with tumor stage. One possible reason for this was the effects of chemoradiation injury. Increased total dose, large treatment fields, and large fractions cause more severe tissue injury (21). After chemoradiation, CAR may reflect radiation-induced inflammation and its effects on nutritional status rather than tumor progression. Systemic chemotherapy, and radiation were reported to substantially affect systemic inflammation (22, 23). Furthermore, the systemic immunoinflammatory response was reported to be a predictor of therapeutic efficacy, cancer

Table III. *Patient characteristics according to C-reactive protein-to-albumin ratio (CAR) and maximum standardized fluorodeoxyglucose uptake value (SUVmax).*

		CAR			SUVmax		
Characteristics	Group	Low (n=10)	High (n=15)	*p*-Value	Low (n=9)	High (n=16)	*p*-Value
Age, years	Mean±SD	70.6 (6.4)	69.8 (8.5)	0.802	72.89 (7.57)	68.56 (7.34)	0.175
Gender, n (%)	Female	0	2 (13.3)	0.500	0	2 (12.5)	0.520
	Male	10 (100.0)	13 (86.7)		9 (100.0)	14 (87.5)	
Clinical response, n (%)	Non-CR	2 (20.0)	8 (53.3)	0.211	7 (77.8)	8 (50.0)	0.229
	CR	8 (80.0)	7 (46.7)		2 (22.2)	8 (50.0)	
cT*, n (%)	1	2 (20.0)	2 (13.3)	>0.999	4 (44.4)	0	**0.018**
	2	1 (10.0)	1 (6.7)		1 (11.1)	1 (6.2)	
	3	3 (30.0)	6 (40.0)		2 (22.2)	7 (43.8)	
	4	4 (40.0)	6 (40.0)		2 (22.2)	8 (50.0)	
cN*, n (%)	Negative	4 (40.0)	4 (26.7)	0.667	4 (44.4)	4 (25.0)	0.394
	Positive	6 (60.0)	11 (73.3)		5 (55.6)	12 (75.0)	
pT, n (%)	0-1	4 (40.0)	4 (26.7)	0.117	6 (66.7)	2 (12.5)	**0.001**
	2	1 (10.0)	1 (6.7)		2 (22.2)	0	
	3	5 (50.0)	4 (26.7)		1 (11.1)	8 (50.0)	
	4	0	6 (40.0)		0	6 (37.5)	
pN, n (%)	Negative	8 (80.0)	10 (66.7)	0.659	9 (100.0)	9 (56.2)	**0.027**
	Positive	2 (20.0)	5 (33.3)		0	7 (43.8)	
Residual tumor, n (%)	Negative	9 (90.0)	9 (60.0)	0.179	9 (100.0)	9 (56.2)	**0.027**
	Positive	1 (10.0)	6 (40.0)		0	7 (43.8)	
Postoperative complications, n (%)	Negative	9 (90.0)	10 (66.7)	0.345	6 (66.7)	13 (81.2)	0.63
	Positive	1 (10.0)	5 (33.3)		3 (33.3)	3 (18.8)	

CAR: C-Reactive protein-to-albumin ratio; SD, standard deviation. *Diagnosed before initial chemoradiotherapy/radiotherapy. Statistically significant *p*-values are shown in bold.

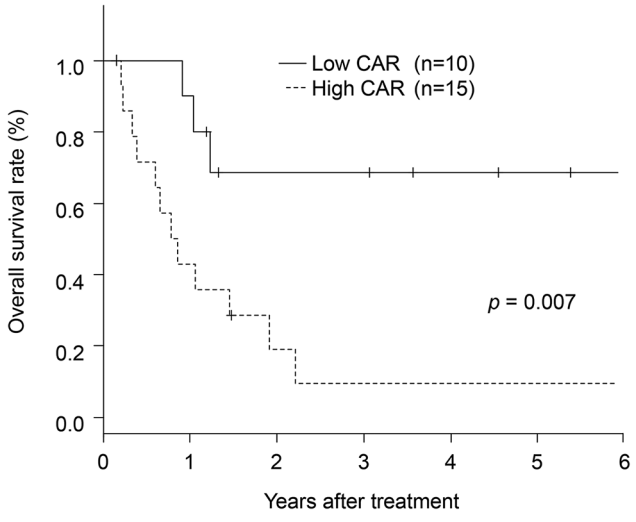

Figure 1. *Kaplan-Meier curves for overall survival according to the C-reactive protein-to-albumin ratio (CAR).*

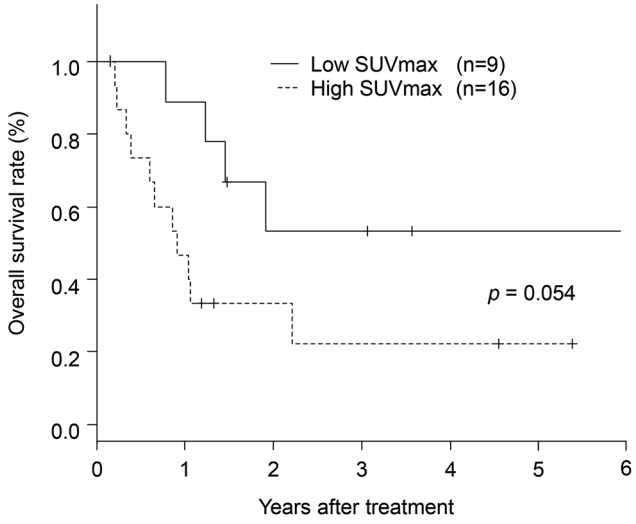

Figure 2. *Kaplan-Meier curves for overall survival according to maximum standardized fluorodeoxyglucose uptake value (SUVmax).*

recurrence, and OS of patients undergoing CRT for EC (9). Our findings support those of these reports regarding CAR.

The significance of FDG-PET in patients with EC undergoing chemoradiation has been mainly investigated in the context of response evaluation (24-28). However, the reported data are heterogeneous and the utility of FDG-PET after CRT remains controversial. This may partly depend on the difference in the number of cohorts, the dominant

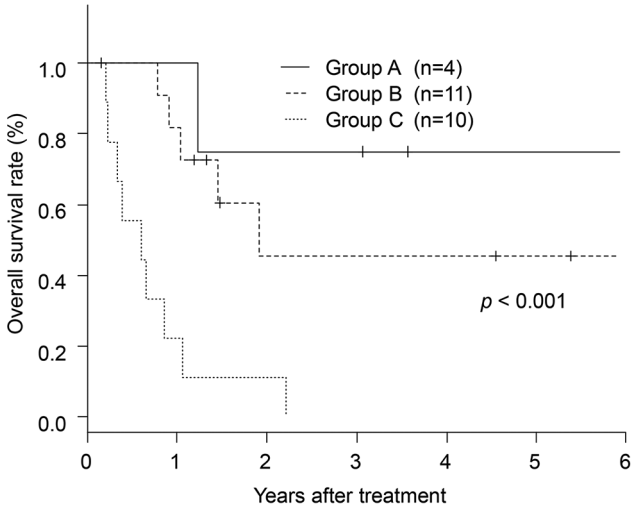

Figure 3. *Kaplan-Meier curves for OS according to the combination of C-reactive protein-to-albumin ratio (CAR) and maximum standardized fluorodeoxyglucose uptake value (SUVmax). Group A: both CAR and SUVmax low; group B: either CAR or SUVmax low; group C: both CAR and SUVmax high.*

Table IV. *Multivariate analysis using residual tumors and the combination of C-reactive protein-to-albumin ratio (CAR) and maximum standardized fluorodeoxyglucose uptake value (SUVmax) for overall survival.*

	Multivariate analysis	
Characteristic	Hazard ratio (95% CI)	*p*-Value
Residual tumor		
Positive *vs*. negative	8.26 (1.70-40.08)	**0.009**
CAR and SUVmax		
Group C *vs*. AB	4.44 (1.32-14.96)	**0.016**

Group A: low CAR/low SUVmax; group B: high CAR/low SUVmax or low CAR/high SUVmax; group C: high CAR/high SUVmax. Statistically significant *p*-values are shown in bold.

histological type, the timing of PET, and the difference in PET parameters. The clinical implications of preoperative FDG uptake in patients undergoing salvage esophagectomy have not been fully assessed. To our knowledge, this is the first study demonstrating that preoperative FDG uptake is associated with tumor aggressiveness and reflective of the poor prognosis of patients undergoing salvage esophagectomy. Although a possible relationship between tumor FDG uptake and host systemic inflammatory responses was previously noted in patients with several tumor types (29), the SUVmax was not correlated with systemic inflammatory markers in our study. Locoregional and systemic inflammation caused by chemotherapy or radiation may alter the fundamental association between FDG uptake and systemic inflammation.

R0 resection (no residual tumor) has been widely recognized as the most important prognostic factor for patients undergoing salvage esophagectomy (4). However, R0 resection is a *postoperative* factor and therefore cannot be used to identify suitable candidates for this high-risk surgery. Thus, the clarification of preoperative prognostic factors of salvage esophagectomy remains a challenge. Furthermore, considering the high morbidity and mortality rates associated with salvage esophagectomy, tumor aggressiveness and physiological condition, including immunoinflammatory status, must be evaluated before surgery. Preoperative CAR had no significant association with clinicopathological features in the present study, whereas the preoperative SUVmax reflected the histopathological features of the tumor. Therefore, the combination of preoperative CAR and SUVmax had prognostic significance by incorporating both the preoperative immunoinflammatory status and tumor aggressiveness. Combining preoperative CAR and SUVmax may be useful to identify promising candidates for salvage esophagectomy.

Our study has several potential limitations. Firstly, this was a retrospective single-institution analysis. Secondly, the cut-off values of SUVmax, CAR, NLR, and PLR may have been biased because they were selected using ROC curves. Thirdly, as we assessed FDG uptake as only SUVmax; it remains unclear whether analysis using other PET parameters, such as the mean SUV, metabolic tumor volume, and total lesion glycolysis, provides the same results as our analysis.

In conclusion, the combination of CAR as a preoperative immunoinflammatory indicator and SUVmax as a marker of tumor aggressiveness was an independently prognostic for salvage esophagectomy. Preoperative evaluation of these factors may be useful to identify suitable candidates for this high-risk surgery.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Study conception and design: M. Sakai; acquisition of data: S. Uchida, A Yamaguchi, T. Watanabe, H. Saito, Y Ubukata, N. Nakazawa and K Kuriyama; analysis and interpretation of data: M. Sakai, M. Sohda, A. Sano, H. Ogawa and T. Yokobori; drafting of article: M. Sakai; critical revision: K. Shirabe and H. Saeki.

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