Hirosaki Med. J. 73 : 54—66, 2023

ORIGINAL ARTICLE

Combined utility of maximum standardized uptake value and its change after neoadjuvant chemotherapy in predicting postoperative recurrence in esophageal cancer

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Abstract

Background: Positron emission tomography (PET) is the standard method for metabolic and quantitative evaluation of therapeutic response to chemotherapy in solid tumors. This study determined the ability of PET parameters used in combination in predicting recurrence-free survival (RFS) after neoadjuvant chemotherapy (NAC) and operation for esophageal cancer.

Methods: This single-center retrospective study included 96 patients who underwent ^{18}F-fluorodeoxyglucose-PET/computed tomography before and after NAC. Maximum standardised uptake value (SUVmax) after NAC and the rate of change in SUVmax following NAC (ΔSUVmax) were determined to examine their relationship with postoperative recurrence and clinicopathological factors.

Results: Receiver operating characteristic curves, with recurrence after NAC as the event, were used to determine optimal cut-off SUVmax and ΔSUVmax of 6.8 and 45.7, respectively. Using these cut-off values, the patients were classified into four groups: Group A, SUVmax > 6.8 and ΔSUVmax ≤ 45.7; Group B, SUVmax > 6.8 and ΔSUVmax > 45.7; Group C, SUVmax ≤ 6.8 and ΔSUVmax ≤ 45.7; and Group D, SUVmax ≤ 6.8 and ΔSUVmax > 45.7. Of the four groups, Group D had the longest RFS compared to the other groups.

Conclusion: Combination of SUVmax with ΔSUVmax was useful for evaluating the effects of NAC in patients with esophageal cancer.

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Key words: esophageal cancer; fluorodeoxyglucose positron emission tomography; standardised uptake value; prognostic factor; neoadjuvant therapy.

Introduction

Esophagectomy with extended three-field lymph node dissection including cervical, mediastinal and abdominal regions is the main treatment approach for patients with locally advanced thoracic esophageal cancer[1, 2)]. In Japan, surgical therapy is recommended over radical chemoradiotherapy for cStage II/III esophageal cancer. However, survival is poor in patients with esophageal cancer, with possible local or distant recurrence. Systemic and local recurrences

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Received for publication, November 7, 2022
Accepted for publication, December 15, 2022

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are frequent, and the 5-year survival rate after surgery alone ranges from 17% to 34%[3, 4]. Neoadjuvant chemotherapy (NAC) or chemoradiotherapy before surgery is associated with survival benefit in patients with resectable esophageal cancer[4-6]. A study in Japan reported that the 5-year survival rates after esophagectomy were 64.6%, 45.3% and 59.3% in patients with stage II, stage III and all-stage esophageal cancer, respectively[7]. Recent studies have demonstrated that neoadjuvant chemoradiation or NAC improves both disease-free survival and overall survival in patients with esophageal cancer. NAC with 5-fluorouracil (5-FU) plus cisplatin (FP) combination therapy was used in patients with cStage II/III esophageal cancer based on the results of the JCOG9907 trial[8]. In the latest study in 2022, the JCOG1109 study (NExT) revealed superiority in overall survival with 5-FU plus cisplatin plus docetaxel combination therapy (DCF) as NAC over FP combination therapy, which has been the standard treatment for NAC[9]. Although DCF combination therapy is expected to be used as the standard treatment for NAC, a certain percentage of early postoperative recurrences have been reported in patients who underwent NAC. Esophagectomy is a highly invasive procedure with occasional serious complications. It is sometimes reported complications of esophageal cancer surgery can be severe. Complications after esophagectomy include suture failure, recurrent laryngeal nerve paralysis, chylothorax. Ischemic necrosis of the esophageal reconstruction organ sometimes forms an airway fistula and can be fatal.

Computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG)-position emission tomography (PET) are generally used for preoperative staging or NAC efficacy assessment in esophageal cancer. Maximum standardised uptake value (SUVmax) which measures the highest intensity of ^{18}F-FDG uptake within a region of interest, is the most commonly used FDG-PET parameter. The effect of NAC can be evaluated based on the change in the size of the esophageal lesion and the number and size of metastatic lymph nodes. However, CT is considered to be insufficient in assessing the effect of NAC on primary tumors of thin-walled gastrointestinal organs and small metastatic lymph nodes. On the other hand, several reports demonstrated the utility of FDG-PET in predicting the efficacy of NAC by showing that a higher SUVmax after NAC was associated with early postoperative recurrence or poor prognosis[10-12]. It has also been reported that patients with a higher percentage reduction in SUVmax following NAC compared to the pre-NAC values had better postoperative prognosis and better histological response to treatment[10, 13-15]. It is speculated that the spread of PET-CT equipment will increase the number of reports on treatment effect evaluation using PET-CT. However, no study to date has compared the clinicopathological factors and the therapeutic histological effects of NAC using the combination of SUVmax and percent reduction in SUVmax as parameters to classify patients into those with good and poor prognosis. In the present study, we aimed to determine clinicopathological factors associated with the histological therapeutic efficacy of NAC in esophageal cancer by classifying patients using both SUVmax and percentage change in SUVmax.

Materials and methods

Patients

This was a single-center, retrospective cohort study including 96 patients with locally advanced esophageal squamous cell carcinoma who underwent curative resection after NAC at Hirosaki University Hospital from January 1, 2010 to September 30, 2018. Patients who received NAC with radiation or definitive treatment and salvage surgery were excluded

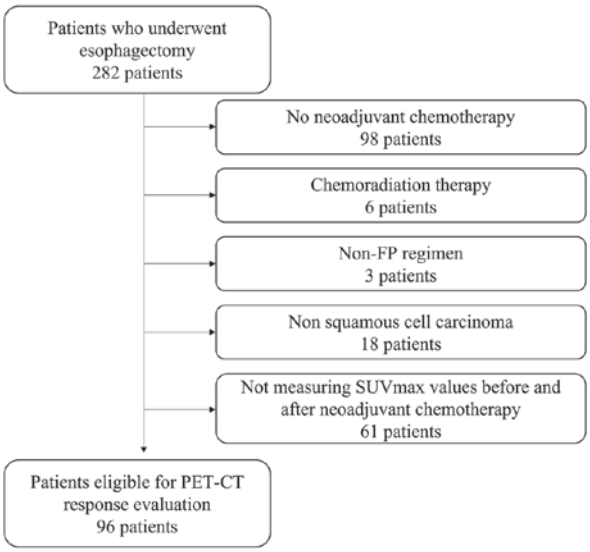

Figure 1 Patient flow diagram of SUVmax evaluation

from this study. Before the planned surgical resection, all patients underwent FDG-PET before and after NAC at Hirosaki University Hospital. Additional PET-CT scans were performed 14–21 days after NAC completion. Of the 282 patients who underwent surgery for esophageal cancer during the observation period, 96 patients who met the criteria were included in the control group (Fig. 1). All patients were under 80 years of age and had adequate cardiopulmonary, respiratory, hepatic and renal function to tolerate chemotherapy and surgery.

All patients were staged before and after NAC according to the International Union Against Cancer criteria[14]. Patients without distant organ metastases underwent surgery after NAC.

Data were retrospectively collected from an electronic medical record system and included information on clinical and demographic characteristics, NAC, pathological stage and duration of postoperative recurrence. The study was approved by the Institutional Review Board of Hirosaki University Hospital before its initiation (2022-032). All study procedures involving participants were performed following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. None of the patients applied for withdrawal of consent.

Treatment

Ninety-five patients received FP chemotherapy, and one patient received low-dose FP chemotherapy. For FP chemotherapy, 70 mg/m^2 cisplatin was administered with rapid intravenous injection on day 1 and 700 mg/m^2 5-fluorouracil was administered as 24-hour continuous intravenous infusion on days 1–5 at 4-week intervals. For low-dose FP therapy, 6 mg/body weight cisplatin was administered rapidly on day 1 and 500 mg/m^2 5-fluorouracil was administered as 24-hour continuous intravenous infusion on days 1–5 at 4-week intervals. All patients underwent surgery after the completion of NAC.

FDG-PET/CT imaging and analysis

Patients fasted for at least six hours before the intravenous administration of 150-335 MBq of ^{18}F-FDG, and scans were started 60 minutes later. Discovery ST Elite (GE Healthcare Japan, Tokyo, Japan) was used for scanning with 3-min emission/bed position. Emission data were corrected for attenuation, dead time and random coincidence. Data were normalised using injection volume and patient weight. Threshold values were adjusted to encompass areas of increased visual uptake. The following parameters were calculated for each tumor volume: SUV = measured radioactivity concentration (Bq/mL) / (injected radioactivity [Bq]/body weight [kg] × 1000); SUVmax = maximum standardised uptake value at visualised foci in esophageal cancer lesion. For all indices, the change in SUVmax (ΔSUVmax) was calculated as follows: ΔSUVmax = [(SUVmax before NAC − SUVmax after NAC) / SUVmax before NAC)] × 100. In addition, coreference PET-CT was performed on all

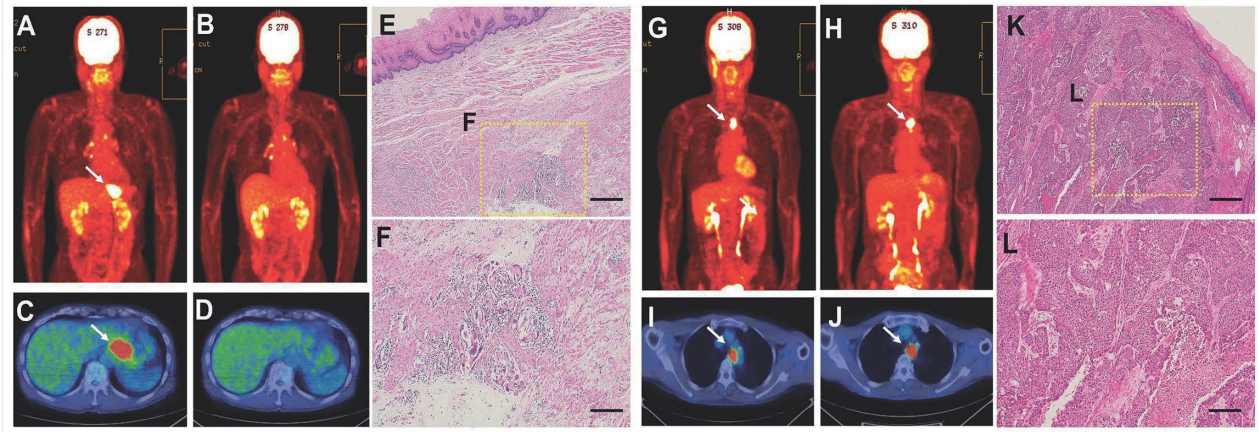

Figure 2 Representative esophageal cancer cases with significant response (A–F) and poor response (G–L) to neoadjuvant chemotherapy

(A) Position emission tomography (PET)-computed tomography (CT) image before neoadjuvant chemotherapy (NAC) showing high SUVmax in the esophagus. (B) PET-CT image after NAC showing the disappearance of high SUVmax in the esophagus. (C) Axial image before NAC. (D) Axial image after NAC. The tumor has disappeared. (E) Haematoxylin/eosin (H&E)-stained specimen showing inflammatory foci in esophageal muscularis propria and the non-neoplastic squamous epithelium. There is no evidence of residual tumor (scale bar; 200 μm). (F) High-magnified H&E-stained specimen exhibiting the absence of tumor; inflammatory cell infiltration, including foreign body giant cells and fibrosis are observed (scale bar, 500 μm). (G) PET-CT image before NAC showing high SUVmax in the esophagus. (H) PET-CT image after NAC showing even higher SUVmax in the esophagus. (I) Axial image before NAC. (J) Axial image after NAC. No change in tumor uptake. (K) H&E-stained specimen showing proliferation of moderate/poorly differentiated squamous tumor cells (scale bar, 200 μm). (L) Magnified image of H&E-stained specimen showing invasive squamous cell carcinoma with keratinisation in some areas (scale bar, 500 μm).

patients using a hybrid PET-CT imager. Fig. 2A–D and 2G–J show representative images of changes in SUVmax after NAC administration.

Pathological analysis

All surgical specimens were fixed with 10% formalin at 25℃ for 48–72 h, and the 4-μm-thick sections were prepared and stained with haematoxylin for 20 min at 25° C, followed by staining with eosin for 3 min at 25° C for histopathological examination. Two expert pathologists (T. Y and H. K), who were blinded to the patients' clinical information, performed pathological evaluation according to the 8th edition of the International Union Against Cancer[16]. According to the 12th edition of the Japanese Classification of Oesophageal Cancer, the histological response to chemotherapy was categorised into five grades[17] : grade 0, no histological response; grade 1a, surviving cancer cells occupying more than two-thirds of the tumor tissue; grade 1b, surviving cancer cells occupying one to two-thirds of the tumor tissue; grade 2, surviving cancer cells occupying less than one-third of the tumor tissue; and grade 3, no surviving cancer cells in the tumor tissue. Fig. 2A–F and 2G–L show representative cases with effective and ineffective NAC, respectively.

Statistical analysis

The Kaplan–Meier method was used for survival analysis, recurrence-free survival (RFS) was used to estimate event rates and the log-rank test was used to compare survival rates among patient groups. Cut-off value of SUVmax and ΔSUVmax were determined using receiver operating characteristic curves. The associations of SUVmax and ΔSUVmax with clinicopathological characteristics were examined using the χ^2 and Fisher's exact probability tests. Continuous variables between two groups were compared using the Mann–Whitney U test. A P value of

Table 1. Patient characteristics

Characteristic	Value[a]			P-value
	All patients (n=96)	Recurrence Group (n=44)	No recurrence Group (n=52)	
Age (years)	65 ±6.9	63 ±7.4	65 ±6.3	0.317
Gender				
Male	89 (93%)	40 (91%)	49 (94%)	0.533
Female	7 (7 %)	4 (9 %)	3 (6 %)	
Tumor location				
Upper third	9 (9 %)	3 (7 %)	6 (12%)	
Middle third	45 (47%)	21 (48%)	24 (46%)	0.729
Lower third	42 (44%)	20 (46%)	22 (42%)	
Histology				
Well differentiated	8 (8 %)	3 (9 %)	5 (10%)	
Moderately differentiated	66 (69%)	32 (73%)	34 (65%)	0.400
Poorly differentiated	19 (20%)	9 (20%)	10 (19%)	
No residual tumor	3 (3 %)	0 (0 %)	3 (6 %)	
Lymphovascular invasion				
Absent	38 (40%)	11 (25%)	27 (52%)	0.007*
Present	58 (60%)	33 (75%)	25 (48%)	
Clinical T				
cT1	5 (5 %)	1 (2 %)	4 (8 %)	
cT2	23 (24%)	11 (25%)	12 (23%)	0.700
cT3	64 (67%)	30 (68%)	34 (65%)	
cT4	4 (4 %)	2 (5 %)	2 (4 %)	
Clinical N				
cN0	33 (34%)	16 (36%)	17 (33%)	
cN1	22 (23%)	7 (16%)	15 (29%)	0.315
cN2-3	41 (43%)	21 (47%)	20 (38%)	
Clinical Stage				
Ⅰ	9 (9 %)	5 (11%)	4 (8 %)	
Ⅱ	29 (30%)	11 (25%)	18 (35%)	0.546
Ⅲ	58 (60%)	28 (64%)	30 (58%)	
Pathological T				
No residual tumor-pT1	26 (27%)	8 (18%)	18 (35%)	
pT2	16 (17%)	8 (18%)	8 (15%)	0.351
pT3	52 (54%)	27 (61%)	25 (48%)	
pT4	2 (2 %)	1 (2 %)	1 (2 %)	
Pathological N				
pN0	31 (32%)	8 (18%)	23 (44%)	
pN1	34 (35%)	19 (43%)	15 (29%)	0.025*
pN2-3	31 (32%)	17 (39%)	14 (27%)	
Pathological Stage				
0-Ⅰ	16 (17%)	4 (9%)	12 (23%)	
Ⅱ	23 (24%)	6 (14%)	17 (33%)	N/A
Ⅲ-Ⅳ	57 (59%)	34 (77%)	23 (44%)	

[a]Data are presented as mead ± SD or n (%) of subjects
*Statistically significant

<0.05 was considered to indicate statistical significance, and all statistical analyses were performed using GraphPad Prism software version 9.0.

Results

Patient characteristics

The characteristics of the 96 patients are summarised in Table 1. The median follow-up was 39.5 (interquartile range, 6.66–60.8) months,

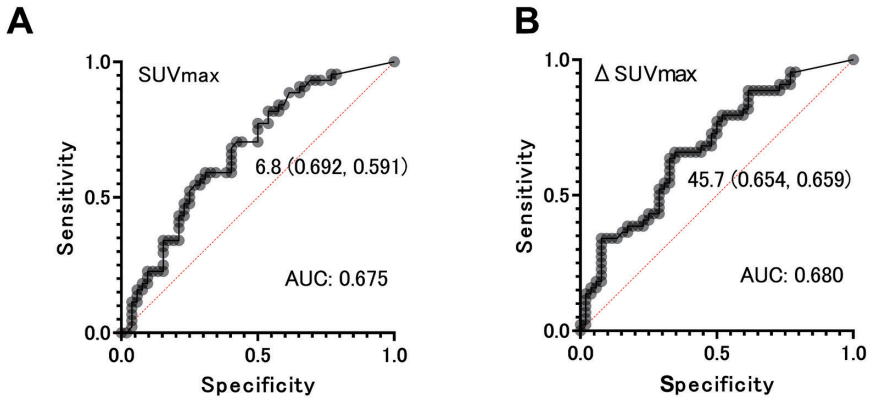

Figure 3 Receiver operating characteristic curves for SUVmax and ΔSUVmax
(A) Receiver operating characteristic (ROC) curve for SUVmax after neoadjuvant chemotherapy. Optimal cut-off for SUVmax after chemotherapy is 6.8. (B) ROC curve for ΔSUVmax after neoadjuvant chemotherapy. Optimal cut-off for ΔSUVmax after chemotherapy is 45.7.

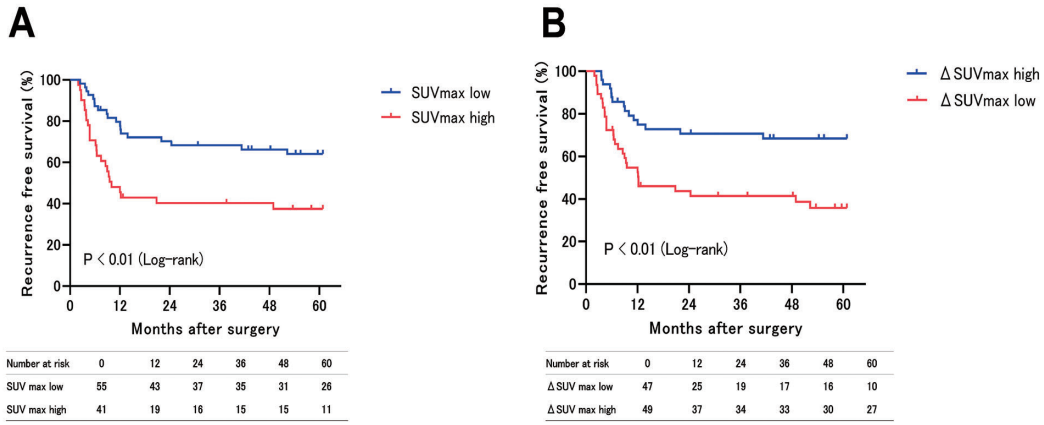

Figure 4 Kaplan–Meier curves for recurrence-free survival according to (A) SUVmax and (B) ΔSUVmax

and 44 patients experienced recurrence (median recurrence months 6.58 months, interquartile range 4.2-12.0 months). In the recurrence-after-surgery Group, the presence or absence of factors of lymphovascular invasion and pathological lymph node metastasis were statistically more frequent than in the not-recurrence after-surgery Group. Still, there were no differences in the clinical and pathological Stages of the primary tumor between two groups.

Association of RFS with SUVmax and ΔSUVmax

The retrospective calculation of SUVmax revealed that the median SUVmax of the esophageal cancer was 15.3 (range 0–59.8) before NAC and 6.10 (range, 0–30) after NAC. Using the retrospectively created receiver operating characteristic curves for SUVmax and ΔSUVmax, with relapse after NAC as the event, the optimised cut-off values for SUVmax and ΔSUVmax were 6.8 and 45.7, respectively (Fig. 3A, B). The patients were classified into the SUV-low (SUVmax ≤ 6.8, n = 55) and SUV-high (SUVmax > 6.8, n = 41) groups based on SUVmax values after NAC. The recurrence rate was significantly lower in the SUV-low group than in the SUV-high group (median RFS, not reached vs 20.6 months; P < 0.01) (Fig. 4A). The patients were also classified into the ΔSUVmax-high (ΔSUVmax > 45.7, n = 49) and ΔSUVmax-low (ΔSUVmax ≤ 45.7, n = 47) groups. The

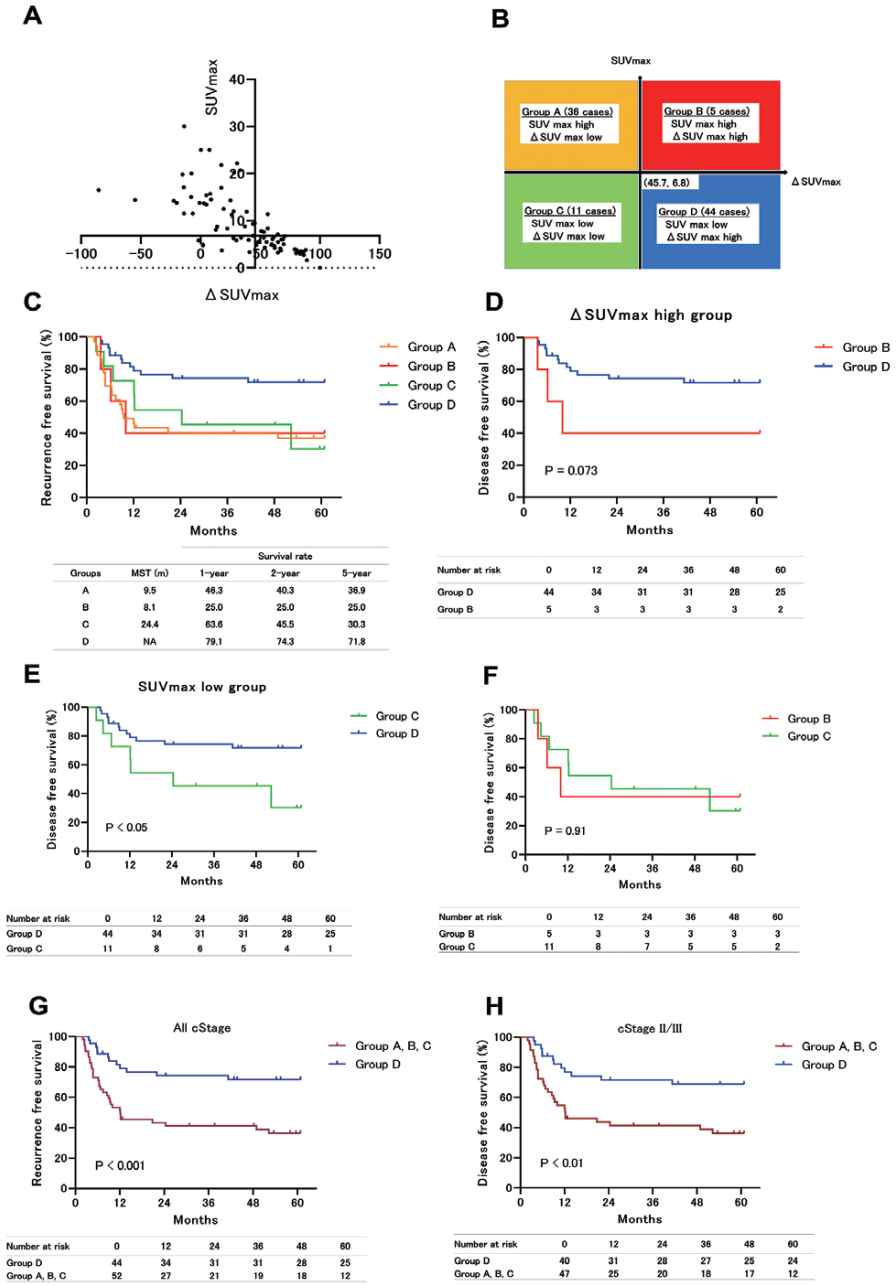

Figure 5 Kaplan–Meier analysis for recurrence-free survival according to the classification using SUVmax in combination with ΔSUVmax

(A) Distribution map of SUVmax and ΔSUVmax. (B) Patients classified into four groups (A, B, C and D) according to SUVmax and ΔSUVmax cut-off. (C) Recurrence-free survival (RFS) after neoadjuvant chemotherapy. (D) Comparison of RFS between the ΔSUVmax-high groups (Group B vs Group D). (E) Comparison of RFS between the SUVmax-low groups (Group C vs Group D). (F) Comparison of RFS between the Group B and Group C. (G) Comparison of RFS between Group D and the combined A+B+C group in all cStages. (H) Comparison of RFS between Group D and the combined A+B+C group in cStage II-III.

recurrence rate was significantly lower in the ΔSUVmax-high group than in the ΔSUVmax-low group (median RFS, not reached vs 12.2 months; $P < 0.01$) (Fig. 4B).

Analysis of RFS using SUVmax in combination with ΔSUVmax

The patients were classified into four groups using the cut-off SUVmax of 6.8 and the cut-off ΔSUVmax of 45.7 (Fig. 5A). As shown in Fig.

Table 2. Correlation of combined SUVmax with ΔSUVmax (Group A, B, C vs D) and clinicopathological factors

Characteristics	Group A, B, C	Group D	P-value
No. of patients	52	44	
Gender			
Man	49	40	0.699
Female	3	4	
Age			
≦65	31	24	0.681
＞60	21	20	
Localization			
Upper /Middle	26	28	0.218
Lower/Abdominal esophagus	26	16	
Histology			
No residual tumor/well/moderately	43	34	0.61
Poorly	9	10	
Lymphovascular invasion			
Absent	12	26	<0.001*
Present	40	18	
Pathological T status			
No residual tumor/T0/T1/T2	14	27	<0.001*
T3/T4	38	17	
Pathological N status			
N0/N1	31	33	0.132
N2/N3	21	11	
Pathological Stage			
0/I/II	11	27	<0.0001*
III/IV	41	17	
Histotological evaluation of therapeutic effect			
0/1a/1b	47	24	<0.001*
2/3	5	20	

*Statistically significant

5B, the study patients were classified as follows: Group A, SUVmax > 6.8 and ΔSUVmax ≤ 45.7; Group B, SUVmax > 6.8 and ΔSUVmax > 45.7; Group C, SUVmax ≤ 6.8 and ΔSUVmax ≤ 45.7; and Group D, SUVmax ≤ 6.8 and ΔSUVmax > 45.7. The RFS was longest in Group D and did not reach the median RFS of the overall cohort (Fig. 5C). The comparison of RFS between the two groups with high SUVmax (Fig. 5D) indicated that although the recurrence rate was low in Group D, there was no statistical difference in RFS compared to Group B ($P = 0.073$). The RFS was significantly different between groups C and D, both of which had low SUVmax ($P < 0.05$) (Fig. 5E). There are no statistical differences in RFS between groups B and C ($P = 0.91$) (Fig. 5F). Finally, comparison of the RFS rate between Group D and other groups revealed that Group D showed a significantly lower reduced recurrence rate in all cStage ($P < 0.001$) (Fig. 5G). In cStage II-III, where NAC was recommended, comparing the RFS rate between Group D and the other groups revealed Group D also showed a significantly lower reduced recurrence rate ($P < 0.01$) (Fig. 5H).

Analysis of clinicopathological and pathological factors using SUVmax in combination with ΔSUVmax

Next, we investigated the histopathological factors associated with clinical response to NAC by comparing Group D with all the remaining groups A, B and C merged together. As shown in Table 2, lymphovascular invasion ($P < 0.001$), T status (no residual tumor/T0/T1/T2 vs T3/T4) ($P < 0.001$), stage (0/I/II vs III/IV) ($P <$

0.0001) and histological therapeutic effect (grade 0/1a/1b vs 2/3) (P < 0.001) were significantly different between Group D and the merged A+B+C group. The clinical stages before NAC were Stage I in 6 cases, Stage II in 13 cases, and Stage III in 33 cases in Groups A, B, and C. In Group D, there were 3 cases of Stage I, 16 cases of Stage II, and 25 cases of Stage III. There was no statistical difference in the clinical stage before NAC between these two groups (P = 0.415). The distribution of histological response to NAC (A+B+C vs. D) is shown in Fig. 5. Briefly, the histological therapeutic grade was 0/1a in 69% (36/52) of the patients in the A+B+C group and only 18% (8/44) in Group D and grade 3 histological therapeutic response was observed only in Group D. Based on the assessment of surgical specimens, the histological therapeutic grade was significantly different between Group D and the other groups (Fig. 6) (P < 0.0001).

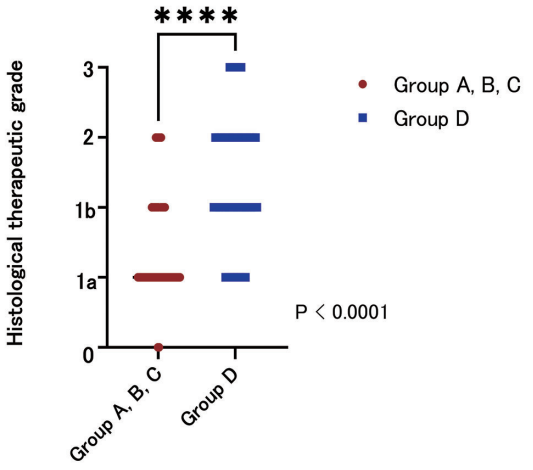

Figure 6 Comparison of the histological therapeutic effect among the groups
Comparison of the histological therapeutic effect between groups D and the others reveals that the rate of patients with higher therapeutic effects is higher in Group D than in the other groups (P < 0.001). Grade 3 histological therapeutic effect is observed only in Group D.

Clinicopathological factors associated with RFS

The univariate analysis of RFS revealed that the presence of lymphovascular invasion (P = 0.007), lymph node metastasis (N0/N1 vs N2/N3) (P = 0.015), stage (0/Ⅰ/Ⅱ vs Ⅲ/Ⅳ) (P < 0.001), histological evaluation (0/1a/1b vs 2/3) (P <0.01) and SUVmax/ΔSUVmax (Group A+B+ C vs D) (P < 0.001) were significantly correlated with RFS. However, multivariate analysis indicated that none of the parameters were significantly associated with RFS (Table 3).

Table 3. Univariate and Multivariate Analysis of the prognostic factors in esophageal cancer

			Univariate analysis		Multivariate analysis	
		N	Median RFS (months)	P-value	Hazard ratio (95% CI)	P-value
Age	≦65	55	21.9	0.143		
	>65	41	NA			
Localization	Upper /Middle	54	N/A	0.961		
	Lower/Abdominal esophagus	42	N/A			
Histology	No residual tumor/well/moderately	77	N/A	0.742		
	Poorly	19	48.9			
Lymphovascular invasion	Absent	38	N/A	0.007*	0.945 (0.407-2.194)	0.895
	Present	58	20.8			
T status	No residual tumor/T0/T1/T2	41	N/A	0.211		
	T3/T4	55	48.9			
N status	N0/N1	64	N/A	0.015*	1.311 (0.657-2.616)	0.443
	N2/N3	32	11.1			
Stage	0/I/II	38	N/A	<0.001*	2.109 (0.835-5.330)	0.115
	III/IV	58	12.2			
Histotological evaluation of therapeutic effect	0/Ia/1b	71	24.4	<0.01*	0.499 (0.177-1.414)	0.191
	2/3	25	N/A			
SUVmax/ΔSUVmax	Group A, B, C	52	12.1	<0.001*	0.537 (0.256-1.128)	0.101
	Group D	44	N/A			

*Statistically significant

Discussion

Several studies have indicated that FDG-PET can aid in assessing NAC response in esophageal cancer. However, the prognosis of locally advanced esophageal cancer remains poor in patients treated with NAC followed by surgery. The correlation of FDG activity with tumor, metabolic and histopathological responses has been reported[18]. The present study aimed to use ^{18}F-FDG-PET values to more accurately classify patients undergoing NAC followed by surgical resection as those with good and poor prognosis using postoperative recurrence as an indicator. By classifying patients into four groups based on SUVmax before and after NAC and the change in SUVmax after NAC, we found that the group with an SUVmax ≤ 6.8 and a ΔSUVmax > 45.7 had significantly fewer postoperative recurrences than the other three groups. Additionally, the same group exhibited significant differences from the other groups in terms of the histological evaluation of surgical resection specimens, including the disappearance of tumor tissue. Previous reports also reported that a high SUVmax after NAC was associated with early postoperative recurrence and poor prognosis[10-12]. Other previous studies reported a lower SUVmax after NAC indicated better histological therapeutic response[10, 11, 19]. Other studies evaluating SUVmax before and after NAC reported that a higher rate of decrease in SUVmax was associated with better histological therapeutic effect and better prognosis[13, 14]. Consistent with previous studies, we also found that the RFS was significantly shorter in patients with higher SUVmax and lower ΔSUVmax (Group A). However, the cut-off SUVmax and ΔSUVmax, which correlated with recurrence and histopathological therapeutic efficacy, differed widely among the previous studies[10-15, 19]. Therefore, we consider the next step in establishing these parameters as predictors of prognosis in these patients should include the determination of optimal cut-off values.

We also classified the patients into four groups based on cut-off SUVmax and ΔSUVmax to determine the association of these groups with recurrence and histopathological therapeutic efficacy. We hypothesised that this classification would identify patients with high ΔSUVmax and SUVmax. In other words, this approach would allow us to identify patients who would be more likely benefit from NAC but would have more residual tumor tissue and worse prognosis, exhibiting refractoriness to treatment. We found that the recurrence rate tended to be higher in patients with high SUVmax in the ΔSUVmax-group and that the recurrence rate was significantly higher in patients with low ΔSUVmax in the SUVmax-low group. These findings suggest that our classification strategy using SUVmax and ΔSUVmax in combination might allow the selection of patients who may exhibit favorable postoperative recurrence outcomes following NAC compared to using each parameter alone. Furthermore, histological evaluation of the surgical resected specimens revealed that the group with the lowest recurrence rate (SUVmax-low and ΔSUVmax-high) had a significantly higher histological response to NAC than the other three groups.

Tumor cells utilise glucose transporters (Glut) on the cell membrane for FDG uptake, which is measured using PET-CT[20]. Glut are overexpressed in tumor cells, and the surrounding environment of highly malignant and proliferating cancer cells is hypoxic. Therefore, hypoxia induced factor 1α, a hypoxia marker, which is elevated in these areas, induces various growth factors, including endothelial growth factors, and Glut[21-23]. The FDG uptake through Glut suggests a correlation between cancer malignancy and SUVmax. Consistently, in

the present study, the recurrence was low in patients with low SUVmax and high ΔSUVmax, who had tumor cells that responded well to chemotherapy and had few residual tumors. In other words, our classification strategy could identify patients with a low postoperative recurrence rate. Still, we were not able to identify patients in which the tumor disappeared after complete response to NAC (grade 3). This finding has been reported in previous studies[14, 19]. The identification of such patients is also essential in avoiding highly invasive surgery including esophagectomy with extended three-field lymph node dissection. Molena et al. suggested that pathological complete response should be determined by a combination of several factors, including a low SUVmax and a high rate of decrease in SUVmax, no residual tumor on endoscopic biopsy and no suspicious tumor thickening on CT images[24]. Future studies are warranted to analyse patients exhibiting pathological complete response to preoperative chemotherapy from multiple perspectives. In addition, new standards incorporating functional diagnostics such as PET-CT should be considered.

We acknowledge that the present study has several weaknesses. First, this was a single-center retrospective analysis. Due to the small number of target patients, generalisation of our findings and the robustness of our conclusions are limited. Multi-institutional studies of patients with cStage II/III esophageal cancer are warranted to assess the prognostic efficacy of the combined use of SUVmax and ΔSUVmax. Second, we examined the relationship between SUVmax and recurrence with clinicopathological considerations. However, tumor malignancy may involve cancer cells, the surrounding environment, stroma and tumor immune cells. Therefore, future studies should include the tumor microenvironment as well.

Conclusion

The results of the present study, which evaluated therapeutic response to NAC in patients with esophageal cancer, suggest that the combined use of SUVmax after NAC and ΔSUVmax obtained with 18F-FDG-PET before and after NAC might be an indicator of RFS, illustrating the clinical relevance of this approach in planning postoperative follow-up in patients undergoing NAC.

Conflict of interest: Authors declare no conflicts of interest.

Funding: This research was not supporting by any funding.

Acknowledgments

The authors thank technical assistants: Ms. Sayumi Kubo.

We would like to thank Enago (www.enago.com) for English language editing.

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