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Maximum standardised uptake value of positron emission tomography as a predictor of oesophageal cancer outcomes

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Abstract

Objectives This study aimed to analyse the value of pre-operative ^{18}F-fluorodeoxyglucose positron emission tomography (PET)-computed tomography that can predict tumour pathological complete response, tumour histology grade, overall survival, and recurrence-free survival in patients with locally advanced oesophageal squamous cell carcinoma who underwent neoadjuvant chemoradiotherapy (NCRT) followed by surgery.

Methods We retrospectively reviewed the cases of patients with locally advanced oesophageal squamous cell carcinoma undergoing NCRT followed by surgery. Patients who did not undergo PET within 3 months of surgery were excluded. We set a pre-operative PET maximum standardised uptake value (SUVmax) of > 5 as the threshold and classified the patients into two groups. We analysed the tumour response and histology grade, and compared the overall survival and recurrence-free survival between the two groups.

Results This cohort included 92 patients with oesophageal squamous cell carcinoma who underwent NCRT followed by surgery; 49 patients had a pre-operative PET SUVmax < 5, and 43 patients had a pre-operative PET SUVmax > 5. The patients' pre-operative PET SUVmax correlated with tumour histology, ypT stage, and tumour response. Patients with a pre-operative SUVmax < 5 had better 2-year-overall survival (78% vs. 62%, $P < 0.05$) and 2-year recurrence-free survival (62% vs. 34%, $P < 0.05$) than those with a pre-operative SUV > 5.

Conclusions Pre-operative SUVmax may be useful to predict tumour response, survival, and recurrence in patients with locally advanced oesophageal squamous cell carcinoma who undergo NCRT followed by surgery.

Graphical Abstract

- Key question: What is the role of ^{18}FDG-PET/CT in evaluating outcomes of oesophageal cancer in patients undergoing NCRT followed by surgery?
- Key findings: Patients with a higher pre-operative PET SUV max > 5 for the primary tumour had worse OS and recurrence-free survival than those with a pre-operative PET SUV max < 5.
- Home Message: Patients with oesophageal cancer who underwent NCRT followed by surgery with a higher pre-operative PET SUVmax of the primary tumour had worse OS and recurrence-free survival.

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Keywords ^{18}FDG-PET/CT, Oesophagal squamous cell carcinoma, Locally advanced oesophagal cancer, NCRT followed by surgery

Introduction

Oesophageal cancer is the seventh most common cancer and sixth most common cause of cancer-related deaths [1]. Neoadjuvant chemoradiotherapy (NCRT) has become the standard treatment for locally advanced disease [2] and surgery has been shown to improve survival in some patients [3]. However, several studies have reported a significant proportion of disease recurrence after surgery [4].

Previous studies have demonstrated the value of positron emission tomography (PET) in predicting the outcomes of oesophageal cancer [1–11]. Hamai et al. published a study on the correlation between the maximum standardised uptake value (SUVmax) after neoadjuvant chemoradiotherapy (NCRT) and tumour histology grading. Marco et al. reported that pre-treatment metabolic tumour volume is a predictor of overall survival (OS) in patients undergoing tri-modality therapy [3]. However, in some hospitals, PET is not routinely performed before surgery or after NCRT.

The aim of this study was to analyse the value of preoperative PET for predicting outcomes in patients who underwent NCRT followed by surgery.

Patients and methods

Ethical statement

The experimental protocol was established in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the Institutional Review Board of Chang Gung Memorial Hospital (Institutional Review Board number:202400862B0). Given the retrospective design, the requirement of informed consent was waived.

Patient selection

We retrospectively reviewed the electronic medical records of patients diagnosed with oesophageal cancer who received NCRT followed by oesophagectomy between January 2014 and December 2018 at Kaohsiung Chang Gung Memorial Hospital. Patients were evaluated by a multidisciplinary team that included surgeons, oncologists, radiologists, and therapeutic radiologists. Evaluations before treatment included panendoscopy, endoscopic ultrasound, chest computed tomography (CT), and PET-CT scan. The 8th American Joint Committee on Cancer (AJCC) staging system was used for cancer staging. Patients were excluded if they had unclear medical records, received treatment at other hospitals, had pathology results other than squamous cell carcinoma, did not undergo a PET scan within 3 months before surgery, or were lost to follow-up.nitially, 110 patients were included in this cohort; 3 patients were excluded because their pathology was adenocarcinoma, 10 were excluded because they did not undergo PET within 3 months before surgery, and 5 were excluded because they were previously treated at another hospital and their medical records could not be obtained.

Treatment plan

After confirming the study and tumour staging, all patients underwent concurrent chemoradiation therapy. The chemotherapy regimen, which included two cycles of cisplatin (75 mg/m^2, administered via a 4-hour infusion) and a 5-fluorouracil-based regimen (1000 mg/m^2, administered as a continuous infusion) on days 1–4 of each 4-week cycle. Radiotherapy was delivered at two different doses: 4140, and 5040 cGy, in daily fractions over five days each week. Patients diagnosed with Stage IV oesophageal cancer, or for whom surgery is not considered adequate based on their condition at diagnosis, will be treated with 5040 cGy, while other patients will receive 4140 cGy. Three-dimensional conformal radiotherapy (CRT) using a four-field technique or intensity-modulated radiotherapy (IMRT) with 6 or 10 MV photons was employed. The gross tumour volume (GTV) was defined as the visible tumours and lymph nodes on computed tomography (CT) and/or whole-body positron emission tomography (PET). The clinical target volume (CTV) included the esophagus, mediastinal lymph nodes, both sides of the neck, and lymph nodes above the clavicle. The planning target volume (PTV) was expanded from the CTV by an additional margin of 0.5–1.0 cm in all directions. After treatment, evaluations were conducted within 3–4 weeks, including CT scans from the neck to the upper abdomen, endoscopic examinations, and/or PET/CT scans to assess the response to treatment. Esophagectomies, performed using the McKeown procedure by two surgeons, were carried out within 3 months following chemoradiotherapy. Consistency was maintained in operating room configurations, team compositions, and surgical instruments. Each surgeon conducted routine lymph node dissections from the subcarinal, paraesophageal, bilateral recurrent laryngeal nerve area, celiac, and perigastric regions. Specimens from the esophagectomies were sent to the pathology laboratory for comprehensive evaluation, including the entire excised esophagus and the thoracic and abdominal lymph nodes. Pathologists assessed tumour characteristics, tumour grade, lymphovascular invasion, resection margins, and staging according to the eighth edition guidelines of the American Joint Committee on Cancer.

Table 1 Associations between PET SUVmax and clinicopathologic parameters in patients with oesophageal cancer undergoing chemoradiotherapy followed by surgery

Parameters	All patient 92	SUVmax before surgery < 5	SUVmax before surgery > 5	*P*-value
Age at diagnosis				
> 60	22	9	13	0.139
≤ 60	70	40	30	
Gender				
Male	88	47	41	0.641
Female	4	2	2	
Clinical stage before treatment				
Stage I	3	1	2	0.303
Stage II	7	6	1	
Stage III	46	23	23	
Stage IV	36	19	17	
ypT stage				
T0	29	25	4	< 0.05
T1/T2	24	12	12	
T3/T4	39	12	27	
ypN stage				
N0	70	37	33	0.524
N1	17	8	9	
N2	3	2	1	
N3	2	2	0	
Histologic grade of the resected tumour				
No malignancy	29	25	4	< 0.001
Well-differentiated	0	0	0	
Moderately differentiated	55	19	36	
Poorly differentiated	8	5	3	
Pathologic Complete response of resected tumour				
Complete response	29	25	4	< 0.001
Residual malignancy	63	24	39	
Location of the primary tumour				
Upper	15	7	8	0.605
Middle	40	20	20	
Lower	37	22	15	
Radiotherapy Dosage				
< 5000	49	13	36	0.257
> 5000	43	8	35	
BMI				
BMI < 20	49	14	35	0.187
BMI ≥ 20	43	17	26	
Lymph node PET uptake before surgery				
SUVmax > 1	50	28	22	0.358
SUVmax < 1	42	21	21	

PET, positron emission tomography; SUVmax, maximum standardised uptake value; BMI, body mass index; T, extent of the tumour; N, extent of spread to lymph nodes; * statistically significant

The x (2) test or Fisher's exact test was used for statistical analysis

18FDG-PET/CT protocol

Patients fasted for 6 h prior to the 18FDG-PET/CT scan, with the exception of water. Following an intravenous injection of approximately 10 mCi of 18FDG via the antero-median vein, a whole-body PET/CT scan was performed using the Discovery PET/CT 710 system (GE Healthcare) 60 min after the radiotracer injection. Before acquiring PET images, a non-contrast, low-dose spiral CT scan with 3.75 mm slice thickness was performed from head to thigh. The reconstructed CT images were then used to generate the parameters needed for PET imaging attenuation correction. A whole-body PET scan was subsequently conducted for 25 min. All PET/CT data analysis, including image fusion, was carried out using Xeleris software (GE Healthcare) following standardized operating procedures [4].

Overall and recurrence-free survival

OS was defined as the period from the date of oesophagectomy to the last contact date. An event was defined as the patient's death; if the patient was alive, it was defined as censored. Recurrence-free survival was defined as the period from the date of oesophagectomy to the date of recurrence or death. If chest CT or PET revealed suspected recurrence and a biopsy revealed malignancy in the oesophagus, we defined it as an event. If it showed stability or regression, it was considered censored.

Statistical analysis

Statistical analyses were performed using the SPSS version 23. X^2 test or Fisher's exact test was used to compare data between variables. We used Kaplan–Meier analysis to evaluate survival outcomes and for univariate analysis. The log-rank test was used to analyse differences between survival curves. For all analyses, $P<0.05$ was considered significant.

Results

Patient characteristics

The baseline characteristics and demographic data of the 92 patients are shown in Table 1. In this cohort, the SUVmax of the primary tumour of 49 patients during the PET performed before surgery were < 5, and those for the remaining 43 patients were > 5. The median age of the 92 patients was 54 years, and the mean age was 54.6 years. Of the 43 patients with a PET SUV > 5 before surgery, the median age was 55 (range, 40–76) years, and the mean age was 55.63 years. For the 49 patients with PET SUV uptake maximum before surgery < 5, the median age was 51 (range, 37–76) years, and the mean age was 53.70 years. There were no significant differences between the two groups regarding age > 60 years, sex, clinical stage before treatment, ypNstage, radiotherapy dosage, BMI > 20, and lymph node PET SUVmax uptake before

surgery. Significant differences were observed between the two groups regarding the ypT stage, histological grade of the resected tumour, and pathologic response of resected tumour .

OS and recurrence-free survival

The results of the log-rank test of clinical parameters for 2-year OS and 2-year progression-free survival are shown in Table 2. Patients with advanced ypT stage and ypN

Table 2 Univariate log-rank analysis of prognostic factors for overall survival and disease-free survival in patients diagnosed with oesophageal cancer who underwent NCRT followed by surgery

Parameters	No. of patients	Overall survival (OS)		Recurrence-free survival (RFS)	
		2-year OS rate (%)	*p*-value	2-year PFS rate (%)	*p*-value
Age at diagnosis					
> 60	22	53	0.333	31	0.453
≤ 60	70	70		68	
Gender					
Male	88	66	0.439	76	0.687
Female	4	75		50	
Clinical stage before treatment					
Stage I	3	33	0.912	0	0.264
Stage II	7	50		38	
Stage III	46	62		49	
Stage IV	36	53		41	
ypT stage					
T0	29	96	< 0.005	82	< 0.001
T1/T2	24	62		49	
T3/T4	39	54		26	
ypN stage					
N0	70	73	0.027	57	0.001
N1	17	57		36	
N2	3	33		0	
N3	2	0%		0	
Histologic grade of the resected tumour					
No malignancy	29	96.6	< 0.001	89.1	< 0.001
Well-differentiated	0	0		0	
Moderately differentiated	55	53.6		48.1	
Poorly differentiated	8	70		37.5	
Location of the primary tumour					
Upper	15	57	0.194	44	0.219
Middle	40	80		62	
Lower	37	60		39	
Radiotherapy dosage					
< 5000	21	77	0.681	64	0.913
> 5000	71	64		70	
BMI					
BMI < 20	31	59	0.626	47	0.647
BMI ≥ 20	61	46		51	
Primary tumour PET uptake before surgery					
SUVmax before surgery < 5	49	78	0.01	62	0.016
SUVmax before surgery > 5	43	55		34	
Lymph node PET uptake before surgery					
SUVmax before surgery < 1	42	76	0.122	58	0.086
SUVmax before surgery > 1	50	62		43	
Pathologic response of resected primary tumour					
Complete response	24	95	< 0.001	91	< 0.001
Residual malignancy	68	58		37	

SUVmax, maximum standardised uptake value; PET, positron emission tomography; NCRT, neoadjuvant chemoradiotherapy; BMI, body mass index; T, extent of the tumour; N, extent of spread to lymph nodes; * statistically significant

The x (2) test or Fisher's exact test was used for statistical analysis

stage had poor OS and progression-free survival. Tumour grade also had an impact on OS ($P=0.001$) and recurrence-free survival ($P<0.001$). Patients with complete tumour response had a significantly better prognosis than those with residual malignancy regarding both the 2-year OS (95% vs. 58%, $P<0.001$) and 2-year recurrence-free survival (91% vs. 37%, $P<0.001$). Additionally, >5 PET SUVmax before surgery also had an impact on both the OS ($P=0,01$, Fig. 1A) and progression-free survival ($P=0.016$, Fig. 1B). The 2-year OS was 55% for patients with a pre-operative PET SUVmax<5, and 78% for those with a pre-operative PET SUVmax uptake<5. The 2-year recurrence-free survival rates between the groups before surgery (<5 and >5) were 62% and 34%, respectively.

Discussion

We analysed the value of pre-operative PET as a tool for the prediction of post-operative outcomes in patients with oesophageal cancer who underwent NCRT followed by surgery. We set the threshold for the PET SUVmax within 3 months before surgery to 5 to predict outcomes; the PET SUVmax had a significant effect on OS and recurrence-free survival, as well as a significant correlation with tumour response, tumour grade, and ypT stage.

Previous studies have discussed the value of PET for predicting the outcomes of oesophageal cancer [1–11]. Some studies highlighted ΔSUVmax (pre-treatment PET SUVmax – post-treatment PET SUVmax) as a predictor of tumour response, pathology grade, and outcome for patients who receive tri-modality treatment [7]. SUVmax has also been used as a predictor of tumour response during radiotherapy [8]. Other studies have used pre-treatment PET as a tool to predict outcomes after oesophagectomy [5, 9, 10]. Mantziari et al. reported that a baseline PET SUVmax>12.7 was associated with early tumour recurrence and poor disease-free survival in patients who underwent both multi-modality treatment and surgery alone [9].

The sensitivity and specificity of PET scans in predicting responses to neoadjuvant therapy for esophageal cancer have been previously discussed. Chen, Y.M., et al. conducted a meta-analysis that found the pooled sensitivity and specificity of 18 F-FDG PET in evaluating neoadjuvant therapy response in patients with esophageal cancer to be 70.3% and 70.1%, respectively [12]. In our study, using an SUVmax>5 as a cut-off point for detecting residual tumors resulted in a sensitivity of 90.1% and a specificity of 51%, with a false positive rate of 9.9%. The false positive rate may be attributed to radioactive esophagitis following radiotherapy.In our study, the pre-operative SUVmax correlated with tumour response, which is a significant predictor of good outcomes. Patients with a complete tumour response achieved a 2-year OS of up to 95% and a 2-year recurrence-free survival of up to

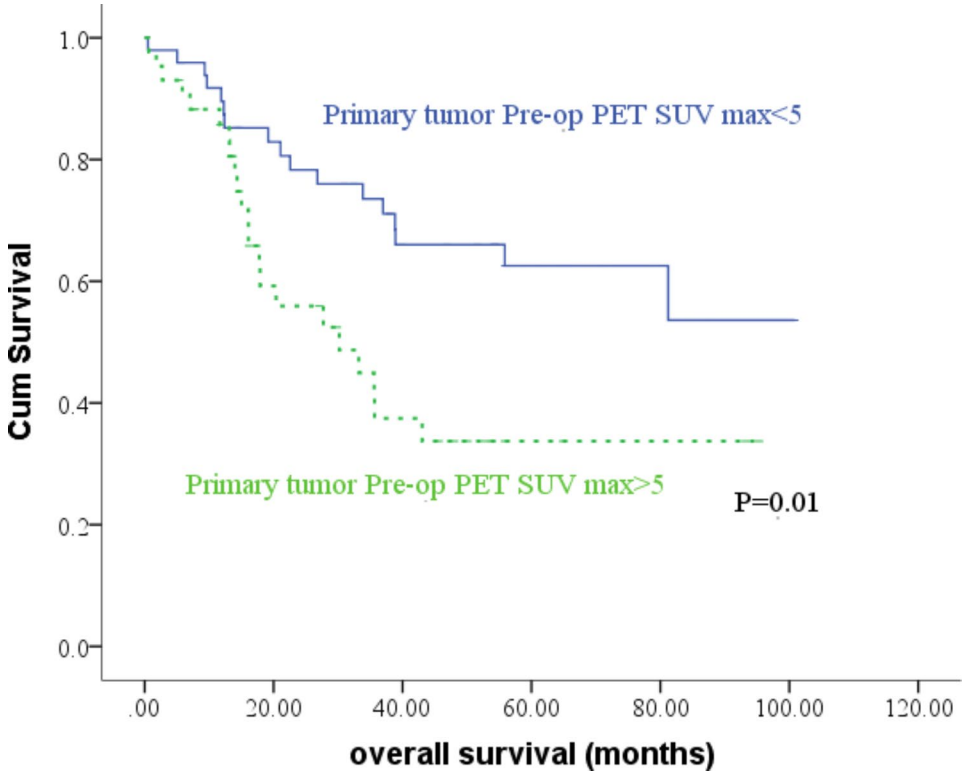

Fig. 1A Overall survival curve of pre-operative (pre-op) PET SUVmax (>5 and <5). SUVmax, maximum standardised uptake value; PET, positron emission tomography

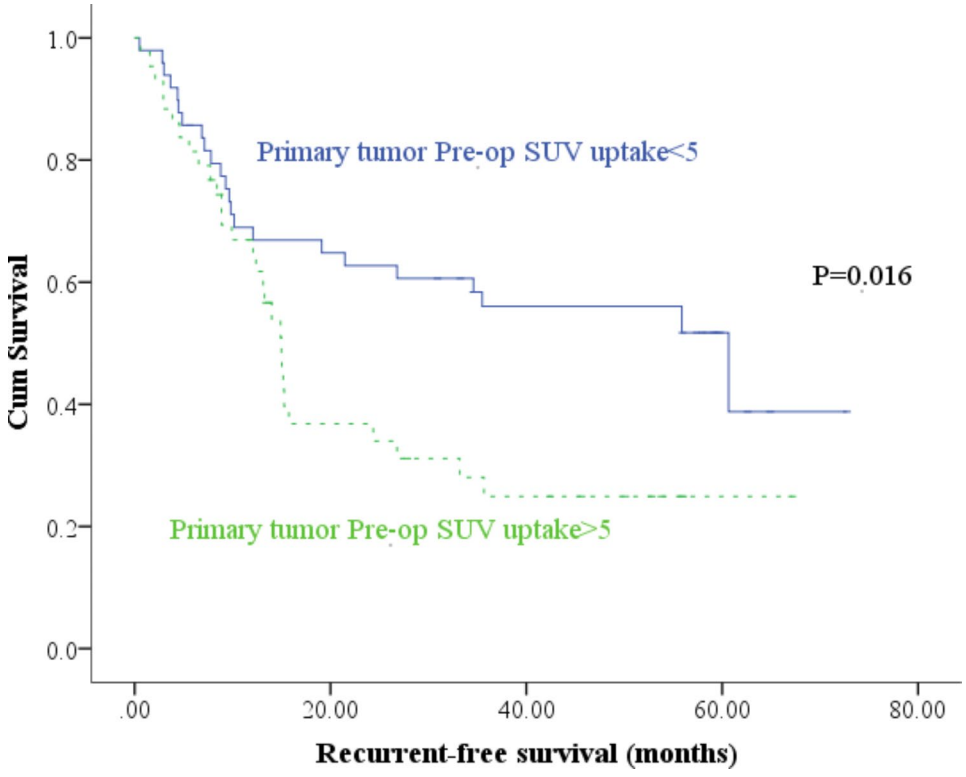

Fig. 1B Overall survival curve of pre-operative (pre-op) PET SUVmax (>5 and <5). SUVmax, maximum standardised uptake value; PET, positron emission tomography

91%, while those with residual malignancy only achieved 58% and 37%, respectively. Several studies have reported similar results [4, 11]. However, each study sets a different threshold. Sasaki et al. set a pre-operative SUVmax of >5.5 as a cut-off value according to the ROC curve [11] while the study by Feng et al. set SUVmax of >3 as the threshold. In our opinion, the higher the pre-operative SUVmax, the higher the risk of poor prognosis; however, a larger cohort and further studies are required for a definitive threshold.

Our study had several limitations, including the retrospective design and the fact that it was a single-centre study, which may have caused selection bias and small. Additionally, we did not exclude patients who died of surgical complications; this may have affected the accuracy of our results.

In conclusion, for patients who have undergone NCRT followed by surgery, pre-operative PET may be used as a tool to predict tumour response, and post-operative outcome and may be used as a reference for sharing decision-making with patients before surgery.

Abbreviations

^{18}FDG-PET/CT	^{18}F-fluorodeoxyglucose positron emission tomography (PET)-computed tomography
AJCC	American Joint Committee on Cancer
BMI	body mass index
CCRT	concurrent chemoradiotherapy
CT	computed tomography
NCRT	neoadjuvant chemoradiotherapy
PET	positron emission tomography
SUVmax	maximum standardised uptake value

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-024-03072-4.

Supplementary Material 1

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Author contributions
Conceptualization: Hsing-Hua Lai and Wei HoData curation: Chien-Ming LoFormal Analysis: Hsing-Hua Lai and Wei HoInvestigation: Kai-Hao ChuangMethodology: Hsing-Hua Lai and Wei HoProject administration: Chien-Ming LoResources: Chien-Ming Lo , Yu Chen, Li-Chun ChenSoftware: Yu ChenSupervision: Hung-I LuValidation: Yu ChenVisualization: Chien-Ming LoWriting – original draft: Hsing-Hua Lai and Wei HoWriting – review & editing: Chien-Ming Lo.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
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