Maximum Standardized Uptake Value in Lymph Nodes Measured by ^{18}F -FDG PET/CT Predicts the Outcome of Patients with Oesophagus Squamous Cell Carcinoma

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Research

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Abstract

Background: To investigate the prognostic value of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) in esophagus squamous cell carcinoma (ESCC), PET/CT imaging characteristics were explored in the present study.

Methods: Baseline PET/CT and clinical characteristics were collected in 125 patients with ESCC treated with radical radiotherapy from 2007–2016. The maximum standardized uptake value (SUVmax) of the primary gross tumour (SUVmax-T) and metastatic lymph node (SUVmax-N) were separately measured using X-tile. Overall survival (OS) and progression free survival (PFS) were estimated according to the Kaplan–Meier method. A multivariate Cox model was used to establish the independent prognostic factors.

Results: The gross tumours presented higher ^{18}F -FDG uptake than normal tissues with a median SUVmax-T of 12.5. The OS and PFS did not show significant differences between patients with SUVmax-T ≥ 12.5 and those with SUVmax-T <12.5 ($P>0.05$). However, patients with SUVmax-N ≥ 11 had a significantly worse OS and PFS than those with SUVmax-N <11 ($P<0.05$). A weak correlation was observed in SUVmax-T and SUVmax-N. The OS and PFS of patients with PET-negative LNs was significantly better than those with PET-positive LNs. However, the OS and PFS of patients with one or two PET-positive LNs were not significantly better than those with more than two PET-positive LNs. In the univariate analysis, cT stage, positive or negative lymph nodes on the PET-CT image and the SUVmax-N were established as significant prognostic factors for both OS and PFS. In multivariate analysis, SUVmax-N was proved to be an independent predictor for OS and PFS.

Conclusions: SUVmax-N, but not SUVmax-T, is an independent prognostic indicator for patients with ESCC.

Background

Though progress has been made in evaluation and treatment strategies in recent decades, oesophagus carcinoma remains a lethal disease. In comparison with the consistently increasing occurrence of oesophagus adenocarcinoma in developed countries, oesophagus squamous cell carcinoma (ESCC) still predominates in Asians[1]. Apart from surgery, concurrent chemoradiotherapy (CRT) has been widely accepted as an alternative radical treatment option for patients with inoperable locally advanced or unresectable ESCC, including patients with cervical oesophageal tumours[2]. However, for patients treated with CRT, no precise staging evaluation for tumour size and lymph node metastasis, which are the most significant established prognostic factors, is available due to a lack of specimens[3]. With respect to clinical evaluations of the number of metastatic lymph nodes, even positron emission tomography/computed tomography (PET/CT) and ultrasonography endoscopy can only provide a rough estimation[4, 5]. The underlying implication of lymph nodes has not been fully understood.

By revealing the significantly increased glucose metabolism of tumour cells over that of normal cells, PET/CT has played an important role in the diagnosis, staging and restaging of tumours after neoadjuvant therapies, delineating target volume in radiotherapy, evaluating therapeutic and predicting the prognosis of cancer[5]. A few studies have focused on the correlation of metabolic parameters such as the standard uptake values (SUVs) of gross tumours and survival outcomes in patients with ESCC but have reached controversial conclusions. A meta-analysis that included 10 studies concluded that a high maximum of standard uptake value (SUVmax) of the primary tumour predicted a poor overall survival with a hazard ratio of 1.86 (95%CI,1.53–2.27), but the cut-point to define a high SUV ranged widely in these studies (3–15)[6]. A multi-centre prospective study reported that the SUV of the baseline gross tumour had a negative prognostic value in oesophageal cancer patients[7]. In contrast, few studies have concentrated on metastatic lymph nodes. Yap W.K. et al reported that a high nodal SUVmax predicted poor outcomes in ESCC patients treated with definitive chemoradiotherapy in a cohort of 62 patients[8]. Moreover, the nodal SUVmax correlates with prognosis in patients with head and neck cancer[9]. Therefore, our aim is to explore and validate the prognostic value of the metabolic characteristics of lymph nodes in a large cohort.

Methods

The electronic medical records of patients with ESCC who were treated with radical radiotherapy or concurrent chemoradiotherapy and underwent a baseline PET/CT scan in the XXXX between 2007 and 2016 were retrospectively reviewed. The inclusion criteria were as follows: 1) histologically confirmed squamous cell cancer without clinical evidence of metastasis evaluated by a combination of physical examination, PET/CT and ultrasound of abdomen and neck (if available); 2) treatment with concurrent chemoradiotherapy (radiation dose ≥ 50 Gy) or radiotherapy alone (radiation dose ≥ 60 Gy) as radical primary treatment without endoscopic resection; 3) PET/CT scan within one month before beginning treatment; and 4) clinical records including a complete history, complete physical examination, complete blood count, comprehensive chemistry profile and upper gastrointestinal endoscopy were available. TNM staging was performed according to the American Joint Committee on Cancer (AJCC) seventh edition. The evaluation of cN took the metabolic features of both nodes on PET/CT (SUVmax > 2.5) and size into account. Upper tracheoesophageal groove lymph nodes with lengths > 5 mm and other nodes with lengths > 10 mm were considered clinical metastases, regardless of SUV on PET. This study was approved by the Research Ethics Committee of XXXX.

PET/CT

Pretreatment FDG/PET scans were performed for staging purposes. Patients were asked to fast for at least 6 hours before the examination and were injected intravenously with ^{18}F -FDG (7.4 MBq/kg). Images were acquired approximately 60 min after the intravenous administration of the tracer. Whole-body PET/CT emission scans were obtained from the base of the skull to the mid thigh. ^{18}F -FDG PET/CT was performed using a Siemens biograph 16HR PET/CT (Knoxville, Tennessee, USA). The FDG-PET images were interpreted by an experienced nuclear medicine doctor and correlated with the computed

tomography images. The maximum standardized uptake value (SUVmax) of the primary gross tumour (SUVmax-T) and metastatic lymph node (SUVmax-N) were separately measured. Lymph nodes with SUVmax > 2.5 were defined as PET positive. The number of PET-positive nodes was also recorded.

Surveillance

The surveillance protocol consisted of follow-up clinic appointments (every 3 months during the first 2 years, every 6 months during the third to fifth years, and every 12 months thereafter). Routine follow-up examinations included a chest CT with contrast, oesophagus barium X and ultrasound examination of the neck and abdominal sites. Upper gastrointestinal endoscopy was performed every 6–12 months or when symptoms indicated recurrence.

Statistical analysis

Analyses were mainly performed using SPSS version 15.0 (SPSS Inc., Chicago, USA) and GraphPad Prism 7.0 (GraphPad Software, Inc., San Diego, USA). All P values are two-tailed, and $P < 0.05$ was considered statistically significant. The correlation was evaluated by Pearson's correlation coefficient. The SUVmax cut-point for survival analyses was determined by X-tile software 3.6.1 (Yale University School of Medicine, New Haven, USA)[10]. The overall survival (OS) time was calculated from the date that treatment began until death or loss to follow-up. Progression free survival (PFS) was defined as recurrence or distant metastasis identified by imaging studies or endoscopy with histological proof and/or requiring clinical interventions. Survival curves were estimated according to the Kaplan–Meier method, and statistical comparisons were performed by log-rank tests. Univariate Cox regression analysis was performed for all prognostic factors with respect to overall survival (OS) and progression-free survival (PFS). Multivariate Cox regression analysis was used to determine the independent prognostic factors.

Results

Characteristics of the Patients

A total of 125 patients who met the inclusion criteria were included in our study (Table 1). The chemotherapy included platinum-based, Fluorouracil-based or Paclitaxel-based regimens. The majority of patients were male (86.4%), and the median age was 64 years (interquartile range 56–70). Nearly two-thirds of the patients were current smokers or ex-smokers, and approximately half of the patients were frequent alcohol consumers. Remarkably, patients with a high SUVmax-N were more likely to have linear relatives who were diagnosed with malignant tumours than patients with a low SUVmax-N, suggesting a genetic basis for tumour generation. A total of 69.6% of the patients presented with cT3 or cT4 tumours, and 75.2% of the patients were recognized to have clinical regional lymph node metastasis. The characteristics of the patients are summarized in Table 1.

Table 1
Patients' clinical characteristics in the study cohort

Characteristic	All patients (n = 125)	LN PET-Negative(n = 42)	SUVmax-N < 11(%) (n = 66)	SUVmax-N ≥ 11(%) (n = 17)	P
Gender					0.179
Male	108(86.4)	39(92.9)	55(83.3)	14 (82.4)	
Female	17(13.6)	3(7.1)	11(16.7)	3(17.6)	
Age					0.916
≤60	40(32.0)	12(28.6)	24(36.4)	4(23.5)	
≥ 60	85(68.0)	30(71.4)	42(63.6)	13(76.5)	
Tobacco					0.364
Yes	81(64.8)	17(40.5)	22(33.3)	5(29.4)	
No	44(35.2)	25(59.5)	44(66.7)	12(70.6)	
Alcohol					0.045
Yes	62(49.6)	26(61.9)	31(47.0)	6(35.3)	
No	63(50.4)	16(38.1)	35(53.0)	11(64.7)	
Family history					0.002
No	13(2.4)	28(66.7)	59(89.4)	16(94.1)	
Yes	112(89.6)	14(33.3)	7(10.6)	1(5.9)	
cT					0.084
T1	2(1.6)	2(4.8)	0	0	
T2	36(28.8)	14(33.3)	19(28.8)	3(17.6)	
T3	51(40.8)	17(40.5)	25(37.9)	9(52.9)	
T4	36(28.8)	9(21.4)	22(33.3)	5(29.4)	
cN					0.021
N0	31(24.8)	0	0	0	
N1	60(48.0)	14(100.0)	37(61.7)	9(45.0)	

Abbreviations: LN: lymph node; SUVmax-N: the maximum standardized uptake value of metastatic lymph node

Characteristic	All patients (n = 125)	LN PET-Negative(n = 42)	SUVmax-N < 11(%) (n = 66)	SUVmax-N ≥ 11(%) (n = 17)	P
N2	32(25.6)	0	22(36.7)	10(55.0)	
N3	2(1.6)	0	1(1.7)	1(5)	
PET-positive LN					0.282
1–2	-	-	41	8	
≥ 3	-	-	25	9	
Site					0.615
Cervical	30(24.0)	10(23.8)	15(22.7)	5(29.4)	
Upper	27(21.6)	12(28.6)	10(15.2)	5(29.4)	
Middle	41(32.8)	9(21.4)	27(40.9)	5(29.4)	
Lower	27(21.6)	11(26.2)	14(21.2)	2(11.8)	
Abbreviations: LN: lymph node; SUVmax-N: the maximum standardized uptake value of metastatic lymph node					

Correlation of SUVmax-T and prognosis

The median overall survival (OS) for all patients was 36.4 months with a median survival of 20.6 months (range: 30.3 -101.2 months). The 2-year, 3-year and 5-year overall survival rates in our cohort were 62.4%, 48.3% and 27.1%, respectively. Sixty-six of the total 125 patients had disease progression in the follow-up, of which the most common progressions were distant metastasis (22/66) and recurrence (20/66). The 2-year, 3-year and 5-year progression-free survival rates were 51.4%, 36.8% and 23.7%, respectively.

The gross tumours of all patients presented higher 18F-FDG uptake than normal tissues with a median SUVmax-T of 12.5 and ranged from 2.9 to 32.8. In total, 83 patients had PET-positive lymph nodes (LNs), and the SUVmax-T of these patients was significantly higher than those with PET-negative LNs (mean: 14.2 vs 10.3, $P < 0.01$). The maximum, mean and median SUVmax-N were 23.7, 8.0 and 7.3 in patients with PET-positive LNs, respectively. As shown in Fig. 1, only a weak correlation was found between SUVmax-N and SUVmax-T (Pearson $r = 0.284$).

The survival analysis using X-tile revealed that no proper threshold of SUVmax-T could distinguish between groups of patients with different prognoses. Taking the median SUVmax-T (12.5) as the cut-point, there was no significant difference in the OS (median survival time: 41.2 vs 30.7 months, $P = 0.902$,

Fig. 2A) or PFS (median survival time: 23.4 vs 27.6 months, $P = 0.972$, Fig. 2B) of patients with high SUVmax-T ($n = 62$) and low SUVmax-T ($n = 63$).

Correlation of SUVmax-N and prognosis

The number of PET-positive LNs also could not predict prognosis properly. The OS (median survival time: 47.0 vs 26 months, $P < 0.01$, Fig. 3A) and PFS (median survival time: 37.3 vs 13.9 months, $P < 0.01$, Fig. 3B) of patients with PET-negative LNs was significantly better than those with PET-positive LNs. However, the OS and PFS of patients with one or two PET-positive LNs were not significantly better than those with more than two PET-positive LNs (OS: median survival time 30.7 vs 25.7 months, $P = 0.96$, Fig. 3A; PFS: median survival time 13.2 vs 13.0 months, $P = 0.70$, Fig. 3B).

An SUVmax-N ≥ 11 was set as the definition for a high SUVmax-N according to the X-tile analysis. Patients with high SUVmax-N had a significantly worse OS and PFS than those with low SUVmax-N (OS: median survival time 30.7 vs 15.9 months, $P = 0.02$, Fig. 3C; PFS: median survival time 19.1 vs 7.2 months, $P < 0.01$, Fig. 3D), suggesting that SUVmax-N is a valuable prognostic indicator. Meanwhile, no correlation was found between SUVmax-N and the number of PET-positive LNs (Pearson $r = 0.12$), cT (Pearson $r = -0.13$) or clinical staging (Pearson $r = 0.05$). In the univariate analysis, cT staging, positive or negative lymph nodes on the PET-CT image and the SUVmax-N were established as significant prognostic factors for both OS and PFS (Table 2), and the multivariate analysis showed that SUVmax-N remained as an independent predictor for OS and PFS.

Table 2
Univariate analysis of potential factors affecting OS and PFS

	OS			PFS		
Variable	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age						
<60	1	-		1	-	
≥60	1.179	0.706–1.969	0.528	1.036	0.625–1.717	0.892
Gender						
Male	1	-		1	-	
Female	0.886	0.419–1.875	0.752	0.762	0.362–1.606	0.475
Tobacco						
Yes	1	-		1	-	
No	1.457	0.850–2.498	0.171	1.635	0.950–2.814	0.076
Alcohol						
Yes	1	-		1	-	
No	1.603	0.980–2.623	0.060	1.573	0.965–2.563	0.069
Family history						
No	1	-		1	-	
Yes	1.817	0.897–3.681	0.097	1.454	0.759–2.784	0.259
cT	1.189	1.078–1.810	0.049	1.087	1.013–1.452	0.047
PET-positive LN						
No	1	-		1	-	
Yes	2.147	1.204–3.830	0.010	2.621	1.416–4.852	0.002

Abbreviations: OS: overall survival; PFS: progression free survival; LN: lymph node; SUVmax-T: the maximum standardized uptake value of primary tumor; SUVmax-N: the maximum standardized uptake value of metastatic lymph node

	OS			PFS		
SUVmax-T	1.022	0.978– 1.068	0.337	1.020	0.976– 1.066	0.384
SUVmax-N	1.071	1.028– 1.115	0.001	1.089	1.048– 1.132	0.000
Abbreviations: OS: overall survival; PFS: progression free survival; LN: lymph node; SUVmax-T: the maximum standardized uptake value of primary tumor; SUVmax-N: the maximum standardized uptake value of metastatic lymph node						

Table 3
Multivariate Cox regression analysis of potential factors affecting OS and PFS

Variable	Hazard Ratio	95% CI	P value
OS			
SUVmax-N	1.075	1.028–1.124	0.001
PFS			
cT			
T1	1		
T2	-	-	0.984
T3	3.447	1.050–11.311	0.041
T4	4.650	1.655–13.063	0.004
PET-positive LN			
No	1	-	
Yes	2.607	1.042–6.519	0.040
SUVmax-N	1.092	1.049–1.138	0.000
Abbreviations: OS: overall survival; PFS: progression free survival; LN: lymph node; SUVmax-N: the maximum standardized uptake value of metastatic lymph node			

To provide a clinically useful tool to predict prognosis, we constructed a nomogram that integrated the SUVmax-N and several clinicopathological risk factors associated with progression-free survival. The T stage, number of PET-positive LNs and SUVmax-N were included in the prediction model (Fig. 4). The C-index of the nomogram was 0.644.

Discussion

In the current study, we investigated the correlation of SUVmax-T, SUVmax-N and prognosis in ESCC. In current analysis, the SUVmax-T of patients with PET-positive LNs were significantly higher than those with PET-negative LNs. SUVmax-T was associated with metabolic tumor burden. Larger tumor burden always promotes local/regional metastasis[11]. Our study did not identify SUVmax-T as an appropriate prognostic predictor. The result was consistent with Vatankulu's study where metastatic lymph node SUVmax had an effect in predicting survival whereas primary tumor SUVmax did not have an effect[12]. This may be due to the fact that SUVmax-T only represented a few pixels instead of the whole tumour. Studies showed that among PET biomarkers, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) both reflect the metabolic tumor burden and are considered to be the strongest prognostic factors, even more so than tumoral maximal standardized uptake values (SUVmax)[13]. Some studies have shown that MTV or TLG, after taking the tumour size into consideration, are better prognostic predictors than SUVmax alone[14, 15]. However, tumour volume was not routinely measured in most hospitals in China, making it less practical for clinical use. Moreover, in studies that found survival differences between patients with high or low tumour SUVmax, the cut-point to define a high SUVmax varied considerably[6]. The range of SUVmax-T varied from 4.5 to 15. Therefore, we believe that SUVmax-T is not a practical prognostic factor that oncologists should consider when making decisions.

Our results were in line with those of a previous report from Yap W K and his colleagues that found that patients with oesophageal cancer treated by definitive chemoradiotherapy who had high nodal SUVmax (≥ 7) on the baseline PET had poor overall survival[16]. Moreover, similar results have been obtained in studies on head and neck carcinoma and gastric cancer[17]. We did not find that the number of PET-positive lymph nodes correlated with survival; the number of PET-positive LNs was not a good reflection of the pathological metastasis of lymph nodes due to the swelling and fusion of nodes, poor sensitivity for recognizing small malignant tissues by PET and the inability of PET to distinguish inflammation from tumour[18]. In Li's analysis study, FDG PET/CT exhibited high specificity of 95.6%, but sensitivity was only 45.0% in diagnosing the cervical lymph node metastasis[19]. This may be one reason why the correlation of lymph node metastasis and prognosis was not significant. Also this was a retrospective analysis. The prognostic value of SUVmax-N should be validated in larger and prospective cohorts. Our study did not contain patients treated with radical oesophagectomy, which is a population that potentially has clinical differences from our patients. In general, patients who have undergone oesophagectomy would have an earlier tumour stage, fewer metastatic lymph nodes and better general conditions than the patients in our study.

In combination analysis, the C-index of the nomogram based on T stage, number of PET-positive LNs and SUVmax-N was 0.644. The predictive index was not satisfied to predict prognosis. In Lee's research, the combined interpretation of an SUVmax of more than 2.6 with iso- or low CT attenuation [area under the curve (AUC): 0.846] showed significantly better diagnostic performance for detecting malignant lymph nodes than SUVmax only (AUC: 0.791) and size (AUC: 0.693) in a receiver operating characteristic curve analysis[20]. Look at this way, combination of PET-CT parameters including SUVmax-T, SUVmax-N and CT attenuation may be better in clinical application.

Conclusions

In summary, SUVmax-N, but not SUVmax-T, is an independent prognostic indicator in patients with ESCC that may be applied in clinical practice.

Abbreviations

LN: lymph node; SUVmax-N: the maximum standardized uptake value of metastatic lymph node; SUVmax-T: the maximum standardized uptake value of primary tumor; OS: overall survival; PFS: progression free survival; PFS: progression free survival

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all patients included in the study. The study protocol was approved by the Ethics Committee of Fudan University Shanghai Cancer Center.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wenjia Ren: Conception and design, analysis and interpretation of data, writing and revision of the article. Weiwei Chen: Development of methodology, acquisition of data. Yun Chen, Qi Liu and Dashan Ai: Administrative, technical, or material support.: Administrative, technical, or material support.: Administrative, technical, or material support. Jiaying Deng and Kuaile Zhao: Acquisition of data, analysis and interpretation of data, study supervision.

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Figures

Figure 1

SUVmax-N and corresponding SUVmax-T of 83 patients with PET-positive lymph nodes Abbreviations: SUVmax-T: the maximum standardized uptake value of primary tumor; SUVmax-N: the maximum standardized uptake value of metastatic lymph node

Figure 2

Kaplan–Meier plot of overall survival (A) and progression-free survival (B) stratified by SUVmax-T. There was no significant difference between these two groups in neither OS or PFS. Abbreviations: OS: overall survival; PFS: progression free survival; SUVmax-T: the maximum standardized uptake value of primary tumor

Figure 3

Kaplan–Meier plot of overall survival and progression-free survival stratified by count of PET-positive nodes (A and B) or SUVmax-N (C and D) . There was no significant difference between patients with different count of PET-positive nodes in neither OS or PFS. However, patients with lower SUVmax-N had better OS and PFS Abbreviations: OS: overall survival; PFS: progression free survival; SUVmax-T: the maximum standardized uptake value of primary tumor; SUVmax-N: the maximum standardized uptake value of metastatic lymph node

Figure 4

Nomogram of 3 year and 5 year progression free survival