Volume 22, No 2 | International Journal of Radiation Research, April 2024

# Maximum PET/CT $^{18}$F-FDG uptake of lymph nodes predicts prognosis in esophageal squamous cell carcinoma

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► ***Original article***

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**Received:** December 2022
**Final revised:** September 2023
**Accepted:** September 2023

***Int. J. Radiat. Res., April 2024; 22(2): 265-270***

**DOI:** 10.61186/ijrr.22.2.265

***Keywords:*** *SUV, positron emission tomography, metabolic lymph node, survival.*

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## ABSTRACT

***Background*:** In the present study, PET/CT imaging characteristics were explored to investigate the prognostic value of 18F–fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in oesophageal squamous cell carcinoma (ESCC). ***Materials and 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 nodes (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 18F-FDG uptake than normal tissues. The OS and PFS did not show significant differences between patients with different SUVmax-T values. 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 lymph nodes (LNs) were 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 multivariate analysis, SUVmax-N was suggested 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.

## INTRODUCTION

Although progress has been made in the evaluation and treatment strategies of oesophageal carcinoma in recent decades, it remains a lethal disease. In comparison with the consistently increasing occurrence of oesophageal adenocarcinoma in developed countries, oesophageal squamous cell carcinoma (ESCC) still predominates in Asians [1]. Apart from surgery, concurrent chemo radiotherapy (CRT) has been widely accepted as an alternative radical treatment option for patients with inoperable locally advanced or unresectable ESCC, including in patients with cervical oesophageal tumors [2]. However, for patients treated with CRT, no precise staging evaluation for tumor 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 positive lymph nodes is not fully understood.

By revealing the significantly increased glucose metabolism of tumor cells over that of normal cells, PET/CT has played an important role in the diagnosis, staging and restaging of tumors after neoadjuvant therapies, delineating the target volume in radiotherapy, evaluating therapeutics and predicting the prognosis of cancer [4]. A few studies have focused on the correlation of metabolic parameters such as the standard uptake values (SUVs) of gross tumors and survival outcomes in patients with ESCC but have reached controversial conclusions. A meta-analysis that included 10 studies concluded that a high maximum standard uptake value (SUVmax) of a primary tumor predicted 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 multicentre prospective study reported that the SUV of the baseline gross tumor had a negative prognostic value in oesophageal cancer patients [7]. In contrast, few studies have concentrated on metastatic lymph

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nodes. With a cohort of 62 patients, Yap W.K. et al. reported that a high nodal SUVmax predicted poor outcomes in ESCC patients treated with definitive chemo radiotherapy [8]. Moreover, the nodal SUVmax correlates with prognosis in patients with head and neck cancer [9]. Therefore, our aim was to explore and validate the prognostic value of the metabolic characteristics of lymph nodes in a large cohort. In addition, we sought the metabolic marker of PET-CT to predict the prognosis of oesophageal cancer patients who received definitive chemo radiotherapy.

## MATERIALS AND METHODS

### *Patients*

The electronic medical records of patients with ESCC who were treated with radical radiotherapy or concurrent chemo radiotherapy and underwent a baseline PET/CT scan at the Fudan University Shanghai Cancer Center between 2007 and 2016 were retrospectively reviewed. The inclusion criteria were as follows: 1) histologically confirmed squamous cell cancer without clinical evidence of metastasis after being evaluated by a combination of physical examination, PET/CT and ultrasound of abdomen and neck (if available); 2) treatment with concurrent chemo radiotherapy (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) available clinical records including a complete history, complete physical examination, complete blood count, comprehensive chemistry profile and upper gastrointestinal endoscopy. TNM staging was performed according to the American Joint Committee on Cancer (AJCC) seventh edition. Finally, a total of 125 patients were included in the analysis. This study was approved by the Research Ethics Committee of Fudan University Shanghai Cancer Center (registration number: 1912212-2, December 2, 2019).

### *PET/CT and evaluation*

Pretreatment FDG/PET scans were performed for staging purposes. The patients were asked to fast for at least 6 hours before the examination and were given an intravenous injection of 18F-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 midthigh. 18F-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 were correlated with the computed tomography images. The maximum standardized uptake value (SUVmax) of the primary gross tumour (SUVmax-T) and metastatic lymph nodes (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. For the evaluation of lymph nodes, the metabolic features of both nodes on PET/CT (SUVmax>2.5) and size were taken into account. Upper tracheoesophageal groove lymph nodes with lengths >5 mm and other nodes with lengths >10 mm was considered clinical metastases, regardless of the SUV on PET. The typical prototype was shown in figure 1.

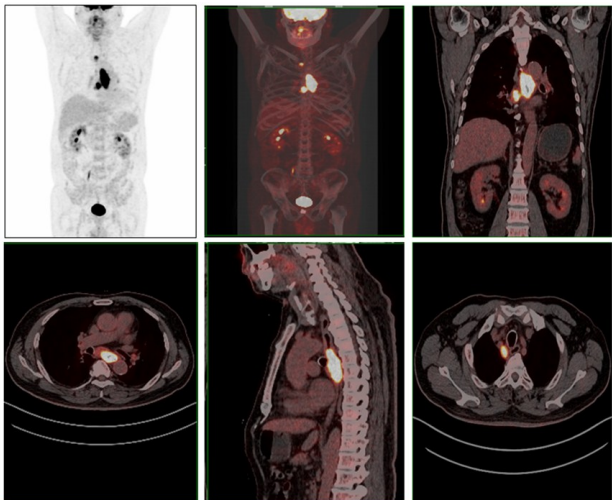


**Figure 1.** A 71-year-old male with locally advanced ESCC who received definitive chemoradiotherapy. The 18F-FDG PET/CT fusion image showed thickening of the middle esophageal wall characterized by increased metabolism. SUVmax-T and SUVmax-N were 27.3 and 11.6, respectively. Right tracheoesophageal sulcus, paraesophageal and subeminence lymph nodes were detected.

### *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 (Siemens, Germany) with contrast, oesophageal barium studies (Siemens, Germany) and ultrasound examinations 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-off point for the 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

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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 OS and 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).

**Table 1.** Patients' clinical characteristics in the study cohort.

| Characteristic | Patients | LN PET-Negative | SUVmax-N<11(%) | SUVmax-N≥11(%) | 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) | |
| 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

Chemotherapy included platinum-based, fluorouracil-based or paclitaxel-based regimens. The majority of the patients was 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 immediate 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.

### *Correlation of SUVmax-T and prognosis*

The median overall survival (OS) for all patients was 36.4 months, and the median survival was 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 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, ranging 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 that of patients 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 figure 2, 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, figure 3A) or PFS (median survival time: 23.4 vs. 27.6 months, P=0.972, figure 3B) of patients with a high SUVmax-T (n=62) compared to patients with a low SUVmax-T (n=63).

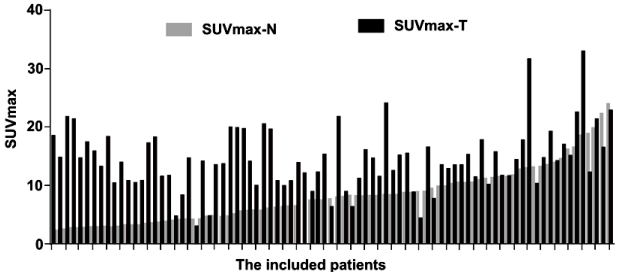



**Figure 2.** SUVmax-N and corresponding SUVmax-T of 83 patients with PET-positive lymph nodes. The ticks in X-axis indicate the included 83 patients.

### *Correlation of SUVmax-N and prognosis*

The number of PET-positive LNs could also not predict prognosis properly. The OS (median survival time: 47.0 vs. 26 months, P<0.05, figure 4A) and PFS (median survival time: 37.3 vs. 13.9 months, P<0.01, figure 4B) of patients with PET-negative LNs were

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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, figure 4A; PFS: median survival time 13.2 vs. 13.0 months, P=0.70, figure 4B).

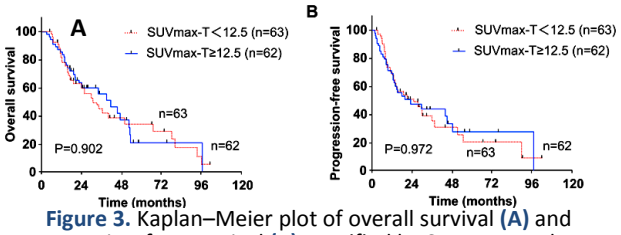



**Figure 3.** Kaplan–Meier plot of overall survival **(A)** and progression-free survival **(B)** stratified by SUVmax-T. There was no significant difference between these two groups in both OS and PFS.

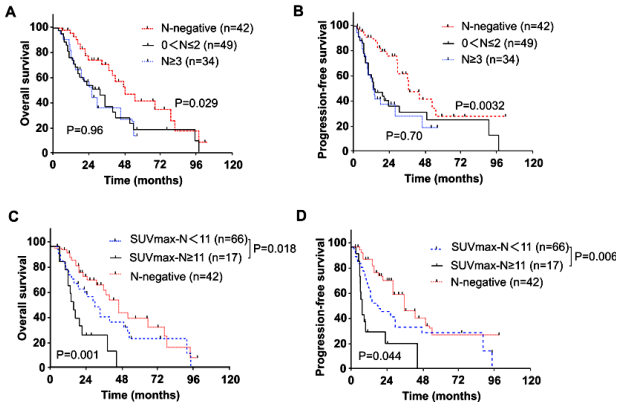



**Figure 4.** Kaplan–Meier plot of overall survival and progression-free survival stratified by number of PET-positive nodes **(A and B)** or SUVmax-N **(C and D)**. There was no significant difference between patients with different number of PET-positive nodes in both OS and PFS. However, patients with lower SUVmax-N had better OS and PFS.

An SUVmax-N ≥ 11 was set as the definition for a high SUVmax-N according to the X-tile analysis, patients with a high SUVmax-N had a significantly worse OS and PFS than those with a low SUVmax-N (OS: median survival time 30.7 vs. 15.9 months, P=0.02, figure 4C; PFS: median survival time 19.1 vs. 7.2 months, P<0.01, figure 4D), 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 SUVmax-N were established as significant prognostic factors for both OS and PFS (table 2), and the multivariate analysis showed that SUVmax-N remained an independent predictor for OS and PFS (table 3).

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 (figure 5). The C-index of the nomogram was 0.644. In the model, the risk score of PET-Positive LN is lower than SUVmax-N.

**Table 2.** Univariate analysis of potential factors affecting OS and PFS.

| | OS | | | PFS | | |
|---|---|---|---|---|---|---|
| **Variable** | HR | 95% CI | P value | HR | 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** |
| **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 | HR | 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.

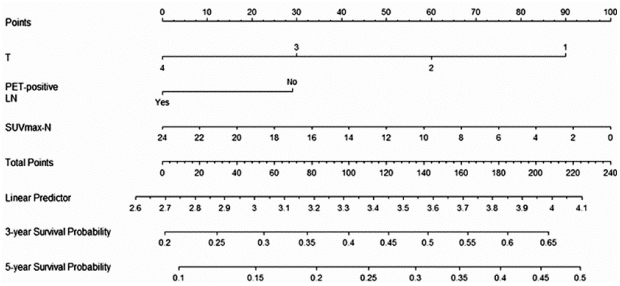



**Figure 5.** Nomogram of 3-year and 5-year progression free survival. The length of each line such as T stage, PET-positive N and SUVmax-N benchmarked to the 'points' line corresponding to a point, respectively. The total points are obtained by adding up each point. The 'total points' line was matched with progression free survival lines.

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## DISCUSSION

In the current study, we investigated the correlation of SUVmax-T, SUVmax-N and prognosis in ESCC. In the current analysis, the SUVmax-T of patients with PET-positive LNs was significantly higher than that of patients with PET-negative LNs. SUVmax-T was associated with metabolic tumour burden. A larger tumour 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 tumour SUVmax did not have an effect [12]. This may be because SUVmax-T only represented a few pixels on imaging instead of the whole tumour. Studies have shown that among PET biomarkers, metabolic tumour volume (MTV) and total lesion glycolysis (TLG) both reflect the metabolic tumour burden and are considered to be the strongest prognostic factors, even more so than 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]. Moreover, to distinguish survival differences, the cut-off value of SUVmax varied considerably from 4.5 to 15, but it was 12.5 in the present study [6]. There was no consensus reached. These inconsistencies might be caused by tumour heterogeneity or differences in the treatment response rate. Although the initial SUVmax does not predict survival, patients with a high initial SUVmax respond better to preoperative chemoradiotherapy [16]. Therefore, we believe that SUVmax-T has its own application limitations.

Regarding nodal SUVmax, some studies found that oesophageal cancer patients treated with definitive chemoradiotherapy who had a high nodal SUVmax (≥7) on baseline PET had poor overall survival [17]. Moreover, similar results to those of the current analysis have been obtained in studies on head and neck carcinoma and gastric cancer [18]. In our study, the number of PET-positive lymph nodes was not correlated with survival. The reason may be swelling and fusion of nodes, poor sensitivity for recognizing small malignant tissues by PET and the inability of PET to distinguish inflammation from tumor [19]. In the same way, FDG PET/CT exhibited a high specificity of 95.6%, but the sensitivity was only 45.0% in diagnosing cervical lymph node metastasis [20]. There is a viewpoint that suggests that the status of PET-LN (negative or positive) is more important than the positive number of lymph nodes and is a more reliable marker to identify the high-risk population for postoperative recurrence [21]. Additionally, our current retrospective analysis may not fully explain the problem. In some studies, a nodal SUVmax greater than 2.5 on FDG-PET before chemoradiotherapy (CRT) was defined as cPET-N(+). An SUVmax less than 2.5 Gy after chemoradiotherapy was defined as CRT-cPET-N(-). Both cPET-N(+) and CRT-cPET-N(-) patients were defined as PET-N responders. PET-N responders had significantly better survival, and PET-N may be a better predictive prognostic marker [22]. Thus, the prognostic value of SUVmax-N should be validated in larger and prospective cohorts.

In the multiple analysis, the C-index of the nomogram based on T stage, number of PET-positive LNs and SUVmax-N was 0.644, which was not satisfactory 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 [23]. Rather than SUVmax, the shortest distance between the farthest PET-positive lymph node and the primary tumour in three-dimensional space after the standardization of the patient body surface area (SDmax(LN-T)) received increasing popularity and acted as an independent prognostic factor in combination with MTV to stratify patient risk [24]. Therefore, using the combination of PET-CT parameters, including SUVmax-N, MTV and SDmax(LN-T), may be better in clinical application.

There are some limitations:

(1) The current study was a retrospective analysis with selection bias. (2) This study had a smaller sample number of included patients. (3) We used the median SUVmax-T of 12.5 as the cut-off value and evaluated a relatively homogeneous group of ESCC patients who received definitive (chemo) radiotherapy.

In conclusion, the OS and PFS of patients with PET -negative LNs were significantly better than those of patients with PET-positive LNs. SUVmax-N rather than PET-positive LNs was suggested to be a better independent predictor for OS and PFS.

**ACKNOWLEDGMENTS**

*This study was financially supported by the National Natural Science Foundation of China Research, China (Grant number: 81903127) and Shanghai Sailing Program, China (No.19YF1409100).*

***Author's contribution*:** Jiaying Deng and Wenjia Ren: conception and design, or analysis and interpretation of data. Jingyi Shen: drafting the article or revising it critically for important intellectual content. Longfei Ma and Kuaile Zhao: final approval of the version to be published.

***Conflict of interest statement*:** The authors declare that they have no competing interests.

***Statement of ethics*:** Written informed consent was obtained from all patients included in the study. The

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study protocol was approved by the Ethics Committee of Fudan University Shanghai Cancer Center.

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[ DOI: 10.61186/ijrr.22.2.265 ]