Oesophageal squamous cell carcinoma: relationship between fluorine-18 fludeoxyglucose positron emission tomography CT maximum standardised uptake value, metabolic tumour volume, and tumour, node and metastasis classification

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Objectives: We aimed to evaluate the relationships between primary tumour, maximum standardised uptake value, metabolic tumour volume and seventh edition American Joint Committee on Cancer (AJCC) classification in oesophageal squamous cell carcinoma (OSCC) patients.

Methods: Fluorine-18 fludeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)-CT scans of 41 consecutive newly diagnosed OSCC patients were retrospectively reviewed. Maximum standard uptake value (SUV_{max}) and metabolic tumour volume (MTV) were recorded. Two-tailed Spearman's correlation was used to analyse the relationships between the metabolic parameters and the AJCC staging system.

Results: Positive correlations were observed between SUV_{max}, MTV and tumour (T) stage, in addition to node (N) stage and AJCC stage. Both metabolic parameters were independent variables that significantly affected the N stage and AJCC stage, and SUV_{max} was the only independent variable that significantly affected the T stage.

Conclusion: The metabolic parameters derived from ¹⁸F-FDG PET-CT were positively correlated with T, N and AJCC stage in primary OSCC. Our findings may suggest a complementary role of these parameters to seventh-edition AJCC staging in the prognostication of OSCC patients.

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Oesophageal cancer is the fifth leading cause of cancer-related mortality in men worldwide. China bore more than half of the global burden of oesophageal squamous cell carcinoma (OSCC) as the dominant type, with a constituent ratio of approximately 90–95% [1]. The tumour size (T), nodal status (N) and distant metastasis (M) system (TNM) of classification for oesophageal cancer by the International Union Against Cancer (UICC) is commonly used in unifying clinicopathological classification, guiding treatment decision making, evaluating prognosis and comparing curative effect. In 2009, the UICC and American Joint Committee on Cancer (AJCC) jointly published the seventh edition of TNM classification of oesophageal malignant tumours according to histological type (squamous or adenocarcinoma), respectively [2]. Tumour metabolic phenotype as a potential prognosticator, however, was not considered [3–5].

Maximum standardised uptake value (SUV_{max}), a semi-quantitative parameter in fused fluorine-18 fludeoxyglucose positron emission tomography-CT

(¹⁸F-FDG PET-CT), is known to be a significant factor for locoregional invasion, prognosis and treatment guidance in many malignancies [6–10]. Metabolic tumour volume (MTV), defined as the volume of tumour tissues with increased FDG uptake, is a novel index in ¹⁸F-FDG PET-CT and is the least-studied factor to date. FDG target volume in previous studies was calculated mostly by visual delineation of tumour edge or side-by-side analysis with contrast-enhanced CT scan. On the other hand, MTV in this study was semi-quantitatively measured from attenuation-corrected PET-CT images by using a contouring program, which renders the volume measurement more feasible.

To our knowledge, although there was a report discussing the relationship between SUV_{max}, MTV and the TNM staging in nasopharyngeal carcinoma, few studies to date have examined the relationship in OSCC [11]. Because these quantitative PET parameters also reflect tumour aggressiveness, they may serve as an adjunct to disease staging by characterising the metabolic phenotype of tumours. In this study, we analyse the relationship between SUV_{max} and MTV of the primary tumour, and TNM classification in patient OSCC without pre-operative therapy.

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Methods and materials

Patients

This study was approved by the institutional review board at our institution. Informed consent was waived owing to the retrospective design of the study. This analysis was based on prospectively collected data, and oesophageal patients were included from March 2003 to March 2009 in our hospital. The exclusion criteria included:

- (1) lack of PET-CT as part of the staging workup
- (2) the absence of radical oesophagectomy or lymphadenectomy required resecting of at least 12 nodes (such as the patients with irresectable, R1 resection or metastatic tumour) [12]
- (3) histology other than squamous cell carcinoma
- (4) neoadjuvant chemotherapy or chemoradiation.

The standard pre-operative staging procedure was as the inclusion criteria, including physical examination, laboratory tests, oesophagogastrosocopy, flexible bronchoscopy, bariumoesophagography, CT scan from neck to upper abdomen and whole body PET-CT. The cohort of this study consisted of 41 patients (Stage Ia–IIIC on CT or PET-CT) who met the above criteria. Informed consent was given before entry into the study. The surgical approach was determined by the locations of the proximal pole of the tumour and of the positive lymph nodes, indicated by the pre-operative imaging examinations. 10 patients (8 with upper thoracic oesophageal cancer and 2 with middle thoracic oesophageal cancer) underwent transthoracic oesophagectomy (involving laparotomy, right thoracotomy and cervical anastomosis) with lymph node dissection in 3 fields (thoracic, abdominal and cervical). 22 patients (19 with middle thoracic oesophageal cancer and 3 with lower thoracic oesophageal cancer) underwent left thoracotomy and cervical anastomosis with lymph node dissection in 2 fields (thoracic and abdominal). Nine patients with lower thoracic oesophageal cancer underwent extended left thoracophrenotomy through the sixth intercostal space with lymph node dissection in two fields (thoracic and abdominal). Adjuvant therapy including radiotherapy and chemotherapy after initial curative oesophagectomy was determined after discussion among the surgical, medical and radiation oncologists. Patient characteristics are listed in Table 1.

Positron emission tomography–CT imaging

^{18}F -FDG PET-CT scans were obtained with an advanced PET-CT scanner (Discovery LS; GE Healthcare,

Waukesha, WI). All patients fasted for ≥ 6 h before the PET examination, and each patient's blood glucose level was measured. Patients did not undergo urinary bladder catheterisation and received no oral muscle relaxants. 60 min after intravenous injection of 370 MBq (10 mCi) of ^{18}F -FDG, emission scans were obtained from head to thigh for 5 min per field of view, each covering 14.5 cm, at an axial sampling thickness of 4.25 mm per slice. The PET-CT system was used for 4-slice helical CT acquisition, followed by a full-ring dedicated PET scan of the same axial range. The CT component was operated with an X-ray tube voltage peak of 120 keV, 90 mA, a 6:1 pitch, a slice thickness of 4.25 mm and a rotational speed of 0.8 s per rotation. Both the PET scans and the CT scans were obtained during normal tidal breathing. PET images were reconstructed with CT-derived attenuation correction using ordered-subset expectation maximisation software. The attenuation-corrected PET images, CT images and fused PET-CT images were available for review in axial, coronal and sagittal planes, as was a cine display of maximum intensity projections of the PET data, using the manufacturer's review station (Xeleris; GE Healthcare). Firstly, a team of experienced nuclear medicine physicians, unaware of the patient's clinical history and the results of previously performed conventional imaging tests, interpreted the ^{18}F -FDG PET images with side-by-side review of the CT images. Secondly, fused PET-CT images were reviewed by a combined team of nuclear medicine physicians and radiologists. When an area of presumed lymph node showed ^{18}F -FDG uptake that was focally prominent compared with surrounding tissues and was not related to normal physiological uptake, the area was considered to be positive for malignancy. A site of increased ^{18}F -FDG uptake was defined as negative when it was related to a known non-malignant process or to the physiological biodistribution of ^{18}F -FDG. Disagreements concerning the final interpretation were resolved by a majority opinion. For quantitative analysis of FDG uptake, the SUV was assessed. We used the SUV_{max} instead of the mean SUV. The uptake of each lesion was determined in the slice with the SUV_{max} . An $\text{SUV}_{\text{max}} > 2.5$ was considered positive. A volumetric region of interest (ROI) around the outline of the primary tumour was placed on the axial PET images using the semi-automatic software. The borders of the ROI were adjusted manually by visual inspection of the primary tumour outline to avoid overlapping on adjacent FDG-avid structures or lesions. The regions equal to or greater than an SUV of 2.5 were selected to delineate MTV [13–15]. If the primary tumour was not visualised or could not be distinguished from the background, MTV was set as a single voxel with volume of 0.1 cm^3 .

Statistics

The results were analysed using SPSS v. 17.0 (SPSS Inc, Chicago, IL). Two-tailed Spearman's correlation was used to analyse the relationship between T stage and the parameters SUV_{max} and MTV. This was followed by multiple linear regression analysis to study the simultaneous influence of these factors on T stage. All of the above analyses were repeated for N stage and AJCC

Table 1. Patient characteristics ($n=41$)

Parameters	Classification	Number of patients
Age (year)	Median/range	63/(19–75)
Gender	Male/female	31/10
Histology	Well/moderately/poorly	10/23/8
Location	Upper/middle/lower	8/21/12
T stage	T1a/T1b/T2/T3/T4a/T4b	1/2/9/27/2/0
N stage	N0/N1/N2/N3	17/11/13/0
AJCC stage	Ia/Ib/IIa/IIb/IIIA/IIIB/IIIC/IV	1/2/6/11/9/10/2/0

AJCC, American Joint Committee on Cancer; N, node; T, tumour.

stages. The relationship between MTV and SUV_{max} was also analysed. Association between these factors was assessed using Spearman's correlation coefficient at a 5% level of significance. Continuous variables are expressed as mean $\pm$ standard deviation.

Results

The average time from PET-CT to surgery was 3 days (range, 1–7 days). The mean SUV_{max} and MTV of the primary tumour was 12.01 ± 5.77 (range, 1.70–24.00) and 21.29 ± 21.29 (range, 0.1–88.30), respectively. On average, 16.4 lymph nodes were dissected in each patient. The locations (number) of lymph node metastases in patients with upper thoracic tumours were: right tracheal lymph nodes (2), upper paraoesophageal lymph nodes (2), left recurrent nerve lymph nodes (1), right recurrent nerve lymph nodes (1) and left cervical paraoesophageal lymph nodes (1). The sites (number) of positive lymph node in patients with middle thoracic tumours were: middle paraoesophageal lymph nodes (8), subcarinal nodes (5), left paracardial nodes (4), nodes along the left gastric artery (3), nodes along the lesser gastric curvature (2), lower paraoesophageal lymph nodes (2), right tracheal lymph nodes (1), hilar lymph nodes (1), right cervical paraoesophageal lymph nodes (1) and upper paraoesophageal lymph nodes (1). As for patients with lower thoracic tumours, those were: lower paraoesophageal lymph nodes (4), nodes along the left gastric artery (3), left paracardial nodes (3), nodes along the lesser gastric curvature (2), middle paraoesophageal lymph nodes (1), subcarinal nodes (1), posterior mediastinal lymph nodes (1), common hepatic artery lymph nodes (1), hilar lymph nodes (1) and right tracheal lymph nodes (1). The relationship between positive PET-CT findings and pathology results was evaluated. The sensitivity, specificity and accuracy of PET-CT in detecting regional lymph node metastasis were 69.8%, 89.98% and 88.4%, respectively.

Spearman's correlation analysis and multiple linear regression analysis revealed SUV_{max} to be the only independent variable that significantly affected T stage ($p=0.003$, $\rho=0.459$; $p=0.004$, adjusted $\rho^2=0.464$; Figure 1). The mean SUV_{max} of the primary tumour in patients with T1a, T1b, T2, T3 and T4a stage were, respectively, 3.8, 4.10 ± 0.42 , 10.22 ± 6.48 , 13.07 ± 5.08 and 17.80 ± 2.97 . On Spearman's correlation analysis, a positive correlations was found between SUV_{max} and N stage ($p=0.002$, $r=0.477$). A positive correlation was also found between MTV and N stage ($p<0.001$, $\rho=0.563$), and the results were confirmed by the multiple analysis ($p<0.001$, adjusted $\rho^2=0.348$; Figures 2 and 3). At the same time, both SUV_{max} and MTV positively correlated with the AJCC stage ($p=0.002$, $\rho=0.460$; $p<0.001$, $\rho=0.539$, respectively), and the results were confirmed by the multiple analysis ($p<0.002$, adjusted $\rho^2=0.238$). The mean SUV_{max} of the primary tumours in patients with N0, N1 and N2 stage was 8.84 ± 4.69 , 13.77 ± 6.65 and 14.68 ± 4.48 , respectively, whereas the mean MTV in those patients was 10.79 ± 9.95 , 16.08 ± 16.43 and 39.42 ± 24.82 , respectively. The mean primary tumours SUV_{max} in Ia, Ib, IIa, IIb, IIIa, IIIb and IIIc stage was 3.8, 11.35 ± 9.83 , 11.53 ± 3.24 , 6.77 ± 3.85 , 16.74 ± 13.61 , 17.80 ± 2.97 and 12.01 ± 5.77 , respectively, whereas the mean MTV was 0.3, 6.45 ± 8.98 , 13.62 ± 14.18 , 9.87 ± 6.71 , 29.25 ± 25.04 , 13.95 ± 4.60 and 21.29 ± 21.29 , respectively. No positive correlation was found when the analysis was repeated for differentiation and location. The relationship between SUV_{max} and MTV was found to be statistically significant ($p=0.001$, $\rho=0.501$).

Discussion

The prognosis for patients with OSCC depends on the complex interplay of TNM classifications, as well as non-anatomical factors, including histopathological cell type, histological grade and cancer location. Many studies

Figure 1. Spearman's correlation between maximum standardised uptake value (SUV_{max}) and tumour stage ($p=0.003$, $\rho=0.459$). AJCC, American Joint Committee on Cancer; MTV, metabolic tumour volume.

Figure 2. Spearman's correlation between maximum standardised uptake value (SUV_{max}), metabolic tumour volume (MTV) and N stage ($p=0.002$, $\rho=0.477$; $p<0.001$, $\rho=0.563$).

suggest the value of PET-CT, which is able to coregister both anatomic and functional information, in staging as well as prediction of treatment response and prognosis, but few reports have discussed the relationships of both MTV and SUV_{max} measured by PET-CT and stage in oesophageal cancer, particularly classified by the last edition staging system. In this study, we found significant correlation between metabolic parameters SUV_{max} and T stage in patients with initially diagnosed OSCC. T stage of the AJCC/UICC classification system describes the depth of invasion, whereas SUV has been associated with histological and immunohistochemical markers of aggressiveness [16, 17]. Thus, our findings are consistent with the notion that more aggressive OSCCs, as

reflected by glycolytic uptake, invade more extensively the surrounding tissues and result in an advanced T stage. We also found no significant positive association between MTV and advancing T stage in this study, although the MTV slightly favoured advanced T stage ($p=0.053$). The reason is mainly due to the presence of multifocal neoplasia and submucosal metastasis.

Although EUS is highly effective in defining tumour invasion depth and nodal involvement in oesophageal cancer, its accuracy was reportedly less for tumours >5 cm in diameter or located at the oesophagogastric junction [18–20]. Furthermore, most patients had dysphagia with near total obstruction of the oesophageal lumen, which made endoscopic ultrasound (EUS)

Figure 3. Spearman's correlation between maximum standardised uptake value (SUV_{max}), metabolic tumour volume (MTV) and American Joint Committee on Cancer (AJCC) stage ($p=0.002$, $\rho=0.460$; $p<0.001$, $\rho=0.539$).

unfeasible. Also, the EUS procedure is operator dependent, invasive and unable to evaluate tumours that prevent passage of the endoscope [18–20]. In this study, PET-CT, which is a more objective and less invasive method, was used to evaluate nodal involvement. Although positive PET-CT findings and pathological findings of regional lymph node involvement were significantly correlated, the ability of PET-CT to predict lymph node metastasis remained unsatisfactory. The sensitivity and specificity for detecting regional nodal involvement were 69.8 and 89.98%, respectively. Our result was comparable with the pooled sensitivity and specificity reported in a systematic review [21]. However, we found that both the primary tumour SUV_{max} and MTV were significantly related to N stage. Therefore, the primary uptake on PET-CT indicates the presence of lymph node metastasis and the severity of nodal involvement, providing a quantitative measure of lymph node involvement unobtainable by EUS. Therefore, in the diagnosis of lymph node metastasis, the value of primary lesion SUV_{max} and MTV is a factor that should not be ignored, in addition to considering the imaging of lymph nodes themselves. As for AJCC, larger MTV and higher SUV_{max} were markers for a poor disease stage. Therefore, a larger MTV or higher SUV_{max} could need more aggressive treatment. Finally, no positive correlation was found between metabolic parameters, differentiation and location.

Conclusion

Our study found both quantitative metabolic parameters of ¹⁸F-FDG PET-CT to be associated with N stage and AJCC stage in OSCC, even as classified by the new seventh-edition AJCC staging system, and only SUV_{max} is a marker for T stage. We await the results of our continuing prospective study to determine whether these parameters will be predictive of patient outcome in our cohort of OSCC patients.

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