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Clinical usefulness of dual-time FDG PET–CT in assessment of esophageal squamous cell carcinoma

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ABSTRACT

Purpose: We conducted this study to investigate the value of the dual-time 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography–computed tomography (PET–CT) in assessment of the primary tumor, loco-regional lymph node and distant metastasis in patients with esophageal squamous cell carcinoma.

Methods: Twenty-six patients with histologically proved esophageal squamous cell carcinoma underwent dual-time FDG PET–CT before radical surgery. The standardized uptake values (SUV_{max}) were obtained including early SUV_{max} and delayed SUV_{max}, respectively. The retention index (RI) was also calculated. The results were evaluated retrospectively according to the final pathologic findings. Four diagnostic criteria including (1) early $SUV_{max} \geqq 2.5$ alone, (2) $RI \geqq 10\%$ alone, (3) a combination of early $SUV_{max} \geqq 2.5$ and $RI \geqq 10\%$, and (4) a combination of early $SUV_{max} \geqq 2.5$ or $RI \geqq 10\%$ were used for differentiating malignancy from a benign lesion, respectively.

Results: The sensitivity of FDG PET–CT in detecting the primary tumor with combination of early $SUV_{max} \geqq 2.5$ or $RI \geqq 10\%$ was 96.2%. It was statistically significantly higher than the results using the other three criteria ($p < 0.0001$). For loco-regional lymph node detection, there was no significant difference among the 4 criteria. For distal metastases, the significantly higher specificity (100%) was found when using combination of early $SUV_{max} \geqq 2.5$ and $RI \geqq 10\%$ or using early $SUV_{max} \geqq 2.5$ alone than using the other two criteria ($p = 0.0058$). With regard to accuracy, no significant correlations were observed among primary tumor, loco-regional lymph nodes and distant metastasis ($p > 0.05$).

Conclusion: The preliminary result of this study demonstrated that dual-time point FDG PET–CT had limited value in detection of primary tumor and loco-regional lymph nodes metastasis. For the distant metastasis, the sensitivity and specificity would be improved if $RI \geqq 10\%$ is used as a supplemental criterion. Efforts should be made to improve the ability of the dual-time FDG PET–CT technique to assess primary tumor and loco-regional lymph nodes metastasis.

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1. Introduction

Esophageal cancer is a lethal malignant cancer with a poor prognosis. The 5-year survival rate for most cases diagnosed in the advanced stage is only 10–30% for resectable tumors and 5% for unresectable ones [1]. Information regarding tumor invasion depth, lymph node involvement, and distant metastasis is important in deciding the appropriate treatment for esophageal cancer. Accurate assessment of tumor extent and nodal involvement is essential for curative resection.

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Various imaging tools, such as computed tomography (CT) scan and, endoscopic ultrasonography (EUS) are widely used in routine clinical practice. These imaging tool are useful for evaluating the extent of the disease but have limitations when determining lymph nodes metastasis [2–4]. In the past, computed tomography (CT) scanning was the major staging method, but recently, 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scanning has become more widely used [5]. The FDG PET is used for diagnosis, initial staging, restaging, prediction, and monitoring of treatment response, surveillance, and prognostication in a variety of cancers [6–8]. However, FDG PET does not allow for the precise localization of landmarks, making it difficult to identify the foci of the increased FDG uptake [9]. The role of FDG PET in the detection of nodal metastasis is still controversial and its efficacy is far from ideal.

Integrated FDG PET–CT is a new functional and metabolic imaging tool. Many reports indicate that FDG PET–CT is more sensitive and specific in the diagnosis and staging of several types of malignancies than FDG PET [6,10,11]. However, FDG uptake is not tumor specific. Traditionally, a threshold for a single time point standardized uptake value (SUV) of 2.5–3.5 has been proposed as the optimal threshold for distinguishing between benign and malignant lesion in various literatures. Many researchers found that when SUV is measured, there is a correlation between the FDG uptake and time. In tumor, the uptake of FDG uptake continues to increase for several hours after FDG injection whereas such prolonged period of FDG uptake is rare in inflammatory/infectious or normal tissues. This may be related to the graded concentration of FDG in tumor cells, low glucose-6-phosphatase activity, and increase glucose uptake through glucose transporter in these cells [12–17].

Therefore, recognition of these imaging pitfalls is an important step in patient assessment. Various cell types exhibit varying rates of FDG uptake. Dual-time-point scanning of FDG PET has been widely applied in many kinds of cancers. Most of them seem useful in differentiating between inflammation and malignancy because of the additional qualitative and quantitative information derived from these scans [12,15–17]. Hence, the method has been routinely used in all FDG PET scans of our institute. However, poor discriminability of dual-time-point method has also been found in few studies. Nevertheless, the efficacy of such method for esophageal cancer is seldom reported or discussed in the literature. Thus, the purpose of current study is aimed to analyze the relation between findings of dual-time-point FDG PET–CT and clinical/pathological results of the primary tumor, lymph nodes and distant metastasis of the esophageal cancers retrospectively, and tries to discuss the potential use of dual-time-point method in such circumstance [12,18–21].

2. Materials and methods

2.1. Patient population

Twenty-six patients (all men; age range, 42–72 years old; mean age, 60.4 years) who underwent preoperative FDG PET–CT scan and subsequent surgical resection of esophageal cancer between October 2009 and April 2010 in China Medical University Hospital were retrospectively included in this study. All patients histologically proved to have squamous cell carcinoma and had received esophageal resection and regional lymph nodes dissection (Table 1). Surgical pathology results were used to provide the final diagnosis with which the FDG PET–CT results were compared, including those with distant metastases. The visual interpretation of the FDG PET–CT and surgical pathology stage was classified according to the sixth edition of the AJCC Cancer Staging System. This study was approved by the Ethics Committee of the China Medical University Hospital (DMR-99-IRB-010).

2.2. FDG PET–CT imaging protocol, interpretation and calculation of related parameters

All patients were asked to fast for at least 4 h before FDG PET–CT imaging. Imaging was performed with a PET–CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI, USA). Whole-body FDG PET–CT images were acquired approximately 45 min after intravenous injection of 370 MBq (10 mCi) of FDG. Delayed FDG PET–CT images were obtained approximately 70 min after FDG injection. PET emission images were acquired after CT scans at 2 min per field of view (FOV) in the 3-dimensional acquisition mode. The CT images were reconstructed onto a 512×512 matrix with a section thickness of 3.75 mm, then reconstructed onto a 128×128 matrix, and converted into 511-keV-equivalent attenuation factors for attenuation correction of the corresponding PET emission images (Fig. 1). The suspected tumoral FDG uptake was defined as focally increased radioactivity, greater than those in the surrounding background or blood pool, in the esophagus, lymph node or other recognizable morphological lesional sites on the CT component of FDG PET–CT by visual interpretation. A semiquantitative parameter, standardized uptake value (SUV), was defined as "tracer activity in the tumor per unit mass divided by amount of injected radioactivity per unit body mass", and calculated from each region of interest with increased FDG radioactivity in the suspected tumoral region. The maximum standardized uptake value (SUV_{max}) of esophageal cancer and metastasis on early and delayed FDG PET–CT images were measured. The retention index (RI) based on the measured SUV_{max} was calculated as $100\% \times (\text{delayed } SUV_{max} - \text{early } SUV_{max})/\text{early } SUV_{max}$.

Early and delayed PET images were reviewed on the computer monitor in the trans-axial, coronal, and sagittal planes along with maximum-intensity-projection images. Two experienced nuclear medicine physicians independently evaluated FDG uptake both visually and semiquantitatively. The evaluating physicians were unaware of the clinical history and the PET images were compared with the corresponding CT images for accurate anatomic identification of the tumor. Any difference of opinion was resolved by consensus.

2.3. Statistical analysis

We used 4 diagnostic criteria to evaluate the sensitivity, specificity and accuracy of dual-time FDG PET–CT in differentiating malignancy from a benign lesion among the primary tumor, locoregional lymph nodes, and distant metastases. The 4 criteria included (1) early $SUV_{max} \geqq 2.5$ alone, (2) $RI \geqq 10\%$ alone, (3) combination of early $SUV_{max} \geqq 2.5$ and $RI \geqq 10\%$, and (4) combination of early $SUV_{max} \geqq 2.5$ or $RI \geqq 10\%$. Fisher's exact test was applied to compare each difference in the sensitivity, specificity and accuracy. SPSS software was used for the analysis. A p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Primary tumor

The sensitivity of FDG PET–CT in detecting the primary tumor site with combination of early $SUV_{max} \geqq 2.5$ or $RI \geqq 10\%$ was 96.2%. It was statistically significantly higher than the other 3 criteria. The p value of Fisher's exact test was <0.0001 and it was statistically significant (Table 2).

3.2. Regional lymph nodes

The sensitivity of early $SUV_{max} \geqq 2.5$ alone was 30.0%, but it increased to 70% when combination of early $SUV_{max} \geqq 2.5$ or

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Table 1
Tumor staging, SUV_{max} and RI of the primary tumor, loco-regional lymph node and distant metastasis.

Patient	Tumor location	Pathology tumor staging (AJCC 6)			SUV of positive PET–CT finding						PET–CT staging		
		pT	pN	pM	Primary tumor		Locoregional LN		Distant Metastasis		T	N	M
					SUV early	RI (%)	SUV early	RI (%)	SUV early	RI (%)			
1	M/3	2	0	0	2.4	13.9	2.3	4.7	Absent	NA	X	1	0
2	M/3	2	0	0	4.3	2.2	0.8	20.8	Absent	NA	X	0	0
3	U/3	3	0	1a	9.1	16.8	1.3	8.5	1.3	11.0	X	1	1a
4	L/3	3	1	1a	11.8	5.6	1.6	−15.1	2.0	−13.8	X	0	1a
5	U/3	3	0	0	6.3	6.9	1.3	−3.8	Absent	NA	X	1	0
6	U/3	3	1	0	10.0	3.8	1.2	−0.3	Absent	NA	X	1	0
7	U/3	4	1	0	10.3	0.3	0.6	91.7	1.7	11.3	X	1	1a
8	M/3	3	1	1b	3.5	5.4	Absent	NA	3.5	12.3	X	0	1b
9	U/3	1	0	0	3.9	37.2	0.8	67.6	Absent	NA	X	1	0
10	M/3	4	1	1a	4.1	55.6	1.1	54.1	1.5	1.3	X	1	1a
11	U/3	3	1	0	9.1	9.3	3.3	81.9	Absent	NA	X	1	0
12	U/3	3	1	0	12.6	13.8	3.3	28.3	1.8	39.1	X	1	1b
13	M/3	2	0	0	14.9	12.2	1.4	11.1	Absent	NA	X	0	0
14	U/3	3	0	0	8.2	30.6	2.6	15.5	Absent	NA	X	0	0
15	U/3	3	0	0	3.4	3.5	1.5	−8.2	Absent	NA	X	1	0
16	U/3	4	1	0	11.2	10.4	1.0	30.4	Absent	NA	X	1	0
17	M/3	1	0	0	1.8	38.0	1.1	−0.1	Absent	NA	0	0	0
18	M/3	1	0	0	4.3	23.9	1.5	16.8	Absent	NA	X	0	0
19	L/3	3	1	0	13.4	18.4	0.9	26.0	Absent	NA	X	1	0
20	M/3	3	0	0	8.4	19.0	2.1	−4.4	Absent	NA	X	0	0
21	M/3	1	0	0	3.1	12.7	1.1	1.1	Absent	NA	X	0	0
22	M/3	3	0	0	7.7	14.6	1.4	15.0	1.6	22.9	X	1	1b
23	M/3	3	0	0	9.0	7.6	0.8	14.5	Absent	NA	X	0	0
24	U/3	4	0	1b	2.1	8.3	0.9	−12.5	Absent	NA	X	0	0
25	L/3	3	0	1b	9.0	36.6	Absent	NA	1.7	63.7	X	0	1b
26	U/3	3	1	0	9.6	2.4	3.4	4.1	Absent	NA	X	1	0

NA: not applicable. X: representing positive for malignancy but difficult to denote T stage.

Table 2
Sensitivity of different diagnostic criteria in the detection of primary tumor.

Diagnostic criteria	Sensitivity (%)
SUV early ≧ 2.5	88.5
RI ≧ 10%	57.7
SUV early ≧ 2.5 and RI ≧ 10%	50.0
SUV early ≧ 2.5 or RI ≧ 10%	96.2[a]

[a] Stastitically significantly higher than the other 3 criteria.

Table 3
Sensitivity, specificity and accuracy of different diagnostic criteria in the detection of loco-regional lymph node metastasis.

Diagnostic criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
SUV early ≧ 2.5	30.0	93.8	69.2
RI ≧ 10%	60.0	56.3	57.7
SUV early ≧ 2.5 and RI ≧ 10%	20.0	93.8	65.4
SUV early ≧ 2.5 or RI ≧ 10%	70.0	56.3	61.5

RI ≧ 10% was used. However, the p value was only 0.1181 and hence not significant. For the specificity, the result was reversed. When using early SUV_{max} ≧ 2.5 alone, it was 93.8% but it decreased dramatically to 56.3% when combination of early SUV_{max} ≧ 2.5 or RI ≧ 10% was used. Similarly, the p value was not significant ($p = 0.0756$) (Table 3). With regard to accuracy, there was no significant correlation among the four diagnostic criteria ($p > 0.05$).

3.3. Distant metastasis

When using combination of early SUV_{max} ≧ 2.5 and RI ≧ 10%, the sensitivity and specificity were 16.7% and 100%, respectively. The same result was found when early SUV_{max} ≧ 2.5 was used alone. However, when RI ≧ 10% was used alone, the sensitivity increased dramatically to 50% but the specificity dropped to 85%. Furthermore, a similar poor result was found when combination of early SUV_{max} or RI ≧ 10%, was used (Table 4). A significantly higher specificity was found when using combination of early SUV_{max} ≧ 2.5 and RI ≧ 10% or using early SUV_{max} alone than using the other 2 parameters ($p = 0.0058$ by using Fisher's exact test). The sensitivity, however, was somewhat different ($p = 0.4906$). For the accuracies, the detection rate was between 76.9% and 80.8%, which did not reach statistical significance ($p > 0.05$).

Table 4
Sensitivity, specificity and accuracy of different diagnostic criteria in the detection of distant metastasis.

Diagnostic criteria	Sensitivity (%)	Specificity (%)	Accuracy (%)
SUV early ≧ 2.5	16.7	100.0[a]	80.8
RI ≧ 10%	50.0	85.0	76.9
SUV early ≧ 2.5 and RI ≧ 10%	16.7	100.0[a]	80.8
SUV early ≧ 2.5 or RI ≧ 10%	50.0	85.0	76.9

[a] Stastitically significantly higher than the other 2 criteria.

4. Discussion

FDG PET–CT is widely used with cancer patients. Its role as a non-invasive imaging modality has been widely investigated but the exact SUV_{max} cutoff value for esophageal cancer remains controversial. To accurately distinguish malignant from benign lesion is challenging because FDG is taken up not only by tumor cells but by inflammatory cells as well [11,20–23].

Although the potential of dual-time FDG PET in evaluating various cancers has been reported, the diagnostic value of this technique for esophageal cancer has not been fully investigated [12,18,19]. To our knowledge, only one report has demonstrated the potential of dual-time FDG PET in evaluating the loco-regional lymph nodes in esophageal cancer [24]. Furthermore, there have been few reports on the sensitivity, specificity and accuracy of dual-time FDG PET–CT in evaluation of primary tumor and distant metastasis.

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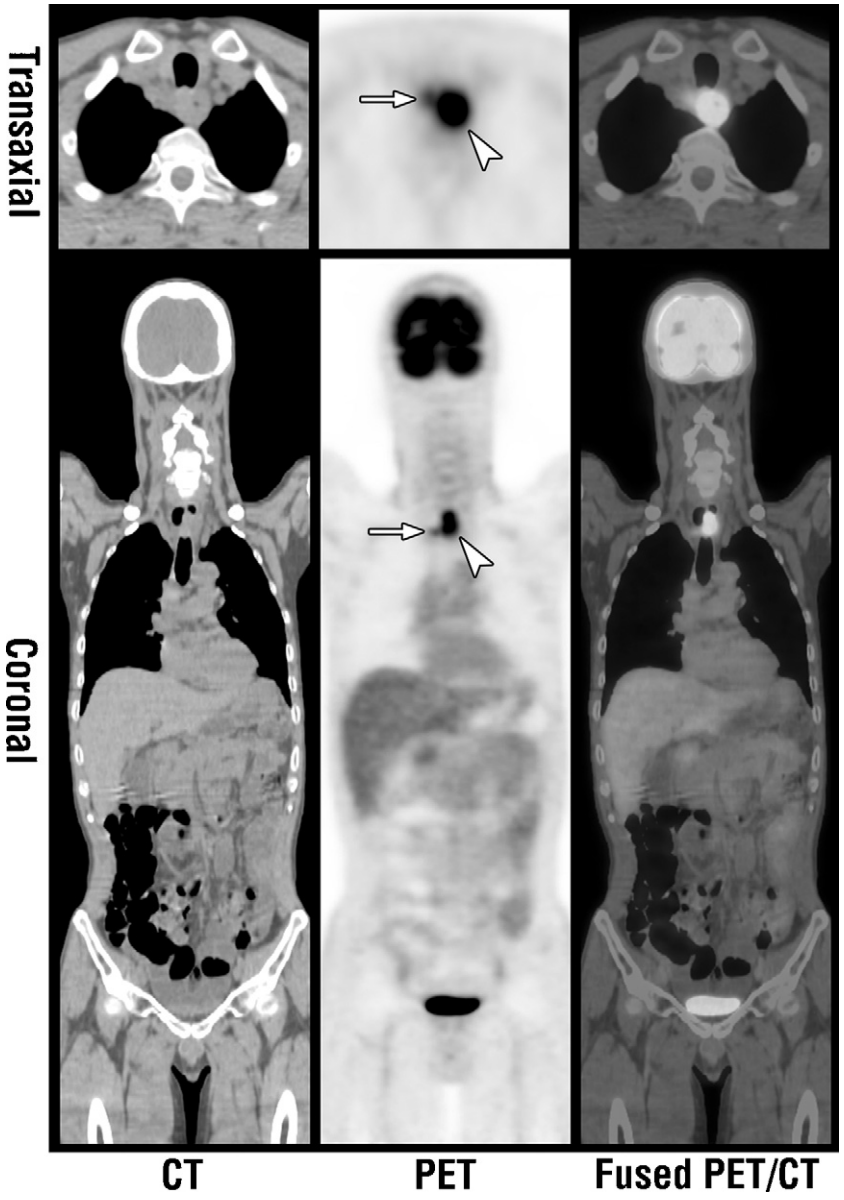

Fig. 1. Example of an FDG PET/CT scan. A 52-year-old man was diagnosed with squamous cell carcinoma in the upper third of thoracic esophagus. The FDG PET/CT scan clearly demonstrated intense FDG uptake suggestive of malignancy in the annually thickened esophagus (arrowheads; SUV_{max} = 9.6) and a regional lymph node (early SUV_{max} = 3.4).

In our study, we assessed whether dual-time FDG PET–CT would have more value than conventional FDG PET–CT imaging in differentiating between malignant and benign esophageal lesions. An arbitrary cutoff as SUV_{max} of 2.5 has been used in various malignancies, most in lung cancers. Nevertheless, the frequent effective discriminability with this arbitrary value among those previous studies results in frequent citations in newly conducted studies for various tumors, especially in the initial applications. Therefore, the current preliminary study assumed that a SUV_{max} of 2.5 might be a potential useful cutoff for differentiation of esophageal cancer in addition to the visual interpretation [15–17,25,26]. Various studies have shown that the FDG uptake in inflammatory lesions normally reached a peak at approximately 60 min after injection. However, in some malignant lesions the uptake continuously increased for 120–180 min. In order to increase the detection rate, we proposed using the percentage of change in the lesion between early SUV_{max} and delayed SUV_{max} as an alternative in the diagnosis of esophageal cancer (RI > 10%). We also hypothesized that the sensitivity, specificity and accuracy would increase if the SUV_{max} and retention index were used simultaneously [13,15–17].

Statistically, when using early $SUV_{max} \geqq 2.5$ alone as the diagnostic criterion, the sensitivity for the primary tumor was approximately 88.5%, which is consistent with the finding of other recently published reports [27,28]. When combination of early $SUV_{max} \geqq 2.5$ or RI $\geqq$ 10% was used as the diagnostic criteria for imaging reading, the sensitivity reached 96.2% and that was significantly higher than with the other three criteria. Therefore, we conclude that combination of early $SUV_{max} \geqq 2.5$ or RI $\geqq$ 10% is a reliable tool in detecting the primary site of esophageal carcinoma.

For loco-regional lymph node involvement, many studies reported that sensitivity varied, ranging from 22% and 72% [2,29,30]. In a retrospective study, Hsu et al. [27] reported sensitivities and specificities rates for regional lymph node involvement of, 57.1% and 83.3%, respectively. In comparison, our data demonstrate that the combination of early $SUV_{max} \geqq 2.5$ or RI $\geqq$ 10% produced a sensitivity of 70% and specificity of 56.3%. When compared with the usual FDG PET results, these results were unsatisfactory. This

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could be related to the relatively low glucose utilization of the small lymph node or a limited microscopic spread. Tracer uptake in physiologic structures at the thoracic cage, motion or high FDG uptake in the adjacent primary tumor can lead to an underestimate of the FDG uptake of the regional lymph nodes [24]. Furthermore, the size and morphology of the lymph nodes, a complicated lymphatic drainage network, an uneven margin between the tumor and the nodal extension, inadequate surgery and failure to detect peri-tumoral nodes during resection may also influence the final histology finding. The number of lymph nodes examined must also be taken into account when assessing the results [31]. In conclusion, we believe that the ability of dual-time FDG PET–CT to detect loco-regional lymph node metastasis using different diagnostic criteria remains to be demonstrated.

In our study, high specificities were achieved in the detection of distant metastasis of esophageal carcinoma using dual-time FDG PET–CT, in a range from 85% to 100%. Our results are in agreement with those of several FDG PET studies [10,32,33]. In contrast, the low sensitivities of early $SUV_{max} \geqq 2.5$ alone as the single diagnostic criteria in recognizing metastatic lesions might be due to variable volumes of the metastatic lesions. When RI is applied, significantly improvement was noted. Therefore, based on our study, we recommend combination early $SUV_{max} \geqq 2.5$ and/or RI $\geqq 10\%$ in order to increase the accuracy.

One limitation of this study was the small number of cases. This may have affected the statistical calculations. Therefore, studies with a larger number of patients should be conducted to determine the appropriate cutoff values of SUV_{max} and RI for esophageal cancer. Besides, short interval of follow up may also cause some false negative results. However, on the basis of the data reported, to some extent, the dual-time point FDG PET–CT has more value than standard PET imaging for detecting esophageal cancer. Therefore, we recommend that FDG PET–CT be considered in routine examination prior to the treatment of esophageal cancer in order to guide optimal clinical management for possible distal metastases to avoid unnecessary operation.

5. Conclusion

The preliminary result of this study demonstrated that dual-time point FDG PET–CT had limited value in detection of primary tumor and loco-regional lymph node metastasis. For the distant metastasis, the sensitivity and specificity would be improved if RI $\geqq 10\%$ was used as a supplement criterion. Efforts should be made to improve the ability of the dual-time FDG PET–CT technique to assess primary tumor and loco-regional lymph nodes metastasis.

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