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ORIGINAL PAPER

Value of ^{18}F-FDG PET/CT in differentiating malignancy of pulmonary artery from pulmonary thromboembolism: a cohort study and literature review

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Abstract

To determine the value of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in differentiating malignancy of pulmonary artery (PA) from pulmonary thromboembolism (PTE) based on a larger number of cases by pooling our cases and those from the literature. Consecutive patients with a PA lesion who had undergone ^{18}F-FDG PET/CT in our hospital were retrospectively reviewed. Moreover, PubMed, Embase, and Medline were searched for literature reporting individual maximum standardised uptake value (SUV_{max}) of the malignant PA lesion and/or PTE. ^{18}F-FDG activity was compared between PA malignancy and PTE by pooling the data from literature and our patients. Receiver operating characteristic curve analysis was performed to determine the ability of SUV_{max} to differentiate PA malignancy from PTE. From our database, we identified 11 patients with pulmonary artery sarcoma (PAS), and nine cases of PTE. Fifty patients with a malignant PA lesion (40 cases of PAS and 10 cases of tumor embolism) and 22 subjects with PTE were extracted from the literature. In our cases, the SUV_{max} of PAS (11.1 ± 4.9, range: 5.5–19.9) was significantly higher than that of PTE (1.9 ± 0.6, range: 1.1–3.2; $P < 0.001$). There was no significant difference in the SUV_{max} between the literature data and our cases in malignant lesions or in PTE. Based on the pooled analysis of the literature data and our cases (61 cases of malignant lesions and 31 cases of PTE), the area under the curve for SUV_{max} to differentiate PA malignancy from PTE was 0.996 (95% CI: 0.989–1.000). At a cutoff value of 3.3, the sensitivity, specificity, and accuracy were 98.4%, 96.8%, and 97.8%, respectively. The ^{18}F-FDG uptake value is an accurate index for determining PA malignancy.

Keywords Pulmonary artery · Sarcoma · Pulmonary thromboembolism · ^{18}F-FDG · SUV_{max}

Abbreviations

AUC	Area under the curve
CT	Computed tomography
CTPA	CT pulmonary angiography
FDG	Fluorodeoxyglucose
MRI	Magnetic resonance imaging
MRPA	Magnetic resonance pulmonary angiography
PA	Pulmonary artery
PAS	Pulmonary artery sarcoma
PET	Positron emission tomography
PTE	Pulmonary thromboembolism
ROC	Receiver operating characteristic
ROI	Region of interest
SUV_{max}	Maximum standardised uptake value

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Introduction

The malignancy of the pulmonary artery (PA), such as pulmonary artery sarcoma (PAS), is rare. Since its clinical and imaging findings resemble the pulmonary thromboembolism

(PTE), physicians are puzzled over its differentiation and occasionally make a misdiagnosis [1–3].

Previous studies have indicated that contrast-enhanced computed tomography (CT) can help differentiate PAS from PTE by showing a low-attenuation filling defect occupying the entire diameter of the proximal or main PA, extraluminal tumor extension, or expansion of the involved artery. However, the above-mentioned CT imaging manifestations usually appear in the advanced stage; thus, probably leading to an inoperable and incurable condition [4]. Magnetic resonance imaging (MRI) has also been proven to be helpful in differentiating between these two diseases. Nevertheless, MRI has some disadvantages and contraindications, such as the need for a longer breath-hold time, which is more difficult for patients with a PA lesion [5]. Therefore, alternative or complemantary imaging modalities and/or invasive inspection are needed in some cases to further clarify the diagnosis.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been widely used to discriminate malignancy from benign lesion. Recently, some case reports and small series studies have reported the utility of ^{18}F-FDG PET/CT for distinguishing PA malignancy from PTE. Although the ^{18}F-FDG activity in PA malignancy has been found to be higher than that in PTE either by visual assessment or semi-quantitative analysis employing the maximum standardised uptake value (SUV_{max}), only limited number of cases have been recruited in each single study [4, 6–8]. In addition, an optimal cutoff value of SUV_{max} for differentiating PA malignancy from PTE need to be further clarified.

Therefore, the aim of this study was to determine the value of ^{18}F-FDG PET/CT in differentiating malignancy of PA from PTE based on a larger number of cases, which included our cases and those from the literature.

Methods

Our cases

Patient selection

This retrospective study was approved by the Institutional Ethics Committee of Beijing Chaoyang Hospital, and the requirement for obtaining informed consent entering this study was waived due to its retrospective nature. Patients, who presented with a lesion in the PA and who underwent ^{18}F-FDG PET/CT in our hospital from June 2010 to November 2018, were identified. The PA malignancy and PTE was confirmed either by pathological examination of the biopsy specimen or based on a comprehensive clinical evaluation and follow-up [9].

PET/CT

PET/CT scans were performed on a GE Discovery STE device using a standard protocol. Patients fasted for 14–17 h (mean 14.9 ± 0.8 h) and had a blood glucose level of < 153 mg/dL before ^{18}F-FDG administration. Whole-body or chest PET/CT scans were obtained 55–90 min (mean 66.7 ± 10.3 min) after intravenous injection of 3.7 MBq/kg (0.1 mCi/kg) of ^{18}F-FDG. CT parameters were as follows: 140 kV, 120 mA, pitch of 1.375, collimation of 16 × 0.625 mm, and section width of 5 mm. PET parameters were as follows: 2.5 min/bed from the skull base to the upper thighs and 5 min/bed for head in three-dimensional mode. Attenuation-corrected PET images (voxel size, 3.9 × 3.9 × 3.3 mm) were reconstructed from the CT data using a three-dimensional ordered-subset expectation maximization algorithm (14 subsets, two iterations). Integrated PET and CT images were obtained automatically on AW VolumeShare2 (GE Healthcare).

Two nuclear physicians (MFY and XYX) evaluated the PET/CT images separately and a final consensus was reached on all of the imaging findings. Both observers were blinded to all of the other clinical information. CT pulmonary angiography (CTPA) or magnetic resonance pulmonary angiography (MRPA) had been performed in all of the included patients within 2 weeks of PET/CT imaging. The region of interest (ROI) was drawn on a PET/CT fused image with reference to the anatomic location identified by CTPA or MRPA, and SUV_{max} was calculated on the basis of body weight.

Literature search and study selection

Citations were compiled up to August 2018 from the following databases: Embase, Medline, and PubMed. The terms "(pulmonary artery) and (fluorodeoxyglucose or FDG)" were used for searching the literature. To further identify the related studies, a secondary search was performed by reading the title and abstract of the literature searched during the primary search. Literature reviews, conference abstracts, and non-English literature were excluded in this phase of screening. Then, only literature containing at least one case of a PA malignancy or PTE with SUV_{max} available (from the text, table, or figure legend) was included through the full-text review. Two authors (XYX and WG) independently performed literature screening, and any disagreement was resolved by consensus.

Statistical analysis

All of the statistical analyses were performed using SPSS version 19.0 (SPSS, Chicago, USA) and GraphPad Prism version 5.01 (GraphPad Software inc., San Diego, USA).

Continuous variables were described as mean ± standard deviation or medians with range, according to the normality of distribution assessed using Kolmogorov–Smirnov test. The unpaired *t* test or Mann–Whitney rank sum U test was used for comparisons between the two groups of data, depending on the normality of distribution. Receiver operating characteristic (ROC) curve analysis was performed to determine the ability of SUV_{max} to differentiate PA malignancy from PTE, and the cutoff value was identified using the Youden index. A $P < 0.05$ was considered to be statistically significant.

Results

Our cases

Eleven patients were identified as having PA malignancy (males: 6/11), and all of these cases were of PAS (Fig. 1 shows 10 cases who had one PET/CT, and Fig. 2 shows another patient who underwent twice PET/CT). Since another case of PAS had been previously reported [10], it was excluded from this cohort study and was included in the pooled analysis. Nine patients (males: 6/9) were included for having PTE (Fig. 3). There was no significant difference in age between the two groups (53.1 ± 10.6 years versus 50.1 ± 15.3 years, $P = 0.613$). Out of the 11 patients with PAS, the diagnosis was confirmed by histopathology in nine patients. Of the nine patients with PTE, the diagnosis was confirmed by histopathology in three patients (pneumonectomy, n = 1; pulmonary thromboendarterectomy, n = 1; PA aspiration biopsy, n = 1). In the remaining two cases of PAS and six cases of PTE without histology confirmation, the diagnoses were made on the basis of a comprehensive evaluation of imaging, clinical features and follow-up (Table 1). Of the nine patients with PTE, six patients were diagnosed as having chronic PTE and three patients were diagnosed as having acute PTE (within 2 weeks of the onset of PTE). In one patient, PAS occurred concomitant with PTE. This patient was enrolled in the PAS group (Fig. 1J).

The SUV_{max} of PAS (11.1 ± 4.9, range: 5.5–19.9) was significantly higher than that of PTE (1.9 ± 0.6, range: 1.1–3.2; $P < 0.001$), without any overlap. Additionally, there was no significant difference in SUV_{max} between acute and chronic PTE (median: 1.8, range: 1.6–2.4 versus median: 1.6, range: 1.1–3.2; $P = 0.364$).

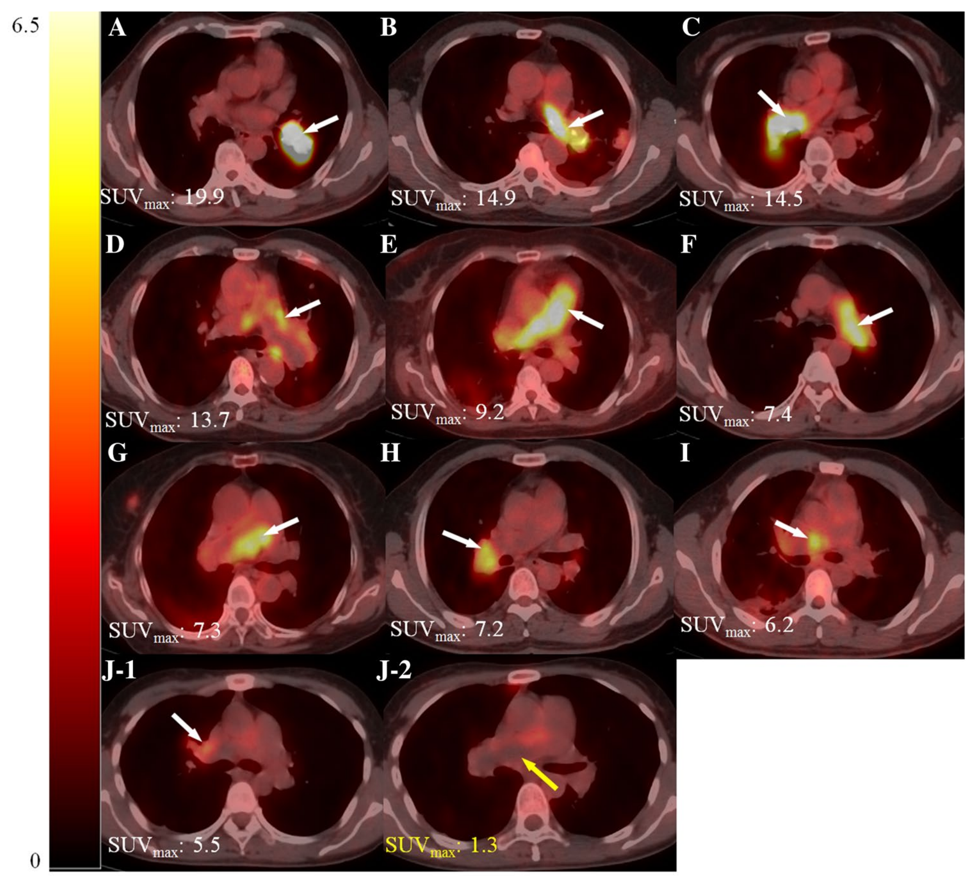

Fig. 1 [18]F-FDG PET/CT images of our 10 cases of PAS (white arrows indicate lesions). J-1 shows the PAS (white arrow) and J-2 indicates the PTE in the same patient (yellow arrow)

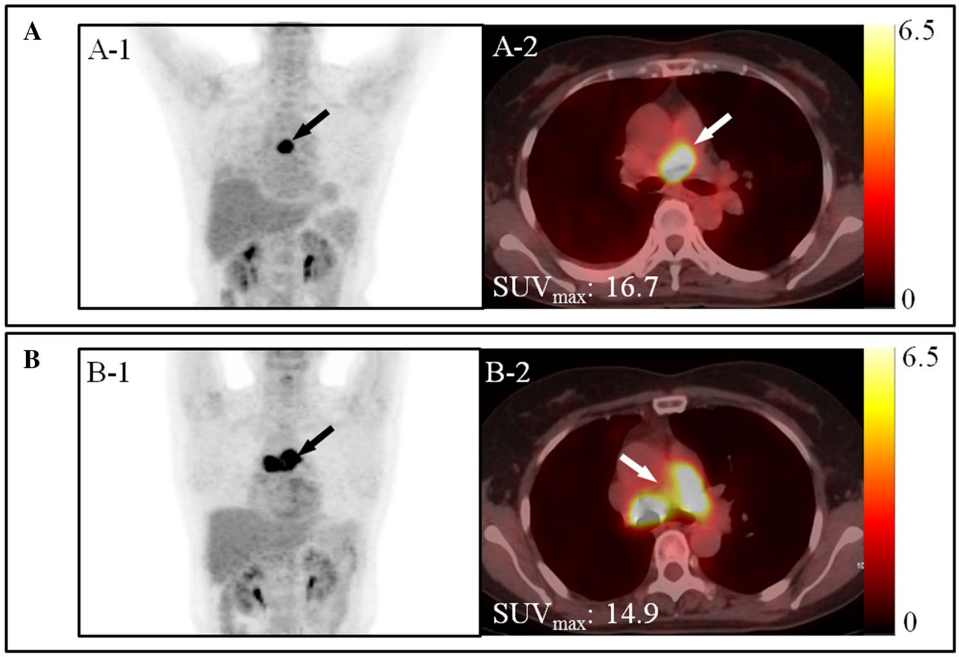

Fig. 2 Twice ^{18}F-FDG PET/CT imaging of one case with PAS. The first PET/CT **a** showed a lesion of high ^{18}F-FDG uptake in the right main PA, highly suggestive of malignancy. However, a subsequent needle biopsy revealed insufficient evidence for the diagnosis. She was then clinically diagnosed as having arteritis and received glucocorticoids therapy. The patient was regularly followed up and had the second PET/CT **b** 17 months later. The images showed the lesion was enlarged and extended to the pulmonary trunk and left PA. She refused the operation. Eleven months later, she was agreed to have a surgical resection for a worsening symptom, and PA sarcoma was confirmed by postoperative histopathology

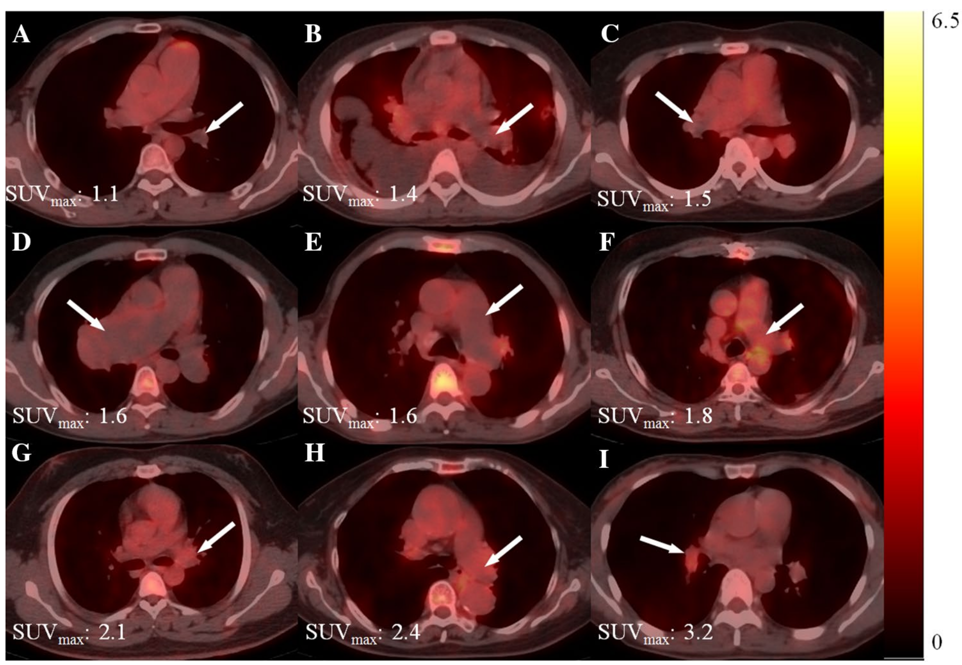

Fig. 3 ^{18}F-FDG PET/CT images of our cases of PTE (arrows indicate thrombus)

Literature review and pooled analysis

Through screening, 37 literatures presenting PA malignancy [4–6, 8, 10–42] and five literatures reporting PTE [4, 8, 31, 43, 44] were selected (Fig. 4). In total, 50 cases with a PA malignancy (40 cases of PAS and 10 cases of a tumor embolus) and 22 cases with PTE were reviewed (Tables 2, 3).

According to the literature, the activity of PA malignancy (SUV_{max}: 9.6 ± 7.0, range: 2.6–42.5) was higher than that of PTE (SUV_{max}: 2.1 ± 0.5, range: 1.5–3.5; $P < 0.001$). Furthermore, there was no significant difference in SUV_{max} between PAS and tumor embolus (9.7 ± 7.4 versus 9.0 ± 5.5; $P = 0.784$). There was no significant difference in SUV_{max} between the literature data and our cases; neither in malignant lesions (9.6 ± 7.0 versus 11.1 ± 4.9; $P = 0.491$) nor in PTE (2.1 ± 0.5 versus 1.9 ± 0.6; $P = 0.181$).

Further, a pooled analysis of 61 cases of PA malignancy (50 literature cases and 11 from our cases) and 31 cases of PTE (22

Table 1 Characteristics of our patients

Characteristics	Pulmonary malignancy (n = 11)	PTE (n = 9)
Age, years	53.1 ± 10.6	50.1 ± 15.3
Male, n (%)	6 (55)	6 (67)
Diagnostic work-up, n (%)		
CTPA	11 (100)	9 (100)
MR pulmonary angiography	8 (73)	3 (33)
Biopsy	7 (64)	1 (11)
Post-surgery pathology	3 (27)	2 (22)
Follow-up imaging	2 (18)	6 (67)

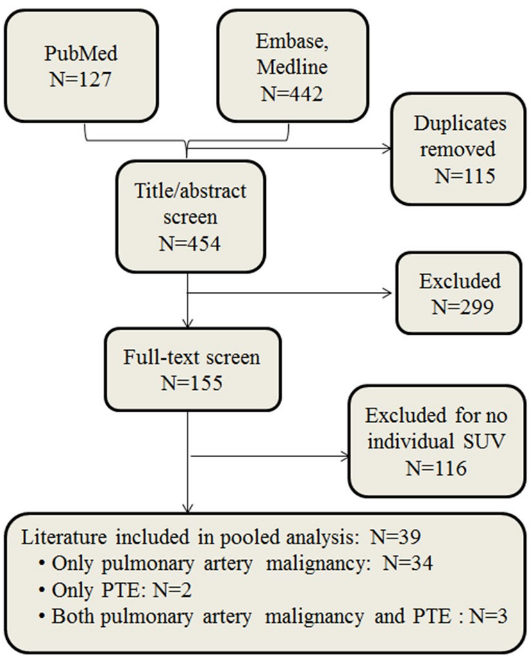

Fig. 4 Flowchart of the literature screening *PTE* pulmonary thromboembolism

cases from the literature and our nine cases) also showed that the SUV_{max} of PA malignancy was higher than that of PTE (9.9 ± 6.7, range: 2.6–42.5 versus 2.1 ± 0.5, range: 1.1–3.5; $P < 0.001$). Based on the pooled data, the area under the curve of SUV_{max} for diagnosis was 0.996 (95% CI: 0.989–1.000). At a cutoff value of 3.3, the sensitivity, specificity, and accuracy were 98.4%, 96.8%, and 97.8% respectively (Fig. 5). Totally, only one case of false-positive and one case of false-negative were present.

Discussion

PA malignancy, such as PAS, has a dismal prognosis [45]. It is occasionally misdiagnosed as PTE, leading to delayed treatment. Therefore, it is important to accurately differentiate PA malignancy from PTE. By pooling the literature and our cases, we observed that ^{18}F-FDG uptake value is a superb index for determining PA malignancy.

^{18}F-FDG activity in PA malignancy

In contrast to PTE, a malignant tumor is more likely to be fed by numerous vessels and has higher metabolic activity. Thus, ^{18}F-FDG PET/CT, as a metabolic imaging modality, has the potential to determine malignancy. Previous reports showed that PA malignancy tended to have higher ^{18}F-FDG uptake compared with PTE [4–6, 8, 10–42]. Lee et al. proposed that at a cutoff point of 3.5 for SUV_{max}, the sensitivity, specificity, and accuracy were 100% for differentiating PA malignancy from PTE [8]. To the best of our knowledge, this is the first study to perform a pooled analysis for discriminating between PA malignancy and PTE using ^{18}F-FDG PET/CT. This study demonstrated that, at a cutoff value of 3.3, SUV_{max} is an accurate index for determining the nature of the PA lesion.

In one of our patients with PAS (Fig. 2), although the initial needle biopsy showed no evidence for diagnosis of PAS, the first PET/CT showed a lesion with intense hypermetabolism (SUV_{max}: 16.7) in the PA, highly suggestive of malignancy. Finally, the postoperative histopathology confirmed it as PAS. This case suggested that the diagnosis other than malignancy should be cautious for the PA lesion showing intense uptake, for the ^{18}F-FDG PET/CT had a higher specificity to determine the malignancy of PA.

Notably, there was one false negative case of PAS (SUV_{max}: 2.6) from the literature report [35]. Moreover, several other literatures have also reported poor ^{18}F-FDG uptake in PAS by visual analysis [46–48]. Therefore, the actual sensitivity may be lower than what we have obtained (98.4%). Contrarily, fewer reports have showed intense uptake in benign PA lesions [31, 49]. Hence, ^{18}F-FDG PET/CT imaging is far more specific than it is sensitive for differentiating PA malignancy from PTE based on the available literatures. Poor uptake in PAS is possibly attributable to low cellularity and abundant myxoid tissue for histopathology [46–48]. Furthermore, tumor necrosis, hemorrhage, or calcification may also correlate with a rare ^{18}F-FDG uptake in the tumor.

Interestingly, in one of our patients with PAS (Fig. 1J), the lesion corresponding to the intraluminal filling defect was composed of thrombi and tumors, and the malignant

Table 2 Characteristics of cases with a malignant lesion of the PA in literature

Study (first author, year)	Number of cases	Age (years)	Sex (M/F)	Disease	Diagnostic method	SUV_{max}
Hmelic 2018	1	60	0/1	PAS	Pathology	10.0
Hajsadeghi 2017	1	69	0/1	PAS	Pathology	10.9
Liu 2017	1	63	1/0	PAS	Pathology	3.5
Mori 2017	1	54	1/0	PAS	Pathology	4.2
Desmarais 2016	1	66	1/0	PAS	Pathology	7.9
Li 2016	1	59	1/0	PAS	Pathology	14.3
Evison 2015	1	61	0/1	PAS	Pathology	8.6
Guo 2015	1	32	0/1	PAS	Pathology	10.3
Kaira 2015	1	58	1/0	PAS	Pathology	3.3
Kessler 2015	1	53	0/1	PAS	Pathology	6.8
Leuzzi 2015	1	60	1/0	TE	Pathology	6.7
Vial 2015	1	53	1/0	TE	Pathology	24.3
Inoue 2014	1	30	0/1	PAS	Pathology	3.6
Kamaleshwaran 2014	1	58	0/1	PAS	Pathology	11.0
Kumagai 2014	1	67	0/1	PAS	Pathology	23.1
Min 2014	1	18	1/0	PAS	Pathology	9.6
Attina 2013	2	N/A	N/A	PAS	Pathology	3.5; 7.0
Lee 2013	6	26; 29; 43; 58; 60; 70	2/4	PAS	Pathology or serial imaging findings	4.9; 5.2; 6.7; 7.8; 9.7; 42.5
	4	43; 44; 56; 69	1/3	TE	Pathology or serial imaging findings	5.4; 5.7; 7.8; 8.2
Shingyoji 2013	1	63	1/0	PAS	Pathology	12.5
Hibino 2012	1	62	0/1	TE	Pathology	9.0
Nakamura 2012	1	71	0/1	PAS	Pathology	25.2
Celic 2011	1	30	1/0	PAS	Pathology	8.3
Chun 2011	1	67	1/0	PAS	Pathology	6.8
Dias 2011	2	61; 66	0/2	PAS	Pathology	14.8; 15.8
Ote 2011	1	58	1/0	PAS	Pathology	6.3
Park 2011	1	79	0/1	PAS	Pathology	18.6
Yamasaki 2011	1	63	0/1	PAS	Pathology	2.6
Halank 2010	1	64	1/0	PAS	Pathology	13
Oberson 2010	1	34	1/0	PAS	Pathology	7.0
Purandare 2010	1	35	1/0	TE	Pathology	7.8
Tueller 2010	1	30	1/0	PAS	Pathology	5.2
Girard 2009	1	29	0/1	PAS	Pathology	4.7
Ito 2009	3	70; 77; 94	1/2	PAS	Pathology	5.3; 8.0; 9.7
Zaheer 2009	1	51	0/1	TE	Clinical findings	8.2
Sone 2008	1	31	0/1	TE	Pathology	7.3
Chong 2007	1	29	1/0	PAS	Pathology	7.0
Strobel 2007	1	40	1/0	PAS	Pathology	4.1

SUV_{max} maximum standardised uptake value, *M/F* male/female, *PAS* pulmonary artery sarcoma, *TE* tumor embolus, *N/A* not available

part had a significantly higher ^{18}F-FDG uptake than thrombi. A previous study suggested that the precise location of the tumor is important for the complete resection of PAS [50]. Therefore, ^{18}F-FDG PET/CT may aid in determining the extent of viable tumors for optimizing the operation scheme.

Since no significant difference was found in SUV_{max} between PAS and tumor embolus, it was difficult to distinguish between these two disease entities using ^{18}F-FDG PET/CT. However, if a patient has a history of primary carcinoma of another organ, metastatic tumor embolus

Table 3 Characteristics of cases with PTE in literature

Study (first author, year)	Number of cases	Age (years)	Sex (M/F)	Diagnostic method	SUV_{max}
Flavell 2014	1	75	0/1	CT	2.0
Lee 2013	9	33; 50; 55; 58; 64; 66; 68; 73; 75	7/2	Pathology or serial imaging findings	1.5; 1.6; 1.7; 1.8; 1.8; 1.8; 1.9; 2.0; 2.1
Park 2011	1	68	0/1	Pathology	3.5
Ito 2009	10	35; 52; 57; 61; 63; 69; 77; 79; 80; 82	5/5	CT	1.6; 1.9; 2.0; 2.2; 2.3; 2.4; 2.5; 2.7; 2.8; 2.9
Manoharan 2007	1	47	1/0	CT	2.3

SUV_{max} maximum standardised uptake value, *M/F* male/female, *CT* computed tomography

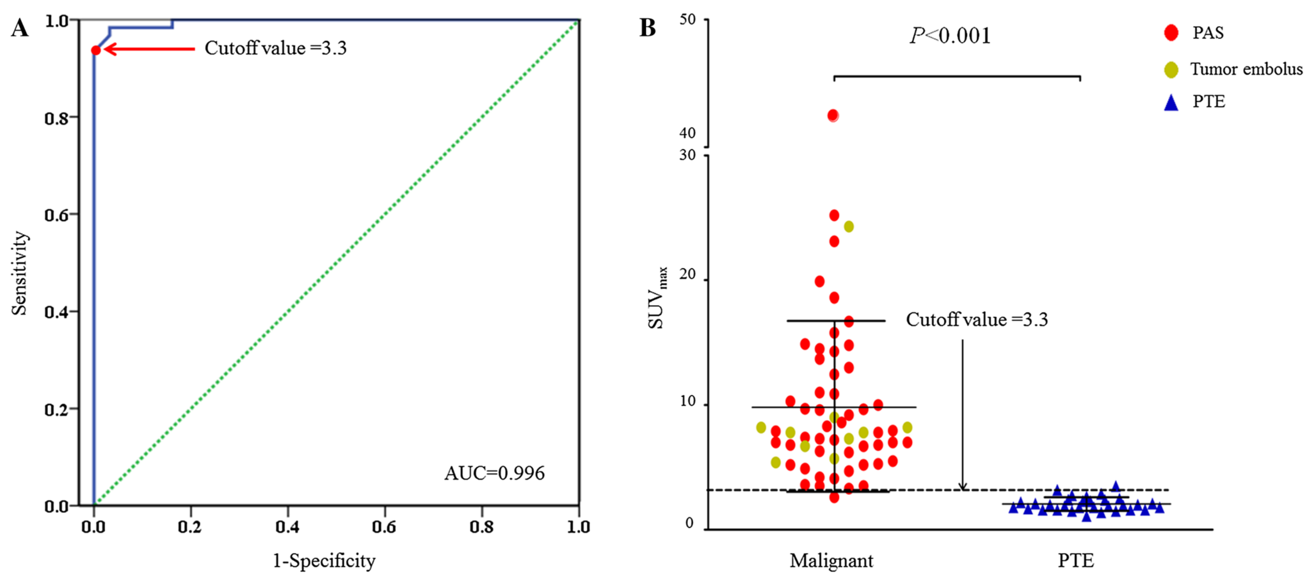

Fig. 5 Pooled analysis of PA malignancy and PTE. Image **a** shows the ROC analysis of SUV_{max} for differentiating PA malignancy from pulmonary thromboembolism. Image **b** shows the scatter plot of SUV_{max} of PA malignancy and PTE. *PAS* pulmonary artery sarcoma, *PTE* pulmonary thromboembolism

should be the first possibility to be taken into consideration when visualizing a PA lesion with ^{18}F-FDG avidity.

^{18}F-FDG activity in benign lesion of PA

Since ^{18}F-FDG PET/CT is not a routine imaging modality for the diagnosis of PTE, the SUV_{max} of PTE was even less reported in previous studies. According to 31 cases of PTE from the literature and our cases, the SUV_{max} of PTE ranged from 1.1 to 3.5. Similarly, in a study of 13 patients with PTE, Wittram et al. [9] found that the SUV_{max} range was 0.45–3.03.

In addition, previous study suggested that the inflammation of a PA thrombus is a dynamic process from the acute to chronic phase [51]. To investigate the difference of ^{18}F-FDG uptake of the thrombus in different stage of PTE, we made a comparison of SUV_{max} between acute and chronic PTE. However, no difference was found. The result might have been affected by drug intervention, sample size, and other factors, and further study with more samples is needed.

In addition to PTE, the benign lesions of PA also include other rare disease entities which might present variable extent of ^{18}F-FDG activity. A prior study [49] had reported higher uptake (SUV_{max}: 4.1) in a case of pyogenic granuloma. Moreover, PA was involved in some case of active arteritis, and increased ^{18}F-FDG uptake in PA can be observed in these cases. However, arteritis is usually characterized by mural thickening, arterial necrosis or aneurysm, and rarely developed to a mass. Whether the early stage of PAS could be confused with active arteritis remains to be further investigated.

Limitations

This study has several limitations. First, many studies only used the qualitative approach (visual analysis) for evaluating the ^{18}F-FDG uptake of the PA lesion, and they were excluded from the current study due to non-availability of SUV. Since some of those excluded studies have reported poor ^{18}F-FDG uptake in PA malignancy by visual analysis [46–48], the present study may have overestimated the ability of SUV_{max} to determine PA malignancy. Second, the SUV measurement is vulnerable to the variability of the patient preparation, the duration between ^{18}F-FDG administration and images acquisition, the performance of imaging equipment and many other conditions, which could have also affected the result of the pooled analysis. Strictly speaking, a direct comparison of SUV_{max} among different studies may be inappropriate. Third, the number of subjects is small for drawing a definite conclusion due to the rarity of PA malignancy and even less patients with PTE underwent ^{18}F-FDG imaging. Therefore, a prospective and multi-center study is anticipated to verify the findings of the present study.

Conclusions

^{18}F-FDG PET/CT imaging is a valuable modality in cases of a PA lesion. SUV_{max} can be steadily used for differentiating PA malignancy from PTE, and at a cutoff value of 3.3, the sensitivity, specificity, and accuracy are extremely high.

Compliance with ethical standards

Conflict of interest All authors declared that they have no conflict of interest.

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