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CLINICAL IMAGING

Shorter-time dual-phase FDG PET/CT in characterizing solid or ground-glass nodules based on surgical results☆

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Abstract

Objectives: We compared the accuracy of shorter-time dual-phase ^{18}F-FDG PET/CT in evaluating 94 different lung nodules classified as solid or ground-glass nodules (GGNs). **Materials and Methods:** Early and delayed maximum standardized uptake values (SUV_{max}) as well as the retention index (RI) of each nodule were determined in 75 solid nodules and 19 GGNs. **Results:** In solid nodules, early SUV_{max}, delayed SUV_{max}, and RI were higher in malignant than in benign lesions. In GGNs, these values were not significantly lower in the malignant than in the benign lesions. **Conclusion:** In the patient group with solid nodules, shorter-time dual-phase ^{18}F-FDG PET/CT could significantly differentiate the malignant from the benign ones.

Keywords: FDG PET/CT; Ground-glass nodules; Dual-phase

1. Introduction

^{18}F-Fluorodeoxyglucose-Positron emission tomography (FDG-PET) has played an important role in differentiating lung cancer from benign lung lesions for nearly a decade [1–4]. FDG-PET detects malignancy by high ^{18}F-FDG uptake which reflects increased glucose metabolic activity of cancer cells. However, there exist limitations of FDG-PET toward lesions with extreme metabolic rate, such as slow ones—bronchioloalveolar carcinoma, carcinoid tumors—and faster ones such as inflammatory lesions. The former (less glucose activity) may give false-negative FDG-PET results, while the latter (higher glucose activity) false positive.

Pulmonary nodules may manifest as solid-pattern or ground-glass nodules (GGNs) in the lung window of computed tomography (CT). Lesions with a solid pattern have been evaluated by applying ^{18}F-FDG PET/CT and using the maximum standardized uptake value (SUV_{max}) to differentiate malignancy from benign lesions. A pulmonary lesion with a SUV_{max} >2.5 is considered to be malignant. But many researchers reported that GGNs with minor metabolic activities and lower SUV_{max} may have high malignant potential [5]. Dual-phase PET/CT was introduced as a method to improve the accuracy of evaluating pulmonary lesions with

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minor metabolic activity, and the results were remarkable [6–8]. However, it is necessary to decrease an unnecessary time-consuming procedure in a very busy PET Center. Therefore, we used a shorter-time procedure of dual-time-point FDG PET/CT scanning for pulmonary nodules [6,9,10].

The aim of this study was to assess the ability of shorter-time dual-time-point ^{18}F-FDG PET/CT in differentiating the malignant or benign status of different types of pulmonary lesions classified morphologically as solid or GGN based on chest CT imaging, using surgical pathology as the reference standard.

2. Materials and methods

2.1. Patients

A total of 94 eligible and consecutive patients (male/female ratio 52:42, age range 24–84 years, mean age 61.69) with solitary pulmonary nodules (SPNs) were enrolled in this retrospective study from 1 January 2009 through 31 December 2009 at China Medical University Hospital. The size distribution of these lung nodules ranged from 1 to 3 cm in diameter by CT images. All patients fulfilled the following criteria: (a) underwent integrated FDG PET/CT and diagnostic chest CT imaging, and (b) had definitive diagnosis determined by surgical pathology. The imaging and clinical data of these patients were reviewed and analyzed retrospectively. Integrated FDG PET/CT images were evaluated by measuring the maximum SUV_{max} in the region of interest at dual time points. The change in SUV_{max} between the two time points was calculated and expressed as a percentage increase or decrease from the value at the first time point. Diagnostic chest CT images were classified dichotomously as solid or ground-glass nodules (GGNs). Patients were separated into two groups according to the solid or GGN classification of their SPNs (Figs. 1 and 2). Within each group, patients were further classified according to the malignant or benign status of the pathological specimens obtained surgically. This study was approved by the ethics committee of our hospital (DMR-99-IRB-010).

2.2. FDG PET-CT Imaging protocol and data analysis

All patients were asked to fast for at least 4 h before FDG PET-CT imaging. Imaging was performed with a

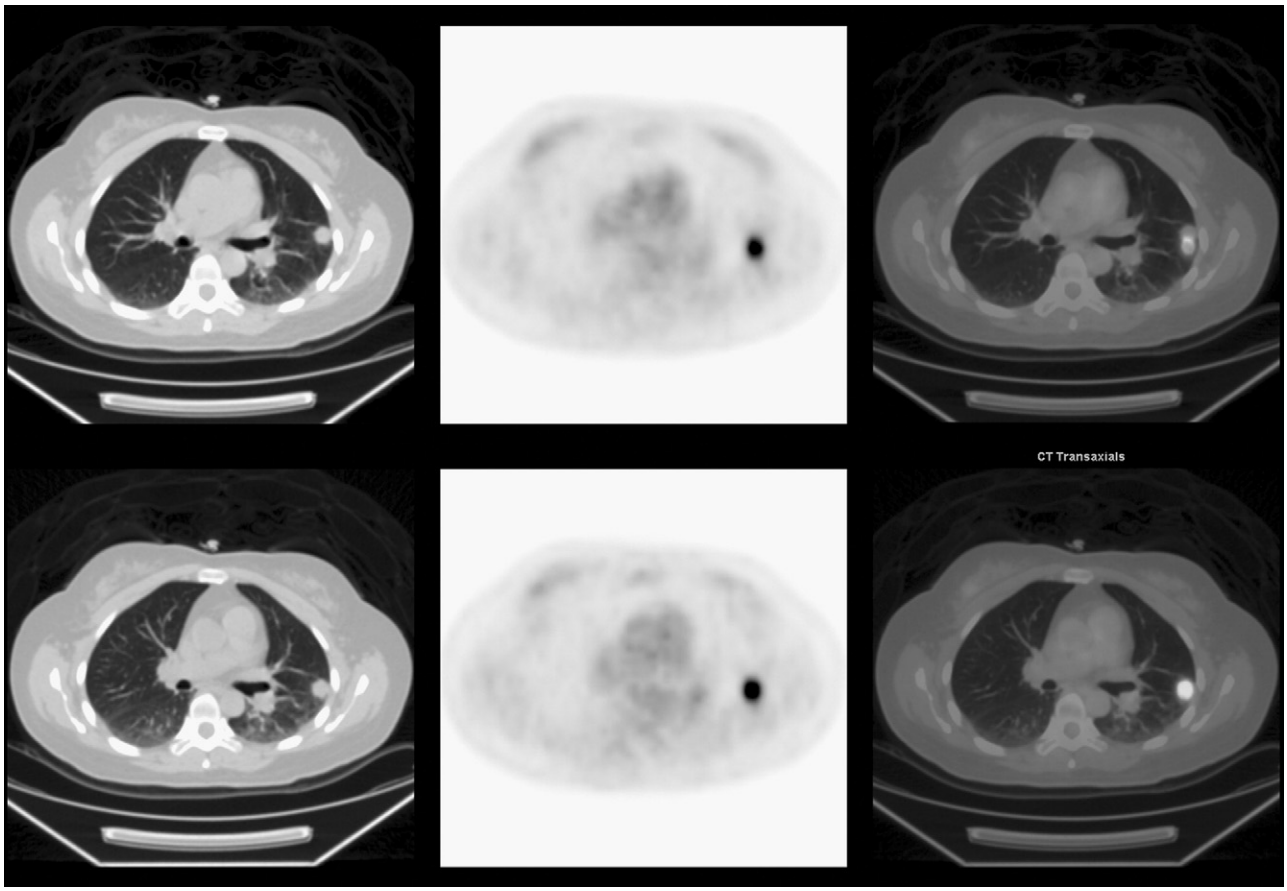

Fig. 1. Images taken from a 45-year-old female patient with a final diagnosis of lung adenocarcinoma. The chest CT images in the left column show a solid nodule in the left upper lobe of the lung. The FDG PET images in the central column show significantly increased FDG uptake in the sold nodule (upper row: early SUV_{max}, 8.84; lower row: delayed SUV_{max}, 9.20; increase, 4.04%). The FDG PET/CT fusion images are shown in the right column.

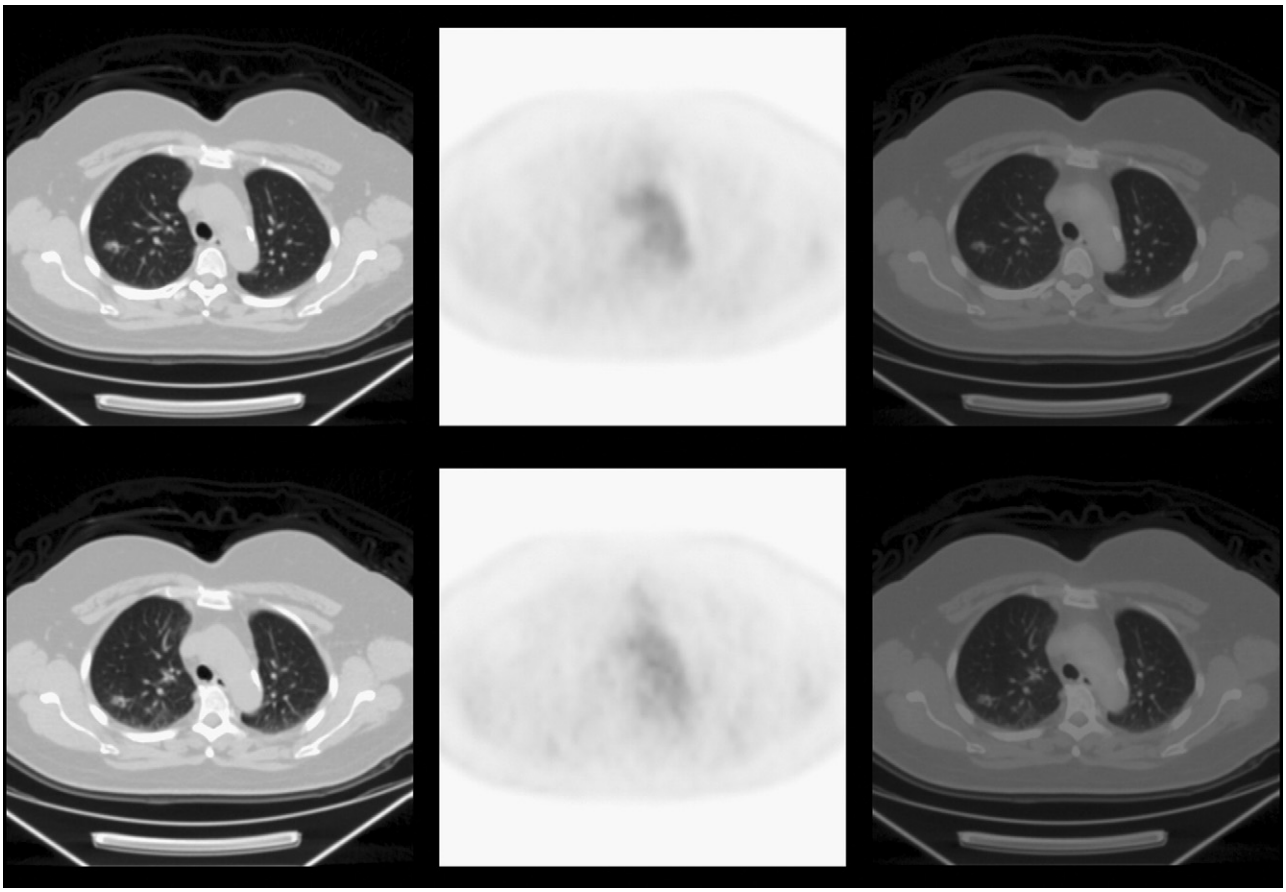

Fig. 2. Images taken from a 60-year-old female patient with a final diagnosis of lung adenocarcinoma. The chest CT images in the left column show a ground-glass nodule in the right upper lobe of the lung. The FDG PET images in the central column show no definite increase in FDG uptake in the ground-glass nodule (upper row: early SUV_{max}, 0.76; lower row: delayed SUV_{max}, 0.93; increase, 22.21%). The FDG PET/CT fusion images are shown in the right column.

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 [6,9,10]. PET emission images were acquired after CT scans at 2 min per field of view in the three-dimensional acquisition mode. The CT images were reconstructed onto a 512×512 matrix with a section thickness of 3.75 mm, reconstructed onto a 128×128 matrix, and converted into 511–keV equivalent attenuation factors for attenuation correction of the corresponding PET emission images. We did CT images twice for every patient. The maximum SUV_{max} of lung nodules on early and delayed FDG PET-CT images were measured. A retention index (RI) based on the measured SUV_{max} was calculated as 100%×(delayed SUV_{max}−early SUV_{max})÷ early SUV_{max}.

2.3. Statistical analysis

Descriptive statistics of the early and delayed SUV_{max} and the percentage change in SUV_{max} were calculated for each of the patient subgroups. The distribution of these FDG uptake measures for each patient subgroup was also presented graphically using conventional boxplots. Within each patient group, the Mann–Whitney *U* test was performed to compare the difference in uptake measures between those with and without malignancy. Receiver operating curve (ROC) analysis was also conducted for each patient subgroup.

3. Results

Of the 94 enrolled patients with SPNs, 75 had solid nodules and 19 had GGNs. Of those with solid nodules, 53 were malignant and 22 were benign. In the group with GGNs, 15 were malignant and 4 were benign. The statistical data and distribution of FDG uptake measures for each patient subgroup are presented in Table 1 and Fig. 3.

In the patient group with solid nodules, mean early maximum SUV was significantly higher in the subgroup with malignancy than in the subgroup with benign pathology [5.78±3.66 (range, 0.85–16.57) vs. 3.41±4.13 (range, 0.60–18.32), respectively; *P*=.002]; mean delayed maximum SUV was also significantly higher in the malignant subgroup than in the benign subgroup [6.75±4.27 (range, 0.64–18.72) vs.

Table 1
Statistical data of FDG uptake measures by patient subgroup

	Solid SPNs			Ground-glass SPNs		
Pathologic status	Benign	Malignant	*P* value	Benign	Malignant	*P* value
Number of patients	22	53		4	15	
Early maximum SUV			.002*			.549
Mean	3.41	5.78		2.86	1.89	
Minimum	0.60	0.85		1.35	0.76	
Maximum	18.32	16.57		6.35	3.46	
Standard deviation	4.13	3.66		2.36	0.85	
Delayed maximum SUV			.001*			.424
Mean	3.79	6.75		3.45	2.20	
Minimum	0.70	0.64		1.73	0.93	
Maximum	19.37	18.72		7.62	4.49	
Standard deviation	4.46	4.27		2.80	1.10	
% Change in max SUV			.181			.230
Mean	11.45	17.51		21.98	15.65	
Minimum	−23.81	−25.03		14.22	−3.12	
Maximum	64.26	69.64		28.24	44.67	
Standard deviation	19.48	18.08		6.23	12.72	

*P values are statistically significant.

3.79±4.46 (range, 0.70–19.37), respectively; P=.001]. In the solid SPN group, mean percentage change in maximum SUV (retention index) was also higher in the malignant subgroup than in the benign subgroup; however, this did not achieve a level of statistical significance [17.51±18.08 (range, −25.03 to 69.64) vs. 11.45±19.48 (range, −23.81 to 64.26), respectively; P=.181].

On the other hand, in the patient group with GGNs, mean early maximum SUV was lower in the malignant subgroup than in the benign subgroup [1.89±0.85 (range, 0.76–3.46) vs. 2.86±2.36 (range, 1.35–6.35), respectively], even though this was not statistically significant (P=.549). In the GGN group, mean delayed maximum SUV was also lower in the malignant subgroup than in the benign subgroup [2.20±1.10 (range, 0.93–4.49) vs. 3.45±2.80 (range, 1.73–7.62), respectively], although this again was not statistically significant (P=.424). In this patient group, mean percentage change in maximum SUV was also lower in the malignant subgroup than in the benign subgroup [15.65±12.72 (range, −3.12 to 44.67) vs. 21.98±6.23 (range, 14.22 to 28.24), respectively], but this still did not achieve statistical significance (P=.230).

ROC analysis for the patient subgroup with solid pulmonary nodules revealed an area under the curve (AUC) of 0.733, 0.747, and 0.599 for early, delayed, and

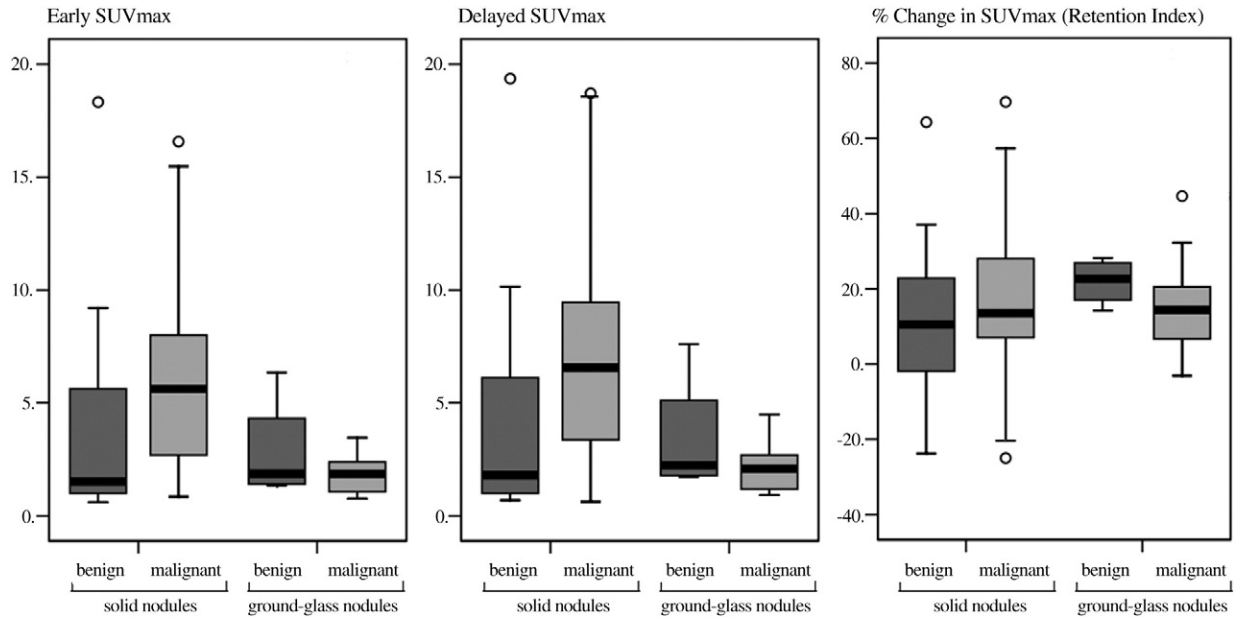

Fig. 3. Distribution of FDG uptake measures by patient subgroup.

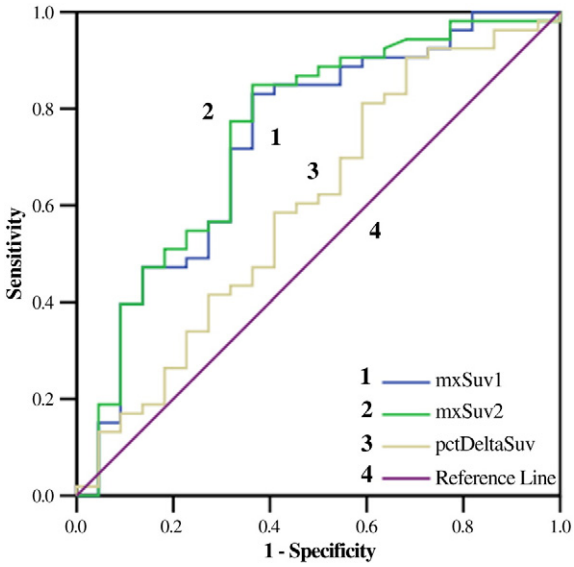

Fig. 4. ROC analysis of early, delayed, and percentage change in maximum SUV (curve 1, mxSuv1; curve 2, xSuv2; curve 3, pctDeltaSuv; curve 4, reference line) for the patient subgroup with solid pulmonary nodules.

percentage change in maximum SUV, respectively (Fig. 4). ROC analysis for the GGN subgroup was not shown due to the limited number of patients in this subgroup.

4. Discussion

In this study, we compared the accuracy of shorter-time dual-phase ^{18}F-FDG PET/CT in evaluating different types of lung lesions classified morphologically as solid or GGN based on diagnostic chest CT imaging. While most published studies assessing the accuracy of this technology in differentiating malignant from benign lesion used a combination of different tests as the reference standard, such as histopathology for some study participants and clinical follow-up with additional imaging for others, surgical pathology was the sole definitive reference standard used in all patients in our study.

The SUV is a commonly used semiquantitative measure used in the differentiation between malignant and benign lesions. A variety of factors other than malignancy status influence the level of SUV measured in the clinical setting, including patient characteristic (e.g., serum glucose level, lesion size, body habitus, pattern of respiratory motion) and technical factors (e.g., length of uptake interval after FDG injection, image acquisition, and reconstruction protocol) [11].

Despite the many factors that may affect the level of SUV measured, a higher SUV generally implies a greater probability of malignancy, due to the higher metabolic activity in most malignant lesions compared to that in benign lesions. However, increased FDG uptake may also be found in many inflammatory or infectious lesions [12–14] which commonly cause false-positive results on PET. This lack of specificity may be especially problematic in regions where granulomatous diseases are prevalent. Compared with other developed countries, Taiwan has a relatively high prevalence rate of pulmonary tuberculosis which makes the application of PET in the evaluation of pulmonary lesions more challenging.

Dual-phase FDG PET was introduced as a method to increase the accuracy in differentiating between malignant and benign lesions in the thorax [15], based on the hypothesis that malignant lesions exhibit increasing SUVs over time, whereas benign lesions show decreasing or stable SUVs over time. While this strategy may prove advantageous under certain conditions, some types of malignant lesions have minimal metabolic activity with minor SUVs. These controversial lesions frequently exhibit a ground-glass pattern on chest CT imaging.

In our study, we attempted to compare the performance of shorter-time dual-phase FDG PET/CT in the evaluation of two different morphological types of lung lesions detected on CT imaging. The results suggest that FDG uptake pattern not only may differ between malignant and benign lesions, but also may depend on the morphological type of the lesion. Among patients with solid nodules, malignant lesions typically have higher SUVs and RIs compared to benign lesions. This positive correlation between malignancy and FDG uptake not only does not exist for patients with GGNs, but there seems to be a tendency toward a reverse relationship between malignancy and FDG uptake in GGNs, even though the number of patients with benign GGNs in our study population is small. This tendency for a reverse or no significant relationship for GGNs is supported by previous research. Chun et al. [16] reported a paradoxical result in part-solid nodules and no difference in maximum SUVs between pure GGNs and benign inflammatory lesions. Therefore, while the level of metabolic activity is useful in evaluating lung lesions, additional information regarding the morphology of these lesions on CT imaging may improve the accuracy of FDG PET/CT.

Our current study attempted to assess the relationship between malignancy and FDG uptake in GGNs on shorter-time dual-phase PET/CT in a busy PET center using surgical pathology as reference standard. The results are limited because of the small number of patients with benign GGNs. Future research with a larger patient population with GGNs and additional information regarding the pathology of these lesions, such as tumor size, cell type, and degree of differentiation, may provide a more precise and conclusive assessment of the utility of FDG PET/CT in the evaluation of these lesions. In addition, we used surgical pathology results as the gold standard, which proved effective. However, this standard brought significant patient-selection bias, which also renders the conclusions less convincing. The main purpose of dual-time FDG imaging is not only to increase the sensitivity of the examination but also to reduce false-positive results. Most benign lung lesions would have less FDG uptake in both early and delayed images, which will result in much smaller likelihood for the patients to receive

surgery. Without including long-term clinical follow-up of those patients without undergoing surgery, the accuracy of this dual-time imaging method cannot be determined since most patients with presumed "negative" scans were excluded in the analysis and specificity was not being considered.

5. Conclusion

In the patient group with solid nodules, shorter-time dual-phase ^{18}F-FDG PET/CT showed significantly higher early and delayed SUV_{max} in the subgroup with malignancy compared to the subgroup with benign ones. In addition, based on the areas under the ROC curve in Fig. 4, early SUV_{max} or delayed SUV_{max} is better than RI in differentiating malignant from benign lesions in solid nodules. Because dual-time imaging is time consuming, if the lung lesion is solid, only early SUV_{max} may be enough to differentiate malignant from benign lesions. However, the shorter-time dual-phase protocol demonstrates reverse findings—decreasing FDG uptake pattern with a lower early and delayed SUV_{max} in the group of 19 patients with pulmonary GGNs—although the differences were not significant. Because expensive medical resources such as FDG-PET/CT should be used as effective as possible, if the lung lesion is GGN, high-resolution CT would be enough and PET is not necessary.

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