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Precise characterization of a solitary pulmonary nodule using tumor shadow disappearance rate-corrected F-18 FDG PET and enhanced CT

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Abstract

We aimed to characterize solitary pulmonary nodule (SPN) using imaging parameters for F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) or enhanced CT corrected by tumor shadow disappearance rate (TDR) to reflect the tissue density.

We enrolled 51 patients with an SPN who underwent PET/CT and chest CT with enhancement. The FDG uptake of SPN was evaluated using maximum standardized uptake value (SUVmax) on PET/CT. The mean Hounsfield unit (HU) for each SPN was evaluated over the region of interest on nonenhanced and enhanced CT images. The change in mean HU (HUpeak-pre) was quantified by subtracting the mean HU of the preenhanced CT from that of the post-enhanced CT. TDR was defined as the ratio of the tumor area, which disappears at a mediastinal window, to the tumor area of the lung window. We investigated which parameters (SUVmax or HUpeak-pre) could contribute to the characterization of SPN classified by TDR value and whether diagnostic performance could be improved using TDR-corrected imaging parameters.

For SPN with higher tissue density (TDR <42%, n = 22), high value of SUVmax (≥3.1) was a significant factor to predict malignancy (P = .006). High value of HUpeak-pre (≥38) was a significant factor to characterize SPN (P = .002) with lower tissue density (TDR ≥42%, n = 29). The combined approach using TDR-corrected parameters had better predictive performance to characterize SPN than SUVmax only (P = .031).

Applying imaging parameters such as SUVmax or HUpeak-pre in consideration of tissue density calculated with TDR could contribute to accurate characterization of SPN.

Abbreviations: 2D = two-dimension, FDG = F-18 fluorodeoxyglucose, GGO = ground-glass opacity, HU = Hounsfield unit, NPV = negative predictive value, PET/CT = positron emission tomography/computed tomography, PPV = positive predictive value, ROC = receiver operating characteristic, SPN = solitary pulmonary nodule, SUV = standardized uptake value, TDR = tumor shadow disappearance rate.

Keywords: F-18 FDG, Hounsfield unit, lung cancer, solitary pulmonary nodule, tumor shadow disappearance rate

1. Introduction

A solitary pulmonary nodule (SPN) is a single nodular lesion in a lung without distal atelectasis or local adenopathy. It has a variable size up to 3.0 cm.[1] It is important to characterize SPN because the 10% to 68% of SPNs have been diagnosed as malignant on pathological examination and a malignant nodule

can grow and metastasize to local lymph nodes or distant organs when it is misdiagnosed as benign or missed on follow-up.[2]

There are several imaging modalities to characterize SPNs. Contrast-enhanced computed tomography (CT) shows good sensitivity, with a cutoff value of 15 Hounsfield units (HU) for enhancement.[3] However, it has low specificity because the nodular lesion due to the inflammatory disease also presents with high enhancement.[4] F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) also has been used to characterize SPNs. Although it shows a favorable diagnostic performance for SPNs >1.0 cm,[5] it also has a limitation regarding diagnosis of some histologic types (such as carcinoid and mucinous tumors or adenocarcinoma with ground-glass opacity [GGO] regions.[6–9])

Tumor shadow disappearance rate (TDR) is defined as the ratio of the tumor area, which disappears at a mediastinal window to the tumor area of the lung window.[10] This area has a correlation with tissue density when the energy of X-ray is maintained consistently.[11] The GGO portion in a malignant nodule usually has low FDG uptake because it does not get filled with tumor cells and usually shows a low tissue density. Considering these points, TDR has important implications in application of FDG uptake of SPN differently according to tissue density.

We aimed to characterize SPN using imaging parameters for F-18 FDG PET/CT or enhanced CT corrected by TDR to reflect the tissue density.

2. Methods

2.1. Patients

We initially enrolled 74 patients who had SPNs with 0.8 to 3.0 cm solid portion and underwent PET/CT and chest CT within 2 months between March 2007 and October 2015. Patients with a previous history of cancer (n=13), malignant lymph node in the mediastinum (n=5), multiple nodules (n=3), and nodules with pure GGO (n=2) in the lung were excluded. Finally, 51 patients were enrolled in this study. All nodules were evaluated pathologically using bronchoscopic biopsy or surgical resection. This retrospective study was approved by the Institutional Review Board, and the need for written informed consent was waived.

2.2. Image acquisition

Patients received an injection of 5.55 MBq FDG per kilogram of body weight after they fasted for at least 6 hours. The level of blood glucose was measured before the injection of FDG. Image acquisition was performed by combined PET/CT scanners (Discovery ST System, GE Medical Systems) approximately 50 minutes after the FDG injection. PET images were acquired with a 15.7-cm axial field of view in 2-dimension (2D) with a 128 × 128 matrix and multiple bed positions from the middle thigh to the base of the skull.

All patients underwent conventional enhanced CT using 16-channel MDCT (LightSpeed; GE Medical Systems) or 64-channel MDCT (LightSpeed VCT; GE Medical Systems) scanner. They were scanned from the level of the supraclavicular area to the upper pole of the right kidney with craniocaudal scanning in the supine position and at end-inspiratory suspension during a single breath-hold. Contrast-enhanced CT was carried out after

intravenous injection of an iodinated contrast agent, iopromide (Ultravist 300; Schering, Berlin, Germany); 120 mL of contrast agent was administered at the rate of 3 ml/s. The scanning parameters were 120 kVp, 120 to 160 mAs, a 512 × 512 matrix, and a 2.5-mm reconstruction thickness with 1-mm reconstruction interval. The average acquisition time was 15 seconds. The evaluation began with the 2D transverse CT images.

2.3. Image analysis

We measured the maximum standardized uptake value (SUV-max) of volume of interest drawn over an FDG uptake lesion matched with an SPN in CT images. We also measured the mean Hounsfield unit (HU) over the region of interest of SPN drawn on nonenhanced and enhanced CT images. For quantification of HU change between nonenhanced and enhanced CT, we determined CT imaging parameter (HUpeak-pre) by subtracting the mean HU of nonenhanced image from the mean HU of enhanced image for each SPN.

For calculation of TDR, we measured the maximum dimensions of the tumors (maxD) and the largest dimension perpendicular (perD) to the maximum axis on transverse images of both lung (width, 1500 HU; level, −700 HU) and mediastinal (width, 400 HU; level, 20 HU) window images (Fig. 1).[12] TDR was defined as:[10]

$$TDR(\%) = \left[1 - \frac{maxD \times perD\,on\,mediastinal\,window\,images}{maxD \times perD\,on\,lung\,window\,images} \right] \times 100.$$

As SUVmax is not a reliable parameter for tumor with low tissue density, we evaluated whether the tissue density is sufficient to trust the SUVmax of the nodule by the TDR. Thus, we performed the stepwise approach to characterize SPNs by applying imaging parameters such as SUVmax or HUpeak-pre in consideration of tissue density calculated with TDR (Fig. 2).

In the first step, to find the TDR range for the reliable SUVmax, we defined the cutoff point of the TDR value from the receiver operating characteristic (ROC) curve when the PET had the highest accuracy for malignancy in the nodules with SUVmax <2.5. Using this cutoff point, all nodules were classified into 2 groups: low TDR group or high TDR group. In the second step, we selected the imaging parameter (between SUVmax and HUpeak-pre) that characterized SPNs more precisely using each cutoff point calculated by ROC curve.

Finally, we classified SPNs with high values of imaging parameters (high SUVmax or high HUpeak-pre) in each TDR group as malignant nodules. SPNs with low values of imaging parameters in each TDR group were also classified as benign nodules.

We investigated whether the diagnostic performance could be improved using TDR-corrected imaging parameters compared to single cutoff point of SUVmax (2.5).

2.4. Statistical analyses

Descriptive quantitative data are shown as means ± standard deviations or ranges. Qualitative data are presented as percentages. We used the student t-test and Mann–Whitney U test to compare parameters between the groups classified by biopsy results. The sensitivity, specificity, positive predictive
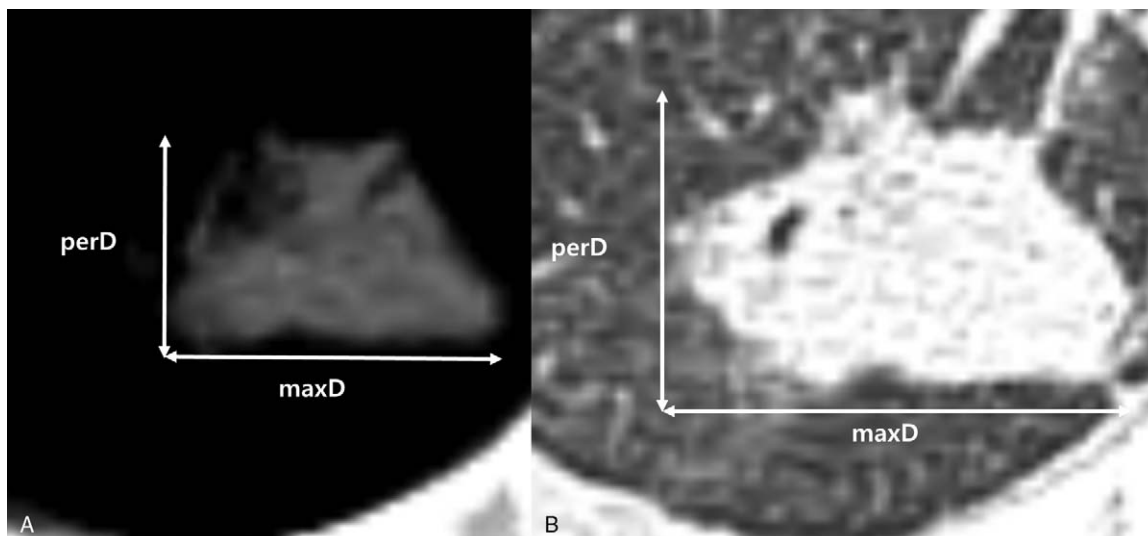
Figure 1. The measurements method for the dimensions of solitary pulmonary nodule (SPN). The images showing measurement method for the maximum dimensions (maxD) and the largest dimension perpendicular to the maximum axis (perD) of SPN on CT with mediastinal window (A) and on lung window (B) settings.
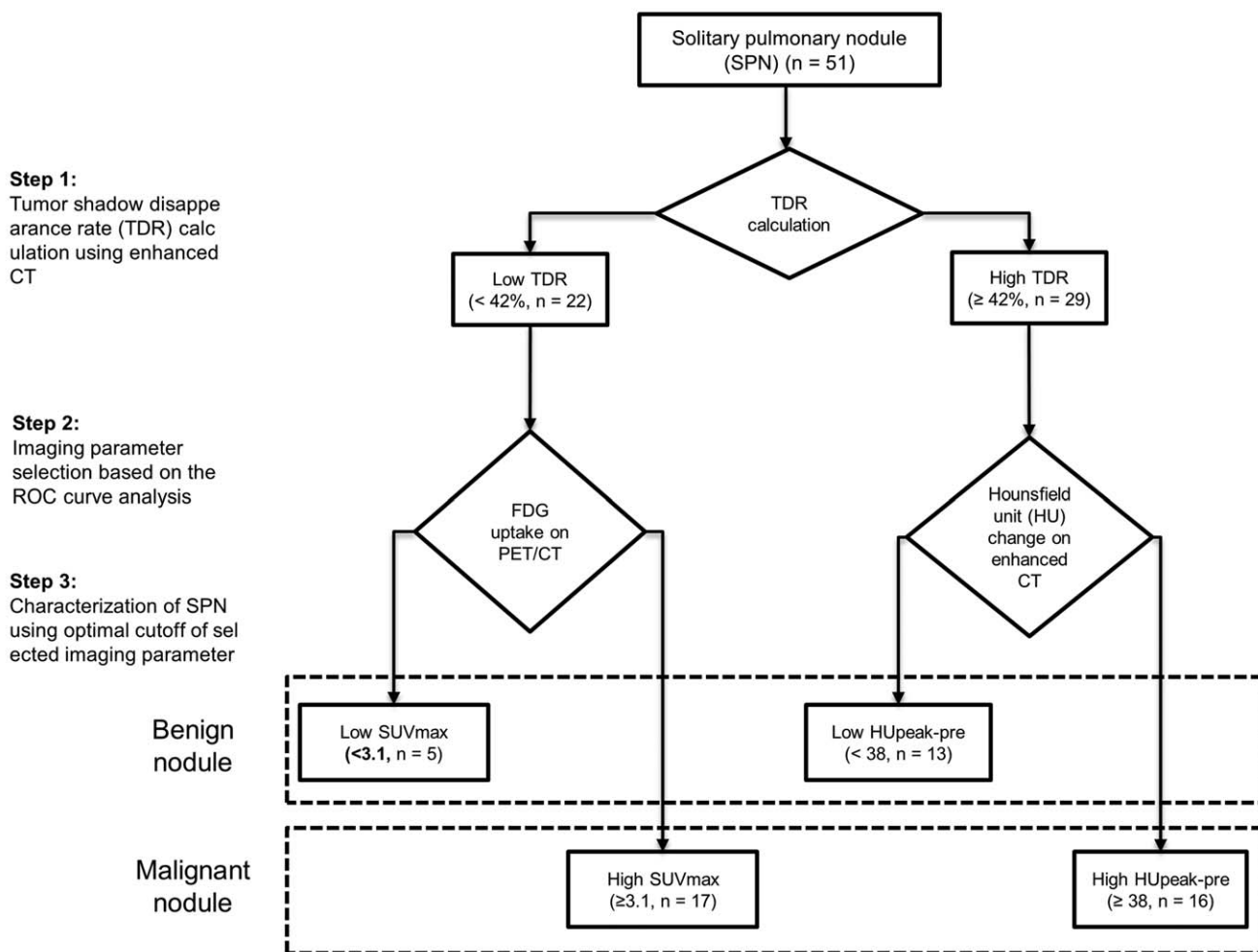
Figure 2. Diagnostic flow-chart for the characterization of solitary pulmonary nodule (SPN) using F-18 FDG PET/CT and enhanced CT based on the tumor shadow disappearance rate (TDR). Maximum standardized uptake value (SUVmax) and enhancement of Hounsfield unit (HUpeak-pre) were optimized using the receiver operating characteristic (ROC) curve analysis in each TDR group.

Table 1

Patients' characteristics.

Parameters	Values
Age (range)	63.5 ± 9.7 (41–80)
Male/female	28 (54.9%)/23 (45.1%)
Smoking history (+/−)	20 (39.2%)/31 (60.8%)
Location of SPN	
Right lung	33 (64.7%)
Upper lobe	14 (27.5%)
Middle lobe	6 (11.8%)
Lower lobe	13 (25.5%)
Left lung	18 (35.3%)
Upper lobe	9 (17.6%)
Lower lobe	9 (17.6%)
Pathologic examination	
Benign	21 (41.2%)
Chronic granulomatous inflammation	10 (19.6%)
Hamartoma	6 (11.8%)
Inflammatory myofibroblastic tumor	2 (3.9%)
Aspergilloma	2 (3.9%)
Pulmonary airway malformation	1 (2.0%)
Malignant	30 (58.8%)
Adenocarcinoma	19 (37.3%)
Squamous cell carcinoma	5 (9.8%)
Large cell carcinoma	3 (5.9%)
Small cell carcinoma	2 (3.9%)
Mucoepidermoid carcinoma	1 (2.0%)
Size on mediastinum window setting	1.6 ± 0.7 (0.8–3.0)
Size on lung window setting	2.2 ± 0.6 (1.1–3.3)

SPN = solitary pulmonary nodule.

value (PPV), negative predictive value (NPV), and accuracy were calculated for each of the analyses. The McNemar's test was used to compare the diagnostic performance between single cutoff of SUVmax (2.5) and TDR-corrected imaging parameters. P values <.05 were considered statistically significant. The analysis was performed using IBM SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY).

3. Results

In total, 51 patients were enrolled, consisting of 28 (54.9%) men and 23 (45.1%) women, with a mean age of 63.5 ± 9.7 years (range, 41–80 years) at the time of diagnostic imaging (Table 1). Of them, 20 (39.2%) patients had smoking history and 31 (60.8%) did not. The number of nodules located in right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe were 14 (27.5%), 6 (11.8%), 13 (25.5%), 9 (17.6%), 9 (17.6%), respectively. Overall, 30 of 51 nodules (58.8%) were revealed to be malignant on pathologic confirmation. Malignant nodules consisted of 19 (37.3%) adenocarcinoma, 5 (9.8%) squamous cell carcinoma, 3 (5.9%) large cell carcinoma, 2 (3.9%) small cell carcinoma, and 1 (2.0%) mucoepidermoid carcinoma. The 21 of 51 nodules (41.2%) were confirmed as benign. Benign nodules consisted of 10 (19.6%) chronic granulomatous inflammation, 6 (11.8%) hamartoma, 2 (3.9%) inflammatory myofibroblastic tumor, 2 (3.9%) aspergilloma, and 1 (2.0%) pulmonary airway malformation. The largest nodule diameter was 1.6 ± 0.7 cm (range, 0.8–3.0 cm) on mediastinal setting image and 2.2 ± 0.6 cm (range, 1.1–3.3 cm) on lung setting image.

The mean age of patients with malignant nodules was higher than that of patients with benign nodules. However, no differences in sex, smoking history, location, or size were found (Table 2). To select imaging parameter between SUVmax and HUpeak-pre based on tissue density, all nodules were classified into 2 groups: low TDR group (TDR <42%, n = 22) and high TDR group (TDR ≥42%, n = 29). In the low TDR group (TDR <42%), SUVmax was selected as the optimal imaging parameter because the SUVmax of malignant nodules was significantly higher than that of benign nodules (P = .006). In the high TDR group (TDR ≥42%), however, HUpeak-pre on enhanced CT was selected because the HUpeak-pre of malignant nodules was significantly higher than that of benign nodules (P = .002).

To characterize SPNs, the optimal cutoff point for each imaging parameter was drawn using ROC curve analysis: SUVmax (3.1) in the low TDR group and HUpeak-pre (38) in the high TDR group (Fig. 2). Malignant nodules were defined as

Table 2

Comparison of clinical or imaging parameters between benign and malignant nodules.

	Benign (n = 21)	Malignant (n = 30)	P
Age	58.8 ± 10.3 (41–76)	66.8 ± 7.9 (47–80)	.003
Sex (M/F)	9: 12	19: 11	.148
Smoking history (+/−)	9: 12	11: 19	.656
Location of SPN			.883
Right upper lobe	5	9	
Right middle lobe	2	4	
Right lower lobe	5	8	
Left upper lobe	4	5	
Left lower lobe	5	4	
Size on mediastinum window setting	1.5 ± 0.6 (0.8–3.0)	1.7 ± 0.7 (0.8–2.7)	.235
Size on lung window setting	2.0 ± 0.6 (1.1–3.1)	2.3 ± 0.7 (1.3–3.3)	.110
TDR <42			
SUVmax	3.74 ± 5.24	8.29 ± 4.26	.006
HUpeak-pre	20.22 ± 32.77	43.62 ± 19.20	.018
TDR ≥42			
SUVmax	3.33 ± 3.11	4.89 ± 3.13	.084
HUpeak-pre	18.42 ± 23.29	53.76 ± 23.66	.002

HUpeak-pre = enhancement of Hounsfield unit, SPN = solitary pulmonary nodule, SUVmax = maximum standardized uptake value, TDR = Tumor shadow disappearance rate.

Table 3

Comparison of diagnostic performance between SUVmax 2.5 and TDR-corrected imaging parameter.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	*P*
SUVmax 2.5	83.3	52.3	71.4	68.8	70.6	.031
TDR corrected parameter	86.7	81.0	86.7	81.0	84.3	

NPV = negative predictive value, PPV = positive predictive value, SUVmax = maximum standardized uptake value, TDR = tumor shadow disappearance rate; TDR corrected parameter, SUVmax 3.1 as the cutoff value for malignancy when the nodules with <42% of TDR, the change of Hounsfield unit 38 as the cutoff value for malignancy when the nodules with ≥42% of TDR.

SPNs with higher values of imaging parameter: SUVmax ≥3.1 in the low TDR group and HUpeak-pre ≥38 in the high TDR group. SPNs with lower values of imaging parameter in each TDR group were classified as benign nodules. Finally, we developed a TDR-corrected parameter to characterize SPNs from this stepwise approach and compared it with single cutoff of SUVmax (2.5).

The sensitivity, specificity, PPV, NPV, and accuracy of single cutoff of SUVmax (2.5) were 83.3%, 52.3%, 71.4%, 68.8%, and 70.6%, respectively, and those of TDR-corrected parameter were 86.7%, 81.0%, 86.7%, 81.0%, and 84.3%, respectively (Table 3). TDR-corrected parameter showed significantly higher diagnostic performance than the single cutoff of SUVmax ($P = .031$). Figure 3 shows representative cases, with improvement in diagnostic performance using TDR-corrected imaging parameters.

4. Discussion

In spite of the success of PET and CT in diagnosing SPNs, the nodules with low tissue density are still difficult to evaluate. We tried to apply the different imaging parameters to characterize SPNs based on TDR, which showed that SUVmax in patients with low TDR (<42%) and HUpeak-pre in patients with high TDR (≥42%) were significant parameters to characterize SPNs, respectively.
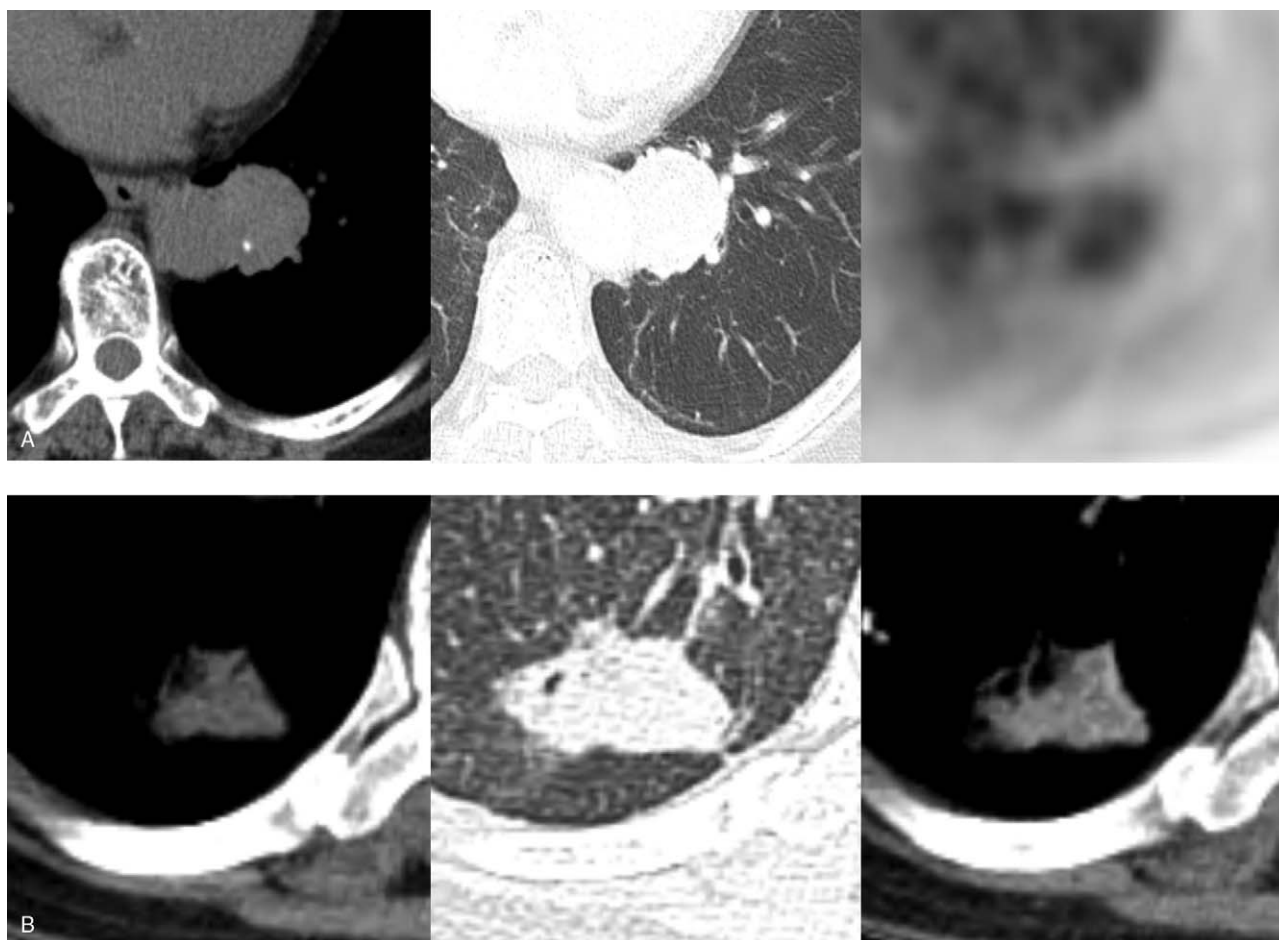
Figure 3. Characterization of solitary pulmonary nodule (SPN) using TDR-corrected imaging parameter. (A) TDR 9.0%, SUVmax 3.0, HUpeak-pre 97; since this nodule had the TDR of 9%, SUVmax was selected as the TDR-corrected imaging parameter. This nodule was classified as benign for TDR-corrected SUVmax 3.1, but malignant for SUVmax 2.5. Pathologic examination confirmed a sclerosing hemangioma. (B) TDR 48.4, SUVmax 2.4, HUpeak-pre 55; since this nodule had the TDR of 48.4%, HUpeak-pre was selected as the TDR-corrected imaging parameter. This nodule was classified as malignant for HUpeak-pre 38, but benign for SUVmax 2.5. Pathologic examination revealed lung adenocarcinoma.

Although nonenhanced CT provides enough radiologic information about SPNs, lung nodule enhancement is an influential factor to discriminate benign nodules from SPNs. In the multicenter trial, it showed 98% sensitivity with ≤15 HU as benign on enhancement.[3] Nevertheless, CT shows a low specificity of 58%, which means the nodules with >15 HU for enhancement include some benign lesions such as granulomas or organizing pneumonia.[13]

Furthermore, F-18 FDG PET has some limitations regarding the diagnosis of SPN. First, the measurement of SUVmax is affected by partial volume effect when the nodule is small.[14] It underestimates the SUVmax of the nodule because the spatial resolution of a modern scanner is not appropriate to evaluate nodules with a diameter of less than approximately 0.7 cm.[15] The spatial resolution of the PET/CT scanners used in this study was also approximately 0.7 cm. Thus, we just evaluated nodules >0.7 cm. In addition, some tumors have low metabolic activity resulting in low FDG uptake. These nodules present with low SUVmax, and sometimes, it is too low to distinguish it from the SUVmax of the benign tumor.[7]

Although the nodules were large enough to be measured, there were still many false-negative results because the SUVmax is affected by low tissue density, especially the GGO portion.[16] The low tissue density indicates few cells, resulting in low SUVmax.[17] In that case, the nodule with low tissue density often seems like a benign lesion. However, we cannot consider the nodule as benign because the GGO portion of the subsolid nodule is an indicator of malignancy.[18] In fact, in this study, 5 malignant nodules had SUVmax <2.5. These nodules were false-negative when we used the SUVmax 2.5 as a diagnostic criterion because these nodules did not have enough tissue density to be evaluated by SUVmax. However, as the TDRs of these nodules were >42%, we did not regard them as benign when we used the TDR-corrected imaging parameter. This result suggests that it is important to know whether the nodule has enough tissue density to be evaluated by the SUVmax.

The TDR for the evaluation of tissue density is the missing area of the tumor on the mediastinal window image compared with the area of tumor on the lung window image. When the tissue density of the nodule becomes lower, the more x-ray can penetrate the tissue, and the TDR becomes higher.[11] Accordingly, if the nodule has GGO portion, it will show high TDR because the GGO portion is filled with air, exudate, or transudate instead of cells. It results in a nodule with low tissue density.[12] Thus, high TDR means SPN contains higher GGO portion or low tissue density portion. Actually, five malignant nodules that showed high TDR were 4 adenocarcinomas with GGO and one mucoepidermoid carcinoma in this study. Therefore, we used TDR as a parameter to determine which method is more appropriate between PET and CT according to tissue density.

We have commonly used SUVmax as an objective parameter when we have evaluated the PET images. It has an advantage for objectivity. However, there was not enough discussion regarding the SUVmax. We have used the SUVmax regardless of tissue density. However, it might have missed some malignant nodules with low tissue density. This study suggested new method to compensate for this problem using TDR. If the TDR is considered for tissue density evaluation, we could determine whether the SUVmax is an appropriate parameter when the nodule shows low SUVmax (Fig. 3A). Therefore, the TDR is a good indicator of whether to trust the SUVmax of SPNs. It also showed better diagnostic performance than ordinary methods (Table 3).

We used enhancement of HU instead of SUVmax for nodules with high TDR. The enhancement of HU is good indicator of tumor growth as the enhancement of 100 HU in nonsolid nodule represents that tumor volume approximately 10% grow.[19] Using HUpeak-pre 38 as the cutoff point for malignancy showed good diagnostic performance in the nodules with TDR ≥42% (Fig. 3B). The specificity of conventional method using HUpeak-pre 15 as the cutoff point for malignancy was 58.3% in the nodule with TDR ≥42%. This suggests enhance CT performance for malignancy can be improved by considering its tissue density. Traditionally, the first purpose of CT in diagnosis of SPN is not to miss malignancy. The cutoff for CT enhancement is based on this purpose. Thus, this cutoff was determined to achieve high sensitivity for SPN, while sacrificing specificity. However, this study suggests the method of preserving the specificity while enhancing CT for SPN.

This study has several limitations. First, this is the retrospective study. We may have a selection bias. We tried to include all the nodules evaluated by pathologic assessment. This made it difficult to register pathologically confirmed benign nodule because it was not usually performed biopsy immediately when nodule was suspected to be benign. This resulted in unbalanced data collection because malignant nodules were relatively easier to register. Nevertheless, pathological confirmation of nodule was necessary because small malignant nodule sometimes grow slowly. Second, although professional radiologist measured HU over SPN and calculated TDR on diagnostic CT, reproducibility issues from manual measurement were inevitable. Automated measurements may be required in future studies. Finally, the location of SPNs could affect imaging parameters including SUVmax because lung movement during respiration depends on their location. Although the location of the enrolled nodules had even distribution and there was no significant relationship between SPN location and other parameters in this study, further studies including more cases are necessary to investigate the difference of clinicopathologic parameters or cutoff points of imaging parameters according to SPN location.

In conclusions, clinical impact of imaging parameter differed to characterize SPN according to the tissue density of SPN. FDG uptake (SUVmax) on PET/CT was the better imaging parameter for high-density nodule (TDR <42%). However, HUpeak-pre on contrast-enhanced CT was a significant parameter for low-density nodule (TDR ≥42%). Different application of imaging parameters based on TDR could contribute to precise characterization of SPNs compared to a single imaging parameter.

Author contributions

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