Noninvasive Differential Diagnosis of Pulmonary Nodules Using the Standardized Uptake Value Index

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Objectives: We previously showed that the standardized uptake value (SUV) index, which was defined as the ratio of the maximum SUV of the tumor to mean SUV of the liver, was a surrogate marker of lung cancer aggressiveness. In this study of patients with pulmonary nodules (PNs), we explored whether the SUV index could be used to differentiate small malignant from small benign PNs.

Methods: A total of 284 patients with solitary PNs ≤2 cm in size underwent positron emission tomography/computed tomography and surgery. The associations between pathological findings and clinical factors were evaluated.

Results: The median SUV indices of lung cancer, metastatic PNs and benign nodules were 1.2, 1.5, and 0.6, respectively (P <0.01). A SUV index cut-off value of 1.2 was used to differentiate benign from malignant nodules. When patients were grouped according to SUV index cut-off values of <1.2 or ≥1.2, the following cases were false-negative: lung adenocarcinoma (P <0.01), kidney as primary site (P <0.01), and metastatic PNs with long disease-free survival (P =0.02).

Conclusions: As a noninvasive diagnostic marker, the SUV index was found to be useful for differentiating benign from malignant small PNs.

Keywords: Pulmonary nodule, Diagnosis, positron emission tomography/computed tomography

Introduction

The preoperative diagnosis of small pulmonary nodules (PNs) is difficult, even with the use of advanced medical technology. Ideally, the decision to perform an invasive lung biopsy to diagnose a pulmonary nodule should be based on the patient’s ability to tolerate the procedure, the patient’s preference, the curability of the lesion, and whether or not the patient will agree to chemotherapy. Therefore, before a definitive pathological diagnosis can be obtained, the radiologic evaluation should be more diagnostically accurate than currently possible before the patient undergoes resection. In the screening setting, chest computed tomography (CT) is the gold-standard imaging modality for detecting PNs. A clinical role of positron emission tomography (PET)/CT for evaluating patients with lung cancer has also been established. PET has been used in the differential diagnosis of PNs. The standardized uptake value (SUV) has frequently been used to identify malignancies in patients undergoing PET. However, because the SUV is affected by blood sugar level, body weight, and PET/CT protocol, cut-off values that provide a more accurate preoperative diagnosis for PNs are still needed. We recently demonstrated that the SUV index is a better value for standardization than a single $SUV_{max}$ value, and
that PET/CT was a clinically effective imaging modality for evaluating patients with non-small cell lung cancer (NSCLC). The aim of this retrospective study was to evaluate the PET/CT findings of patients with small PNs (≤2 cm). To evaluate the effectiveness of a noninvasive radiologic diagnostic assessment of small PNs, we collected information on the outcomes of the patients with these nodules and evaluated the data in relation to the SUV index values determined from PET/CT.

**Materials and Methods**

**Patients**

The institutional ethics committee approved this study and waived the requirement for informed consent from patients, since the patient data remained anonymous. For this study, the data of patients who underwent thoracic surgery was prospectively collected, and entered into a database that had been established to investigate patients undergoing thoracic surgery at our institution. The following data were collected: age, gender, smoking status, comorbidities, maximum tumor size, imaging characteristics of the nodules, chest CT findings, SUV index (ratio of SUV$_{\text{max}}$ of the tumor to SUV$_{\text{mean}}$ of the right lobe of the liver), surgical procedure, and findings. Regarding patients with a metastatic pulmonary nodule, the disease-free interval (DFI), defined as the date of first treatment to the appearance of lung metastasis, was recorded.

We performed a retrospective analysis from May 2004 to December 2013. The exclusion criteria were as follows: multiple lung nodules, incomplete lung resection, induction therapy, severe diabetes, and liver disease. This study evaluated 284 patients with lung nodules ≤2 cm who underwent PET/CT examinations and surgery during the study period.

To evaluate if PET/CT could be used for the differential diagnosis of PNs, we examined the relationships between the pathological diagnoses of PNs and several clinical factors, including the SUV index.

**PET/CT protocol**

PET/CT was routinely performed after informed consent was obtained from the patient. Before PET/CT was performed, chest CT was routinely performed, and thin-section reconstruction CT images with 0.5-mm slice thickness at 0.5-mm reconstruction intervals were obtained. The PET/CT protocol was described previously. A standard dose of F-18 fluorodeoxyglucose ([FDG] 3.75 MBq/kg) was administered intravenously, and PET and CT images were scanned 60 min later using a Discovery LS instrument (General Electric, Milwaukee, Wisconsin, USA) or a Biograph mCT (Simens, München, Germany).

**Surgical procedure**

Those patients with lung nodules without a definitive preoperative diagnosis underwent a wedge resection of the nodule, and the pathologic diagnosis was made from a frozen section during the procedure. Patients diagnosed with lung cancer subsequently underwent lobectomy and mediastinal lymph node dissection as the standard procedure. If the patient had agreed to enter a clinical trial that compared sublobar resection with lobectomy, the patient underwent sublobar resection was used based on that protocol. Lung cancer staging was performed based on TNM staging.

A patient with a metastatic pulmonary nodule either underwent standard wedge resection or another procedure, depending on the location of the nodule.

**Statistical analysis**

For evaluation of the patients’ characteristics, Fisher’s exact test was used for categorical data and analysis of variance or the Student t test were used for continuous data. Receiver operating characteristic (ROC) curve analysis and the Youden index were used to identify the appropriate SUV index cut-off value. Data were analyzed using version 5.0.1 of the JMP software package (SAS Institute Inc., Cary, North Carolina, USA). A P-value < 0.05 was considered statistically significant.

**Results**

Patient characteristics are summarized in Table 1. The histolopathologic findings of the 198 malignant lung nodules were as follows: adenocarcinoma (164 [83%]), squamous cell carcinoma (26 [13%]), and other types (8 [4%]). The pathological stages of the 198 malignant lung nodules were as follows: IA (174 [88%]), IB (15 [8%]), IIA (6 [3%]), and IIIA (3 [2%]). The primary sites of the 56 metastatic pulmonary nodules were as follows: colon/rectum (30 [54%]), kidney (6 [11%]), breast (5 [9%]), stomach (4 [7%]), head and neck (4 [7%]), and others (7 [13%]). Of the 30 benign nodules, 11 (37%) were granuloma, 10 (33%) were hamartoma, and 9 (30%) were others. The median SUV$_{\text{mean}}$ of the liver was 2.2 (range 1.4 to 3.0; mean ± SD, 2.2 ± 0.3). The SUV$_{\text{max}}$ and SUV indices of benign nodules were significantly lower than the values of the malignant nodules.
Figure 1 shows the distributions of the values of the SUV indices of the types of PNs (primary lung cancer, metastatic pulmonary, and benign nodules). ROC analysis and the Youden index found that the SUV index cut-off value that differentiated malignant PNs from benign PNs was 1.27. Table 2 shows the numbers of malignant and benign nodules based on histopathologic diagnosis distributed based on values of SUV index ≥ 1.2 and < 1.2 (P <0.01). An SUV index cut-off value of 1.2 provided a sensitivity of 52.7%, specificity of 90.0%, positive predictive value (PPV) of 97.8%, and negative predictive value (NPV) of 18.4%. There were 100 false-negative lung cancer nodules and 20 metastatic pulmonary nodules. Tables 3 and 4 summarize the characteristics of patients with true-positive and false-negative lung cancer nodules and metastatic pulmonary nodules, respectively. There were significantly higher rates of false-negative lung cancer nodules for the following characteristics: adenocarcinoma, female patients, nonsmokers, low CEA levels, and smaller nodules (Table 3). There were significantly higher rates of false-negative metastatic pulmonary nodules for longer DFI (Table 4).

**Discussion**

Although surgery for patients with PNs provides both histopathologic diagnosis and treatment, an identification or suspicion of malignancy before surgery is preferable. The rates of accurate diagnosis using fluoroscopic-guided bronchoscopy for peripheral malignant PNs <2 cm in diameter are reported to range from 10% to 50%; therefore routine preoperative bronchoscopy is not recommended. The usefulness of endobronchial ultrasound-guided transbronchial biopsy using a thin bronchoscope has been reported. This novel technique provided accurate diagnostic rates of malignancy for lesions ≥20 mm and lesions <20 mm of 82% and 67%, respectively. Since biopsy procedures are not without risk, and the diagnosis of small PNs remains difficult, identifying patients with lung nodules suitable for biopsy depends on the risks and benefits of the procedure.

Chest CT is generally used to determine the characteristics of PNs; however, there may be interobserver variations in interpreting the images. The guidelines of the National Comprehensive Cancer Network (NCCN) for non-small cell lung cancer recommend that PET/CT should be considered for solid noncalcified nodules >8 mm. To confirm the usefulness of PET/CT, we evaluated the use of the SUV index for small PNs. Fletcher et al. compared the accuracies of PET and CT for characterizing lung nodules of 7 and 30 mm in a prospective study, and found that PET had similar sensitivity and superior specificity to CT for the characterization of small lung nodules. Bryant and Cerfolio revealed that the sensitivity of integrated FDG-PET/CT for identifying malignant and benign nodules was 93% and 75%, respectively. A meta-analysis by Gould, et al. found that PET imaging of lung nodules...
provided a diagnostic sensitivity of 94.2% and specificity of 83.3%. The NCCN guideline defines a PET-positive lung nodule as a lung nodule SUV greater than the baseline value of the mediastinal blood pool. The secondary analysis of American College of Surgeons Oncology Group (ACOSOG) Z4031 trial showed the result of diagnostic accuracy of PNs. Unfortunately, the study did not require a standard PET/CT protocol and an SUV cut-off value of 2.5 was the one of the diagnostic indications. These papers suggested that the use of a cut-off point for FDG accumulation or for SUV is controversial. We have demonstrated the usefulness of the SUV index (ratio of tumor SUV \(_{\text{max}}\) to liver SUV \(_{\text{mean}}\)) in previous reports. This study found that an SUV index < 1.2 had a 97.8% NPV and clearly differentiated malignant from benign pulmonary nodules.

| Pathological diagnosis | SUV index \(\geq 1.2\) \((n = 137)\) | SUV index < 1.2 \((n = 147)\) |
|------------------------|---------------------------------------|-------------------------------|
| Malignant \((n = 254)\) | 134                                   | 120                           |
| Benign \((n = 30)\)    | 3                                     | 27                            |

*SUV index: ratio of SUV\(_{\text{max}}\) of the tumor to SUV\(_{\text{mean}}\) of the right lobe of the liver.

**Comparing adenocarcinoma with nonadenocarcinoma. CEA: carcinoembryonic antigen; SUV: standardized uptake value; Ad: Adenocarcinoma; Sq: Squamous cell carcinoma; LCNEC: Large cell neuroendocrine cell carcinoma; SCLC: Small cell lung cancer; AdSq: Adenosquamous.

**The kidney cancer rate was significantly higher in the false-negatives; DFI: disease-free interval.
A major limitation of our study is that PET is less sensitive for nodules <8 mm. The prevalence of malignancy in lung nodules >20 mm has been reported to range from 64% to 82%. Grogan, et al. revealed that PET accuracy improved with increasing sizes of lesions, from 67% for 1–2-cm lesions (sensitivity, 76%; specificity, 35%) to 84% for 3–5-cm lesions (sensitivity, 90%; specificity, 18%; \( P < 0.001 \)).

Our study included 30 patients with nodules \( \leq 1 \) cm. Among them, 12 patients had malignant nodules with SUV indices \( \geq 1.2 \); that is, there were no patients with false-positive results. Because SUV depends on the degree of FDG uptake by abnormal cells, even smaller lesions might be detected by PET/CT. Regarding false-negative PET/CT results, one report showed false-negative results for bronchoalveolar carcinoma of 42%, carcinoid of 29%, and pulmonary metastasis from renal cell carcinoma of 25%. Our study showed a similar trend, in that adenocarcinoma, smaller nodules, and metastasis from kidney cancer were associated with false-negative results. Because tumor size is associated with false-negative results, our study should be interpreted with caution. To clarify the problem, the SUV should be corrected by tumor size.

Conclusion

Since the study participants all underwent surgery, selection bias could not be excluded. However, as a non-invasive diagnostic marker, the SUV index was found to be useful for differentiating benign from malignant small peripheral pulmonary nodules.

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Disclosure Statement

None declared.

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