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The Role of PET/CT in Assessing Pulmonary Nodules in Children With Solid Malignancies

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Abstract

OBJECTIVE—The purpose of this article is to assess the feasibility and utility of PET/CT in distinguishing benign from malignant pulmonary nodules in patients with solid childhood malignancies.

SUBJECTS AND METHODS—This prospective study was conducted between March 2008 and August 2010. We enrolled 25 subjects 21 years old or younger with solid childhood malignancies and at least one pulmonary nodule measuring 0.5–3.0 cm. PET/CT was performed within 3 weeks of diagnostic chest CT. Three panels of three reviewers each reviewed diagnostic CT only (panel 1), PET/CT only (panel 2), or diagnostic CT and PET/CT concurrently (panel 3) and predicted each nodule's histologic diagnosis as benign, malignant, or indeterminate. Interreviewer agreement was assessed with the kappa statistic. Using nodule biopsy or clinical follow-up as reference standards, the sensitivity, specificity, and accuracy for each panel was assessed. Logistic regression was used to assess the nodule's maximum standardized uptake value (SUV_{max}) association with its histologic diagnosis.

RESULTS—There were 75 nodules with a median size of 0.74 cm (range, 0.18–2.38 cm); 48 nodules were malignant. Sensitivity was 85% (41/48) for panel 1, 60% (29/48) for panel 2, and 67% (32/48) for panel 3. All panels had poor specificities. Interreviewer agreement was moderate for panel 1 (0.43) and poor for panels 2 (0.22) and 3 (0.33). SUV_{max} was a significant predictor of histologic diagnosis ($p = 0.004$).

CONCLUSION—PET/CT assessment of pulmonary nodules is feasible in children with solid malignancies but may not reliably improve our ability to predict a nodule's histologic diagnosis. The SUV_{max} may improve the performance of PET/CT in this setting.

Keywords

children; CT; PET; pulmonary nodules; solid malignancies

The treatment of children with solid malignancies hinges on the presence or absence of metastatic disease at the time of diagnosis [1]. Chest CT is the standard modality to screen for pulmonary metastatic disease [2]. A prior report [3] showed that the ability of experienced pediatric radiologists to correctly predict pulmonary nodule histologic diagnoses, on the basis of CT features, in children with solid malignancies is limited; accuracy ranged from 57% to 67%. Furthermore, there was only fair agreement among reviewers regarding nodule histologic diagnosis predictions when using CT alone [3]. Those findings agreed with others who showed that CT parameters have limited value in distinguishing benign from malignant nodules in children with cancer [4]. Therefore, an invasive procedure, such as needle biopsy or surgical resection, may be required for accurate staging. Such procedures carry risks, such as bleeding, infection, and anesthesia complications, and also subject the patient to unwarranted pain and discomfort and add to the cost of medical care. Clearly, better methods should be sought to avoid unnecessary procedures, especially when benign nodules are present, while ensuring that malignant nodules do not go undetected.

Others have shown that ^{18}F -FDG PET/CT provides higher specificity and accuracy for diagnosing malignant pulmonary nodules in adults compared with diagnostic CT or PET alone [5–15]. Many reports have focused on solitary pulmonary nodules detected incidentally in the general population or on lung cancer screening CT scans performed in high-risk populations. In adults, most malignant pulmonary nodules are primary lung cancers, whereas in children, most are metastatic. There are few reports of the value of PET/CT in assessing metastatic pulmonary nodules in adults and, to our knowledge, none that specifically address pulmonary nodules in children with underlying malignancies [13, 15–17]. Therefore, we investigated the feasibility and utility of performing PET/CT to assess pulmonary nodules in patients with solid childhood malignancies.

Subjects and Methods

This prospective study was institutional review board–approved and HIPAA compliant. Our primary objective was to assess the feasibility and utility of performing FDG PET/CT for evaluation of pulmonary nodules in patients with solid childhood malignancies by comparing the sensitivity, specificity, and accuracy of diagnostic CT alone to those of

PET/CT alone and concurrent review of diagnostic CT and PET/CT, in distinguishing benign from malignant nodules. Eligible subjects were 21 years old or younger with a solid childhood malignancy and at least one pulmonary nodule measuring 0.5–3.0 cm on chest CT at diagnosis or after completion of therapy. We did not analyze nodules larger than 3.0 cm because they are known to carry a high risk of malignancy [18]. To clarify, patients with nodules larger than 3.0 cm who also had smaller nodules 0.5 cm or larger were eligible for the study. In such subjects, we did not analyze nodules measuring larger than 3.0 cm. Nodules measuring less than 0.5 cm, when present, were analyzed unless the subject had 10 nodules in the 0.5- to 3.0-cm size range that could be analyzed instead. After obtaining informed assent or consent from the patient or their guardian, PET/CT was performed within 3 weeks of diagnostic CT. To avoid the possible influence of chemotherapy on nodule FDG avidity, patients could not have received therapy for at least 3 weeks before PET/CT.

Image Interpretation

Images were prospectively obtained and then were anonymized by assigning unique identifiers. Using the workstation annotation tools, nodules were numbered by the principal investigator on diagnostic chest CT examinations and PET/CT examinations to ensure consistency among reviewers and accuracy of histologic diagnosis correlations. Imaging was then reviewed by three panels as follows: panel 1, which included three pediatric radiologists with 33, 21, and 31 years of pediatric CT experience, reviewed diagnostic chest CT examinations only; panel 2, which included one double board–certified pediatric radiologist–nuclear medicine physician with 4 years of PET/CT experience and 27 years of pediatric CT experience and two nuclear medicine physicians with 10 and 15 years of PET/CT experience, reviewed PET/CT examinations only; and panel 3, which included three pediatric radiologists with 6, 5, and 5 years of PET/CT experience and 23, 7, and 5 years of pediatric CT experience, reviewed PET/CT examinations and corresponding diagnostic chest CT examinations concurrently. Panelists were aware of subjects' primary diagnosis and age but were blinded to nodule histologic diagnoses and other reviewers' predictions. Reviewers independently assessed all nodules, up to 10 per subject, and predicted nodule histologic diagnoses as benign, malignant, or indeterminate. Panel 1 reviewers were provided published definitions of CT features of pulmonary nodules in children with underlying malignancies to guide their assessments [4].

Specific nodule parameters that were assessed included unilateral versus bilateral distribution, lobar site, distribution in lung (peripheral vs central), shape (round, oval, polygonal, or complex), density (solid, ground-glass, or mixed), margins (sharp or ill defined), calcification (not present, central, noncentral, or totally calcified), presence of mediastinal or hilar adenopathy, and nodal calcification. Each of these reviewers was instructed to independently measure the maximum diameter of each nodule using the workstation measurement tool. Because reports of the predictive value of these CT features in children have been variable and because we sought to simulate clinical practice, these reviewers were instructed to use their own judgment to predict the benign or malignant nature of each nodule [3, 4]. Panel 2 reviewers were instructed to consider FDG foci less than or equal to the mediastinal blood pool as probably benign and those greater than the mediastinal blood pool as probably malignant but to also consider the attenuation correction

CT features at their own discretion, in their final decision. Panel 3 reviewers used criteria similar to those used by panels 1 and 2. Because we wanted a subjective assessment from panelists, PET/CT reviewers were instructed to not use the standardized uptake value (SUV) measurement tool. Diagnostic CT reviewers were instructed to use magnification, window level, and other workstation tools at their discretion. Discrepancies in histologic diagnosis predictions among the three reviewers on each panel were resolved by consensus review by that panel.

CT Protocol

One subject arrived at our institution with adequate outside CT examinations. All others were scanned on a 64-MDCT scanner (LightSpeed VCT, GE Healthcare) using a 1.35:1 pitch. With the arms up, patients weighing 14.4 kg or less were scanned with 3.75-mm slice thickness, and the others were scanned with 5-mm thickness, using 120 kVp, the milliamperesecond function, a preset noise index of 12.35 for patients weighing less than 11.5 kg, and a noise index of 11.57 for heavier patients. Patients able to breath-hold were scanned during suspended inspiration. Iodinated IV contrast material was administered when there was a question of adenopathy or if the chest study was performed in conjunction with abdominal imaging. Images were reviewed at a PACS workstation (Syngo, Siemens Healthcare).

PET/CT Protocol

PET/CT examinations were performed on a PET/CT scanner (LightSpeed Discovery, GE Healthcare). Attenuation-correction CT was performed on the unit's 4-MDCT scanner with auto-milliampereseconds adjusted for body weight (maximum, 90 mAs), a preset noise index of 22.5, 120 kVp, 5-mm slice thickness, and without IV contrast material. Effective dose ranges from PET/CT at our institution during the study period were 12.3–8.5 mSv for a 1-year-old child, 9.9–6.7 mSv for a 5-year-old child, 9.9 mSv for a 10-year-old child, and 9.7–11.6 mSv for an adult size patient. Subjects fasted for 4 hours before receiving 0.15 mCi/kg (5.55 MBq/kg) FDG IV approximately 60 minutes before emission imaging was acquired in 2D mode, at 5 minutes per bed position with arms at the sides. Sedation was used for subjects who could not lie still for the entire examination. Images were reconstructed in axial, coronal, and sagittal planes and were reviewed at a workstation (Hermes Smart Workstation, Hermes Medical Solutions). Pulmonary nodule maximum SUV (SUV_{max}) was measured by the principal investigator using commercial software and a circular 2D region of interest around the nodule on the attenuation-corrected axial image with the greatest visual FDG avidity.

Statistical Analysis

Because our prior study showed that children with underlying solid malignancies and multiple pulmonary nodules can have both benign and malignant nodules, we chose to use the nodule, rather than the subject, as the unit of analysis [3]. Nodule size was determined by averaging the measurements of the panel 1 reviewers. Interreviewer agreement for each panel was examined using kappa statistics. The nodule's histologic diagnosis determined by biopsy within 1 month of PET/CT or clinical follow-up were reference standards. The decision to biopsy or to observe was made at our solid tumor conference by consensus

among oncologists, radiologists, and surgeons on the basis of imaging and clinical parameters. Subjects with nodules that were not biopsied were monitored until the primary physician could make a clinical judgment regarding nodule histologic diagnosis on the basis of histologic analysis of other biopsied nodules, follow-up imaging, and clinical course. Accuracy was defined as the ratio of true-positives and true-negatives to all tests performed; indeterminate cases were considered incorrect results. A McNemar test was used to compare accuracy among panels. Because there were many indeterminate results (especially for panel 2), indeterminate findings were considered as negative when calculating sensitivity and as positive when calculating specificity. We report these “worst case scenario” sensitivities and specificities in the Results section. Spearman correlation coefficient was used to examine the association between SUV_{max} and nodule size. Logistic regression was used to examine associations between nodule size and SUV_{max} with nodule histologic diagnosis; p values 0.05 were considered statistically significant. SAS 9.2 (SAS Institute) and StatXact-9 (Cytel) were used for statistical analysis.

Results

Twenty-seven patients were enrolled from March 2008 to August 2010. Two patients were excluded: one was found to have a benign tumor and the other was found to have a mediastinal lymph node rather than a pulmonary nodule. Demographics and primary diagnoses of the 25 eligible subjects are shown in Table 1. Eight subjects had new diagnoses, and 17 had nodules identified after completion of therapy. The median time from diagnostic CT to PET/CT was 0 days (range, -4 to 21 days). Fifteen subjects received IV contrast agent for the diagnostic CT scan. Five subjects were sedated for PET/CT.

The 25 subjects had a total of 75 nodules, 48 malignant and 27 benign. The median number of reviewed nodules per subject was two (range, 1–10 nodules). Of the 75 nodules, 52 (69%) were 0.5 cm or larger and smaller than 3.0 cm, with an average size ($\pm$ SD) of 1.04 ± 0.42 cm (median, 0.90 cm; range, 0.51–2.38 cm).

Ten subjects had all nodules biopsied, 10 had all nodules observed, and five had some nodules biopsied and others observed. Of the 75 nodules, 30 were biopsied and 45 were observed. Of the 30 biopsied nodules, 26 (in 13 subjects) were malignant and four were benign. The four benign histologic diagnoses were necrotizing granulomas ($n = 2$), a subpleural lymph node, and a subpleural scar. Of the 45 observed nodules, 22 (in six subjects) were malignant and 23 (in nine subjects) were benign. Five of the 75 nodules could not be visualized on the PET/CT attenuation-correction CT examinations. One was a 0.63-cm nodule that blended imperceptibly with two larger adjacent nodules. Another was a 0.94-cm polygonal partly ground-glass nodule located just above the right diaphragm that was difficult to identify separately from the adjacent liver. The remaining three nodules in two subjects, which measured smaller than 0.5 cm, were obscured by atelectasis caused by sedation for PET/CT. For purposes of statistical analysis these five nodules were considered incorrect predictions for panel 2.

Table 2 shows the interreviewer agreement for each panel for all nodules and when categorized by size. Panel 1 had 32 (43%) discrepant predictions and classified 12 of 75

(16%) nodules as indeterminate, panel 2 had 42 (63%) discrepancies and classified 30 of 67 (45%) nodules as indeterminate, and panel 3 had 36 (54%) discrepancies and classified 15 of 67 (22%) nodules as indeterminate. Interreviewer agreements for all three panels were the worst for nodules smaller than 0.5 cm and best for nodules 1.0 cm or larger. Examples of panel predictions are shown in Figures 1 and 2. Table 3 shows the sensitivity, specificity, and accuracy for the three panels for nodules of all sizes and when categorized as smaller than 0.5 cm and 0.5 cm or larger. The specificity for nodules 0.5 cm or larger was highest for panel 3.

Sixty-seven (23 benign and 44 malignant) of the 75 nodules could be evaluated using the SUV_{max} ; the remaining eight nodules could not be identified on PET/CT (five previously mentioned, three because of small size with no visible FDG avidity). There was a significant positive correlation between nodule size and SUV_{max} ($\rho = 0.70$; $p < 0.001$; Figure 3). For all size nodules, the median SUV_{max} was significantly higher for malignant nodules (2.61; range, 0.56–11.51) than for benign nodules (median, 0.99; range, 0.17–4.63; $p < 0.001$). The median SUV_{max} of malignant nodules 0.5 cm or larger was also significantly higher (3.10; range, 0.56–11.51) than that for benign nodules (1.11, range 0.86–4.63; $p = 0.0014$). The SUV_{max} was a significant predictor of malignancy ($p = 0.004$) with an odds ratio of 2.12 (95% CI, 1.27–3.55). There was no evidence that size as a continuous variable was a significant predictor of malignancy ($p = 0.39$). However, nodules < 0.5 cm had a lower incidence rate of malignancy (43%, 10/23) than nodules ≥ 0.5 cm and < 1.0 cm (80%, 24/30) and nodules ≥ 1.0 cm (64%, 14/22).

Discussion

We have shown that, although it is feasible to perform PET/CT to assess pulmonary nodules in children with solid malignancies, including patients as young as 2.9 years, the addition of PET/CT may not reliably improve our ability to correctly predict nodule histologic diagnosis. In our study, the PET/CT alone and concurrent PET/CT and diagnostic CT review panels had substantially more discrepancies and indeterminate classifications than did the diagnostic CT panel. These panels also had only fair-to-moderate interreviewer agreement, even for the largest nodules. These findings suggest that the addition of PET/CT in the assessment of pulmonary nodules in children, even for experienced physicians (such as ours), may introduce greater uncertainty in image interpretation compared with diagnostic CT alone.

Consistent with prior reports, we have shown that, unlike in adults, pulmonary nodule size as a continuous variable is not a predictor of histologic diagnosis in children with underlying solid malignancies [3, 4]. In our study, almost half (10/23 [43%]) of nodules measuring smaller than 0.5 cm were malignant. Therefore, in children with malignant solid tumors, very small nodules cannot be presumed to be benign. We found that CT alone offered the best sensitivity (80% [8/10]) for these small nodules but showed limited specificity (15% [2/13]) and accuracy (43% [10/23]). Neither PET/CT alone nor concurrent review of PET/CT and diagnostic CT improved the sensitivity, specificity, or accuracy for predicting the histologic diagnosis of these small nodules. For nodules 0.5 cm or larger, we found that the concurrent review of PET/CT and diagnostic CT provided superior specificity compared

with CT alone and PET/CT alone. However, this finding should be interpreted with caution given the degree of inter-reviewer variability that we found for PET/CT. Furthermore, the sensitivity and accuracy of diagnostic CT alone remained superior to the PET/CT alone and concurrent review panels for these larger nodules.

Other researchers have shown that the SUV_{max} is a valuable method of objectively assessing pulmonary nodules in adults and leads to higher sensitivity and specificity compared with subjective assessment of FDG avidity and diagnostic CT [7, 13, 14, 19, 20]. We also found that the SUV_{max} of pulmonary nodules was a significant predictor of histologic diagnosis: malignant nodules were more FDG avid than benign nodules. Although we did not have a sufficient number of nodules to determine an SUV cutoff point for distinguishing benign from malignant histologic diagnosis, we found that the median SUV_{max} of malignant nodules (3.10) was significantly higher than that of benign nodules (1.11). For our study, we choose to evaluate the subjective assessment of PET/CT rather than to allow reviewers to use the SUV. It is possible that the addition of the SUV_{max} into decision making could improve the performance of PET/CT in the assessment of pulmonary nodules in children and improve interreviewer agreement.

In our study, several small nodules (< 0.5 cm) were obscured by atelectasis caused by sedation for PET/CT. In young children, sedation is often required for PET/CT to prevent patient movement during the long scan time. Sedation-induced atelectasis and poor lung inflation likely impair the ability to assess pulmonary nodules on attenuation-correction CT images because the resultant areas of dependent consolidation and hazy appearance of the lungs makes characterization of pulmonary nodules challenging. This factor, compounded by breathing motion artifact, limited CT image resolution and misregistration between PET and CT images and likely limits the value of PET/CT alone in the assessment of pulmonary nodules in children.

Our study has several limitations. Because this was a pilot study, our sample size was modest. Although not all nodules were biopsied in our study, those that were not biopsied were observed until a confident determination of probable histologic diagnosis could be made. Because the arms were at the patients' sides during PET/CT, streak artifact may have impaired the attenuation-correction CT image quality. In contrast, all diagnostic CT scans were performed with the arms up. It is possible that PET/CT with the arms raised may improve its performance in this setting. However, we found that this position was not well tolerated by patients because it becomes uncomfortable during the long scan time. Newer PET/CT scanners with higher count sensitivity and, thus, faster scanning may alleviate this problem.

In conclusion, we have shown that, although it is feasible to perform PET/CT for the assessment of pulmonary nodules in children with solid malignancies, its value in distinguishing benign from malignant histologic diagnosis may be limited. Although a concurrent review of PET/CT and diagnostic CT improved the specificity of nodule predictions for nodules 0.5 cm or larger, the interreviewer variability, the number of discrepancies, and indeterminate classifications by the PET/CT panels raises concern over the reproducibility of these findings. The addition of PET/CT in this setting may, in fact,

introduce greater uncertainty into the decision-making process. It is possible that the use of the nodule SUV_{max} could help overcome this limitation. However, unlike in adults, very small nodules (< 0.5 cm) in children with solid malignancies cannot be assumed to be benign, and the accuracy of the SUV in these very small nodules is doubtful because of the limit of spatial resolution of current PET scanners. Furthermore, in the pediatric population, the use of sedation and anesthesia can result in poor lung aeration or atelectasis and subsequently impair the ability to accurately characterize nodules.

An important final consideration in children is the added radiation exposure from PET/CT. At our institution, effective doses from PET/CT during the study period ranged from 6.7 to 12.3 mSv depending on the size of the patient. Although slight, even these low doses carry a theoretic risk of inducing a second cancer. Therefore, the potential benefit of PET/CT to evaluate pulmonary nodules in children with solid malignancies must be balanced against these drawbacks.

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Fig. 1. 12-year-old girl with Ewing sarcoma and malignant pulmonary nodule
A–D, PET/CT (A–C) and diagnostic CT (D) images show malignant pulmonary nodule (arrows), which was correctly predicted by CT alone, PET/CT alone, and concurrent PET/CT and diagnostic CT review panels.

Fig. 2. 13-year-old boy with osteosarcoma and malignant pulmonary nodule
A–D, PET/CT (A–C) and diagnostic CT (D) show malignant pulmonary nodule (*arrows*), which was correctly predicted by CT alone review panel, predicted to be benign by PET/CT alone review panel, and was classified as indeterminate by concurrent review of PET/CT and diagnostic CT review panel.

Fig. 3. Association between nodule size and maximum standardized uptake value (SUV_{max})

TABLE 1

Demographics and Primary Diagnoses of 25 Study Subjects

Characteristic	Value
Sex	
Male	13 (52)
Female	12 (48)
Age at study enrollment (y), median (range)	14.4 (2.9–21.8)
Primary diagnosis	
Osteosarcoma	13 (52)
Rhabdomyosarcoma	4 (16)
Wilms tumor	3 (12)
Ewing sarcoma	2 (8)
Rhabdoid tumor (<i>n</i> = 1), synovial sarcoma (<i>n</i> = 1), and high-grade sarcoma not otherwise specified (<i>n</i> = 1)	3 (12)

Note—Except for age, data are number (%) of patients.

TABLE 2

Kappa Statistics by Nodule Size for Three Review Panels Using Biopsy or Observation as the Reference Standard

Nodule Size	κ (Standard Error)		
	Panel 1	Panel 2	Panel 3
All nodules	0.43 (0.05)	0.22 (0.05)	0.33 (0.05)
< 0.5 cm	0.10 (0.09)	−0.24 (0.10)	0.27 (0.10)
0.5 cm	0.59 (0.06)	0.27 (0.06)	0.33 (0.06)
0.5 < 1.0 cm	0.47 (0.08)	0.17 (0.08)	0.24 (0.09)
1.0 cm	0.73 (0.10)	0.40 (0.10)	0.43 (0.09)

Note—Kappa statistic results for agreement are categorized as follows: poor, < 0.2 ; fair, 0.21–0.40; moderate, 0.41–0.60; strong, 0.61–0.80; and nearly complete, > 0.80 .

TABLE 3

Sensitivity, Specificity, and Accuracy by Nodule Size for Three Review Panels for Nodule Histologic Diagnosis Predictions Using Biopsy or Observation as the Reference Standard

Nodule Size	Panel 1	Panel 2	Panel 3
All nodules			
Sensitivity	85 (41/48)	60 (29/48)	67 (32/48)
Specificity	44 (12/27)	19 (5/27)	48 (13/27)
Accuracy	71 (53/75)	45 (34/75)	60 (45/75)
< 0.5 cm			
Sensitivity	80 (8/10)	0 (0/10)	30 (3/10)
Specificity	15 (2/13)	0 (0/13)	8 (1/13)
Accuracy	43 (10/23)	0 (0/23)	17 (4/23)
0.5 cm			
Sensitivity	87 (33/38)	76 (29/38)	76 (29/38)
Specificity	71 (10/14)	36 (5/14)	86 (12/14)
Accuracy	83 (43/52)	65 (34/52)	79 (41/52)

Note—Data are percentage (no. of nodules/total).