AJR FOCUS ON: AJR JOURNAL CLUB

Utility of FDG PET/CT for Preoperative Staging of Non–Small Cell Lung Cancers Manifesting as Subsolid Nodules With a Solid Portion of 3 cm or Smaller

Young Joo Suh[1,2,3]
Chang Min Park[1,2,4]
Kyunghwa Han[3]
Sun Kyung Jeon[1,2]
Hyungjin Kim[1,2]
Eui Jin Hwang[1,2]
Jong Hyuk Lee[5]
Jin Chul Paeng[6]
Chang Hoon Lee[7]
Young Tae Kim[8]
Jin Mo Goo[1,2,4]

Keywords: cancer staging, CT, non–small cell lung cancer, PET, subsolid nodule

doi.org/10.2214/AJR.19.21811

Received June 4, 2019; accepted after revision August 25, 2019.

Supported by the Basic Science Research Program through the National Research Foundation of Korea (2017R1A2B4008517), which is funded by the Ministry of Science, ICT & Future Planning.

[1]Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea. Address correspondence to C. M. Park (cmpark.morphius@gmail.com).

[2]Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, Korea.

[3]Department of Radiology, Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

[4]Cancer Research Institute, Seoul National University, Seoul, Korea.

[5]Deparment of Radiology, Armed Forces Seoul Hospital, Seoul, Korea.

[6]Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea.

[7]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea.

[8]Department of Thoracic Surgery, Seoul National University College of Medicine, Seoul, Korea.

AJR 2020; 214:514–523

0361–803X/20/2143–514

OBJECTIVE. The objective of our study was to investigate the utility of FDG PET/CT for the preoperative staging of subsolid non–small cell lung cancers (NSCLCs) with a solid portion size of 3 cm or smaller.

MATERIALS AND METHODS. We retrospectively enrolled 855 patients with pathologically proven NSCLCs manifesting as subsolid nodules with a solid portion of 3 cm or smaller on CT. We then compared the diagnostic performances of FDG PET/CT and chest CT for detecting lymph node (LN), intrathoracic, or distant metastases in patients who underwent preoperative chest CT and FDG PET/CT. After propensity score matching, we compared the diagnostic performance of FDG PET/CT in the group who underwent both chest CT and FDG PET/CT with that of chest CT in patients who did not undergo FDG PET/CT.

RESULTS. There were LN metastases in 25 of 765 patients (3.3%) who underwent surgical LN dissection or biopsy and intrathoracic or distant metastasis in two of 855 patients (0.2%). For LN staging, FDG PET/CT showed a sensitivity of 44.0%, specificity of 81.5%, positive predictive value of 9.6%, negative predictive value of 97.0%, and accuracy of 79.9%, which were lower than those of chest CT for accuracy ($p < 0.0001$). FDG PET/CT could not accurately detect any intrathoracic or distant metastasis. After propensity score matching, the diagnostic accuracy for LN staging of FDG PET/CT in the group who underwent both CT and FDG PET/CT was lower than that of chest CT in the group who did not undergo FDG PET/CT ($p = 0.002$), and the diagnostic accuracy for intrathoracic and distant metastases was not different ($p > 0.999$).

CONCLUSION. FDG PET/CT has limited utility in preoperatively detecting LN or distant metastasis in patients with subsolid NSCLCs with a solid portion size of 3 cm or smaller.

FDG PET/CT is recommended for the initial staging workup of mediastinal lymph node (LN) and distant metastases in patients with non–small cell lung cancer (NSCLC) [1, 2]. It is recommended because evidence suggests that FDG PET/CT enables more accurate LN staging and detects unexpected distant metastases, which in turn reduce the futile surgery rate during the preoperative staging of NSCLC [3–6].

Pathologic analysis shows that most persistent subsolid nodules (SSNs) are pulmonary adenocarcinomas or their preinvasive lesions [7, 8]; on CT, the inner solid parts of SSNs correlate well with invasive adenocarcinoma components [9]. In fact, the size of the solid portion in subsolid NSCLCs is a powerful prognostic factor, which offers more prognostic value than does the size of the entire tumor [10, 11]. Accordingly, the lung cancer staging system described in the recent 8th edition of the TNM classification suggests that the clinical T category of subsolid lung cancers should be based on the size of the solid portion, instead of the size of the entire tumor, and defined the clinical T1 category of subsolid lung cancers as those having an inner solid portion size of 3 cm or smaller on preoperative CT [12].

Because patients with subsolid NSCLCs, particularly those with no solid part or small solid parts, are often in the early stage of disease, which has a low probability of LN or distant metastasis [13, 14], FDG PET/CT might offer limited value in cancer staging in this population. Previous studies reporting the diagnostic performance of preoperative PET/CT in SSNs focused on SSNs with no or small solid portions [13–15], which do not account for the current clinical T1-category subsolid NSCLCs. Moreover, no study has compared the accuracies of FDG PET/CT and of chest CT without FDG PET/CT for the preopera-

tive staging of clinical T1-category subsolid NSCLCs. Therefore, we investigated the utility of FDG PET/CT for the preoperative staging of clinical T1-category subsolid NSCLCs in the 8th edition of TNM classification system by comparing its diagnostic performance for detecting LN and distant metastases with that of preoperative chest CT.

Materials and Methods

Patients and Clinical Data Collection

The Institutional Review Board of Seoul National University Hospital approved this retrospective study and waived the requirement for patient informed consent. From our SSN registry [16–20], we identified 947 patients (368 men and 579 women; median age, 62.0 years [25th–75th percentile, 55.0–68.0 years]) who met the following inclusion criteria: first, patients with pathologically proven NSCLC or preinvasive lesions identified between March 2003 and July 2015; and, second, primary tumors appearing as SSNs with a solid portion diameter of 3 cm or smaller on thin-section CT (slice thickness ≤ 1.5 mm) (Fig. 1). We excluded 88 patients: patients with other dominant solid lung cancers (synchronously or metachronously) and patients with resected subsolid NSCLCs that were not the dominant lesions among multiple lung cancers. Additionally, we excluded four patients who underwent surgery for recurrent lesions. Finally, we included 855 patients (335 men and 520 women; median age, 61.0 years [25th–75th percentile, 54.3–68.0 years]). The clinical records of these patients were reviewed, and clinical characteristics, including sex and age, were recorded.

CT Image Analysis

One thoracic radiologist reviewed all the preoperative CT images. Lesion characteristics were classified into two categories according to the presence of an inner solid portion: pure ground-glass nodule (GGN) or part-solid nodule (PSN). The longitudinal diameters of the entire tumor and inner solid portion were measured on axial CT images in the lung window setting (window width, 1500 HU; level, –700 HU) [19]. Previous studies based on data from our SSN registry reported almost perfect interreader agreement (weighted $\kappa = 0.861$) for classifications of nodule type [18] and substantial to excellent intra- and interreader agreement (intraclass correlation coefficient, 0.7–0.98) for size measurements of the solid portion [19, 20]. Therefore, in this study, we did not investigate intra- and interreader agreement for nodule-type classification or size measurement. According to the solid portion size on CT, SSNs were classified into four categories: no solid portion, solid portion of 1 cm or smaller, solid portion ranging from greater than 1 to 2 cm, and solid portion ranging from greater than 2 to 3 cm.

LN assessment was based on size, with a short-axis diameter of 10 mm or greater defined as abnormal [21]. Necrosis within LNs was considered a sign of malignancy regardless of size. If mediastinal or hilar LNs contained nodular or laminated calcification, they were considered benign irrespective of size [22]. The presence of intrathoracic metastasis (M1a) was assessed for contralateral lung metastasis or pleural seeding metastasis. The presence of distant metastasis was assessed in the scanned upper abdomen and bony thorax.

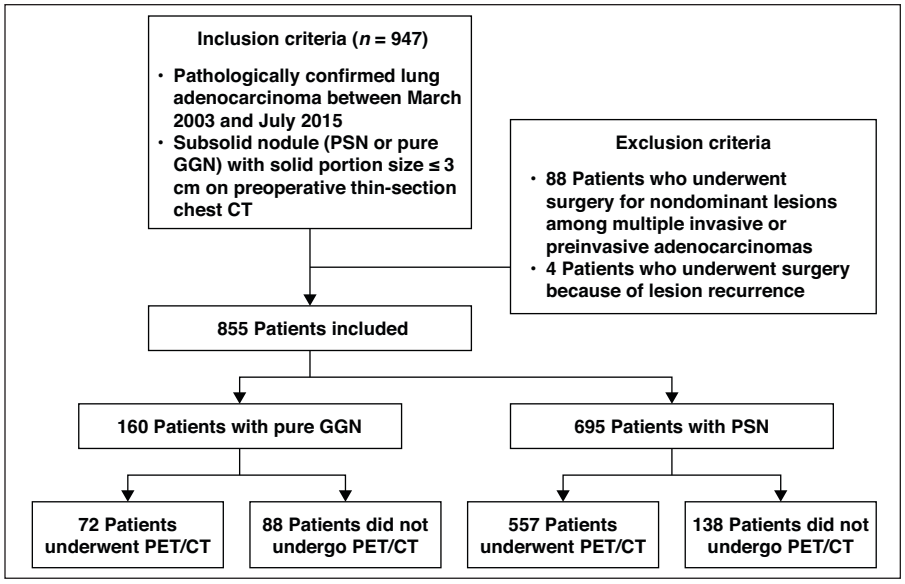
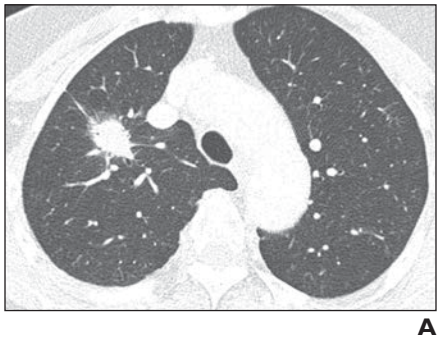


Fig. 1—Flowchart illustrates selection of study population. PSN = part-solid nodule, GGN = ground-glass nodule.



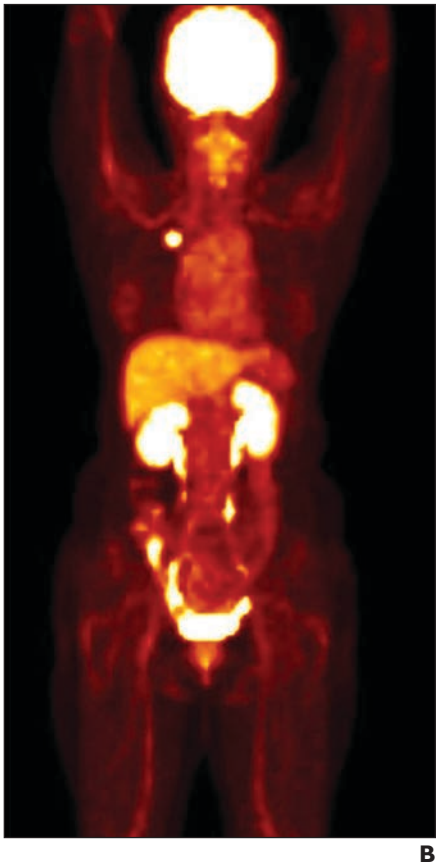


Fig. 2—Representative case of false-negative FDG PET/CT findings for lymph node (LN) metastasis in 60-year-old woman with non–small cell lung cancer.
A, Preoperative chest CT image shows 26.8-mm, part-solid nodule with 21.0-mm solid portion in right upper lobe.
B, Preoperative PET/CT image shows no abnormally increased FDG uptake to suggest mediastinal LN or distant organ metastasis. Patient underwent right upper lobectomy 2 days after chest CT and 17 days after PET/CT, and surgical pathology confirmed presence of invasive pulmonary adenocarcinoma with multistation N2 LN metastases.

A B

Preoperative Staging With FDG PET/CT

The general policy for preoperative FDG PET/CT at our institution follows the current guidelines [1]. However, imaging decisions were based on patient demographics or patient or clinician preference. Preoperative FDG PET/CT was performed in 629 of the 855 patients (73.6%) at a median interval of 14 days (25th–75th interval, 6–27 days) before lung cancer surgery. The FDG PET/CT protocol has been previously described [23]. Briefly, ^{18}F-FDG (5.2 MBq/kg of body weight) was administered IV 1 hour before FDG

TABLE 1: Clinical and Lesion Characteristics

Variable	Group Who Did Not Undergo PET/CT (*n* = 226)	Group Who Underwent PET/CT (*n* = 629)	*p*
Sex			0.477
Male	94 (41.6)	241 (38.3)	
Female	132 (58.4)	388 (61.7)	
Age (y), median (IQR)	59.0 (52.0–66.0)	62.0 (55.0–69.0)	0.001
Pathology[a]			< 0.0001
Invasive adenocarcinoma	127 (56.2)	551 (87.6)	
Minimally invasive adenocarcinoma	41 (18.1)	43 (6.8)	
Adenocarcinoma in situ	41 (18.1)	23 (3.7)	
Atypical adenomatous hyperplasia	17 (7.5)	12 (1.9)	
Lesion type on CT			< 0.0001
Pure ground-glass nodule	88 (38.9)	72 (11.4)	
Part-solid nodule	138 (61.1)	557 (88.6)	
Entire tumor size on CT (mm), median (IQR)	12.4 (10.0–17.0)	19.0 (14.0–25.0)	< 0.0001
Solid portion size on CT (mm), median (IQR)	3.0 (0–6.0)	9.0 (4.4–15.4)	< 0.0001
Solid portion size on CT			< 0.0001
0 cm (no solid part)	88 (38.9)	72 (11.4)	
≤ 1 cm	112 (49.6)	260 (41.3)	
> 1 to 2 cm	22 (9.7)	222 (35.3)	
> 2 to 3 cm	4 (1.8)	75 (11.9)	
Pathologic staging			
N			< 0.0001
0	179 (79.2)	561 (89.2)	
1	0 (0)	9 (1.4)	
2	0 (0)	16 (2.5)	
Unknown	47 (20.8)	43 (6.8)	
M			< 0.0001
0	179 (79.2)	584 (92.8)	
1a	0 (0)	1 (0.2)	
1b	0 (0)	1 (0.2)	
Unknown	47 (20.8)	43 (6.8)	
Surgery			0.963
No	0 (0)	2 (0.3)	
Yes	226 (100.0)	627 (99.7)	
Type of surgery			< 0.0001[b]
Lobectomy	124 (54.9)	527 (83.8)	
Segmentectomy	45 (19.9)	49 (7.8)	
Wedge resection	57 (25.2)	51 (8.1)	
Biopsy	0 (0)	2 (0.3)	

Note—Unless otherwise indicated, data are numbers of patients with percentages in parentheses. IQR = interquartile range.
[a]Pathologic data include data for one patient who did not undergo surgery because of clinical multistation N2 disease.
[b]Statistical analyses are performed after excluding two patients who did not undergo surgery.

TABLE 2: Comparison of Chest CT and PET/CT for the Detection of Lymph Node (LN) and Intrathoracic or Distant Metastases in Patients Who Underwent Preoperative PET/CT and Between Patients Who Underwent PET/CT and Those Who Did Not Undergo PET/CT After Propensity Score Matching

Imaging Finding	No. of Tumors				Performance Value (%)				
	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	Accuracy
Before matching									
LN metastasis									
Chest CT[a]	3	547	14	22	12.0 (3.9–31.3)	97.5 (95.8–98.5)	17.7 (5.8–42.71)	96.1 (94.2–97.4)	93.9 (91.6–95.5)
PET/CT[a]	11	457	104	14	44.0 (26.3–63.4)	81.5 (78.0–84.5)	9.6 (5.4–16.5)	97.0 (95.0–98.2)	79.9 (76.4–82.9)
p					0.017	< 0.0001	0.321	0.434	< 0.0001
Intrathoracic or distant metastasis									
Chest CT[a]	0	583	1	2	0 (0–0)	99.8 (98.8–100.0)	0 (0–0)	99.7 (98.6–99.9)	99.5 (98.4–99.8)
PET/CT[a]	0	580	4	2	0 (0–0)	99.3 (98.2–99.7)	0 (0–0)	99.7 (98.6–99.9)	99.0 (97.7–99.5)
p					> 0.999	0.214	> 0.999	0.996	0.325
Subgroup analysis according to solid portion size									
Solid portion ≤ 1 cm									
LN metastasis									
Chest CT[a]	0	286	9	3	0 (0–0)	97.0 (94.2–98.4)	0 (0–0)	99.0 (96.8–97.0)	96.0 (93.1–97.7)
PET/CT[a]	0	258	37	3	0 (0–0)	87.5 (83.2–90.8)	0 (0–0)	98.9 (96.5–99.6)	86.6 (82.2–90.0)
p					> 0.999	< 0.0001	> 0.999	0.9	< 0.0001
Intrathoracic or distant metastasis									
Chest CT[a]	0	298	0	0	0 (0–0)	100.0 (100.0–100.0)	0 (0–0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)
PET/CT[a]	0	297	1	0	0 (0–0)	99.7 (97.7–100.0)	0 (0–0)	100.0 (100.0–100.0)	99.7 (97.7–100.0)
p					> 0.999	< 0.0001	> 0.999	> 0.999	< 0.0001
Solid portion > 1 to 3 cm									
LN metastasis									
Chest CT[a]	3	261	5	19	13.6 (4.5–34.8)	98.1 (95.6–99.2)	37.5 (12.5–71.5)	93.2 (89.6–95.6)	91.7 (87.9–94.4)
PET/CT[a]	11	199	67	11	50.0 (30.2–69.8)	74.8 (69.3–79.7)	14.1 (8.0–23.7)	94.8 (90.8–97.1)	72.9 (67.5–77.7)
p					0.014	< 0.0001	0.105	0.481	< 0.0001
Intrathoracic or distant metastasis									
Chest CT[a]	0	285	1	2	0 (0–0)	99.7 (95.7–100)	0 (0–0)	99.3 (97.3–99.8)	99.0 (96.8–99.7)
PET/CT[a]	0	283	3	2	0 (0–0)	99.0 (96.8–99.7)	0 (0–0)	99.3 (97.2–99.8)	98.3 (95.9–99.3)
p					> 0.999	0.340	> 0.999	0.994	0.481
After matching									
LN metastasis									
Chest CT[b]	0	178	1	0	NA	99.4 (96.2–99.9)	0 (0–0)	100.0 (100.0–100.0)	99.4 (96.2–99.9)
PET/CT[a]	0	158	20	1	0 (0–0)	88.8 (83.2–92.6)	0 (0–0)	99.4 (95.7–99.9)	88.3 (82.7–92.2)
p (between two groups)					NA	0.027	> 0.999	< 0.001	0.002
Intrathoracic or distant metastasis									
Chest CT[b]	0	179	0	0	NA	100.0 (100.0–100.0)	NA	100.0 (100.0–100.0)	100.0 (100.0–100.0)
PET/CT[a]	0	178	1	0	NA	99.4 (96.2–99.9)	0 (0–0)	100.0 (100.0–100.0)	99.4 (96.2–99.9)
p (between two groups)					NA	> 0.999	NA	> 0.999	> 0.999

Note—Data in parentheses are 95% CIs. TP = true-positive, TN = true-negative, FP = false-positive, FN = false-negative, PPV = positive predictive value, NPV = negative predictive value, NA = not applicable.

[a]In group who underwent PET/CT.

[b]In group who did not undergo PET/CT.

TABLE 3: Comparison of Clinical Variables Before and After Propensity Score Matching

Variables	Before Matching[a]				After Matching			
	Group Who Did Not Undergo PET/CT (*n* = 179)	Group Who Underwent PET/CT (*n* = 586)	*p*	SMD	Group Who Did Not Undergo PET/CT (*n* = 179)	Group Who Underwent PET/CT (*n* = 179)	*p*	SMD
Female sex	100.0 (55.9)	358 (61.1)	0.245	0.106	100.0 (55.9)	93 (52.0)	0.0923	0.078
Age (y), median (IQR)	60.0 (53.0–67.0)	62.0 (55.0–69.0)	0.011	0.230	60.0 (53.0–67.0)	61.0 (53.0–67.0)	0.0027	0.077
Solid portion size on CT			< 0.0001	0.885				0.023
0 cm (no solid part)	61 (34.1)	58 (9.9)			61 (34.1)	58 (32.4)		
≤ 1 cm	92 (51.4)	239 (40.8)			92 (51.4)	95 (53.1)		
> 1 to 2 cm	22 (12.3)	215 (36.7)			22 (12.3)	22 (12.3)		
> 2 to 3 cm	4 (2.2)	74 (12.6)			4 (2.2)	4 (2.2)		
LN metastasis			0.01	NA			> 0.999	NA
No	179 (100.0)	561 (95.7)			179 (100.0)	178 (99.4)		
Yes	0 (0.0)	25 (4.3)			0 (0.0)	1 (0.6)		
Pathologic N category			0.019	NA			> 0.999	NA
0	179 (100.0)	561 (95.7)			179 (100.0)	178 (99.4)		
1	0 (0.0)	9 (1.5)			0 (0.0)	0 (0.0)		
2	0 (0.0)	16 (2.7)			0 (0.0)	1 (0.6)		
Multistation N2 metastases			0.203				NA	NA
No	179 (100.0)	577 (98.5)			179 (100.0)	179 (100.0)		
Yes	0 (0.0)	9 (1.5)			0 (0.0)	0 (0.0)		
Intrathoracic or distant metastasis			> 0.999	NA			NA	NA
No	179 (100.0)	584 (99.7)			179 (100.0)	179 (100.0)		
Yes	0 (0.0)	2 (0.3)			0 (0.0)	0 (0.0)		

Note—Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. SMD = standardized mean difference, IQR = interquartile range, LN = lymph node, NA = not applicable.

[a]Propensity score matching was performed among 765 patients in whom LN dissection or LN biopsy was performed.

PET/CT. Integrated FDG PET/CT was performed using a PET/CT camera (Gemini, Philips Healthcare). Low-dose unenhanced CT for attenuation correction and anatomic localization was performed from the head to knees using a tube voltage of 120 kV; tube current of 50 mA; tube rotation time of 0.75 second per rotation; pitch of 1.5; and slice thickness of 6.5 mm, which matched the PET image section thicknesses. Immediately after CT, PET images were acquired at 150 seconds per bed position in the 3D acquisition mode. PET and CT images were coregistered, and foci showing increased FDG uptake on LNs or distant organs were recorded. FDG PET/CT interpretation was included in the preoperative routine clinical process; hence, an additional image review was not conducted for this study. In clinical practice at our institution, interpreting and reporting results of PET/CT examinations of patients with suspected or histopathologically confirmed lung cancer are performed by one of six attending nuclear medicine physicians under the supervision of another physician dedicated to cardiothoracic nuclear medicine. All LNs in the thorax and extrathoracic regions with definitely discernible FDG uptake were considered positive unless they showed high attenuation (> 70 HU) or benign calcification (central nodular, laminated, popcorn, or diffuse) on unenhanced CT images [4, 22, 24].

Pathologic Diagnosis

All pathologic diagnoses were established using surgical specimens by attending pulmonary pathologists at our institution. The longitudinal diameter of the entire tumor was measured, and the histologic grade was classified as follows: atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma, or invasive adenocarcinoma. In this study, we did not perform pathologic T categorization based on the lung cancer staging system in the 8th edition of the TNM classification, because the size of invasive adenocarcinoma components was not precisely measured before the adoption of the 8th edition of lung cancer staging system at our institution, particularly for those with diameter greater than 1 cm. The presence and location of LN metastases on the pathologic specimen were recorded.

Outcomes

The primary outcome was the diagnostic performance of imaging studies (FDG PET/CT or chest CT) for LN metastasis and intrathoracic or distant metastasis per patient. Moreover, the presence of multistation ipsilateral mediastinal LN metastasis (multistation N2) was assessed on the basis of the pathologic results.

Statistical Analysis

Because clinical characteristics were expected to differ between patients who underwent FDG PET/CT and patients who did not undergo FDG PET/CT, we used propensity score matching. The propensity score was defined as the conditional probability of undergoing FDG PET/CT given a vector of measured covariates. A multivariable logistic regression model was used to estimate the propensity score using the clinical characteristics of sex and age and solid portion size on CT as covariates. We matched patients in the two groups according to their propensity scores using the nearest-neighbor method (caliper, 0.1) and compared the diagnostic performance of FDG PET/CT

TABLE 4: Statistical Models for the Differences in and Prediction of Lymph Node (LN) Metastasis

Variable	Metastasis Present	Metastasis Absent	*p*	Odds Ratio	95% CI	*p*	Adjusted Odds Ratio	95% CI	*p*
LN metastasis									
No. of patients	25	740							
Female sex	17 (68.0)[a]	441 (59.6)[a]	0.525	1.4408	0.6139–3.3812	0.4015	1.3436	0.5496–3.2851	0.5173
Age (y)	61.0 (55.0–66.0)[b]	62.0 (55.0–68.0)[b]	0.633	0.9854	0.9458–1.0266	0.4806	0.9621	0.9202–1.0060	0.0894
Lesion type on CT: part-solid nodule	25 (100.0)[a]	621 (83.9)[a]	0.0292	5.7197	0.3032–7.1286	0.0168	NA	NA	NA
Entire tumor size on CT (mm)	25.1 (21.0–30.6)[b]	17.7 (13.0–24.0)[b]	< 0.0001	1.0801	1.0414–1.1203	< 0.0001	NA	NA	NA
Solid portion size on CT (mm)	18.3 (12.0–25.5)[b]	7.5 (3.0–14.2)[b]	< 0.0001	1.1555	1.0967–1.2174	< 0.0001	1.1625	1.1034–1.2248	< 0.0001
Multistation N2 metastases									
No. of patients	9	756							
Female sex	7 (77.8)[a]	451 (59.7)[a]	0.447	2.3670	0.4884–11.4708	0.2846	2.472	0.5006–12.2077	0.2667
Age (y)	61.0 (60.0–67.0)[b]	62.0 (55.0–68.0)[b]	0.566	1.0240	0.9527–1.1006	0.5196	1.013	0.9387–1.0931	0.7399
Lesion type on CT: part-solid nodule	9 (100.0)[a]	637 (84.3)[a]	0.1955	1.1287	–0.8047 to 6.1318	0.2880	NA	NA	NA
Entire tumor size on CT (mm)	23.1 (22.3–26.8)[b]	18.0 (13.1–24.0)[b]	0.045	1.0454	0.9809–1.1143	0.1719	NA	NA	NA
Solid portion size on CT (mm)	18.3 (12.0–21.0)[b]	7.5 (3.1–14.5)[b]	0.006	1.1135	1.0287–1.2053	0.0078	1.1125	1.0264–1.2058	0.0095

Note—NA = not applicable.
[a]Number (%) of patients.
[b]Median (95% CI).

in the group who underwent FDG PET/CT with that of chest CT in the group who did not undergo FDG PET/CT to detect LN, intrathoracic, and distant metastases. To assess the degree of imbalance, we calculated the standardized mean difference (SMD) between the two groups before and after matching. The small absolute values of SMD (< 0.2) for each covariate indicated that the two matched groups were well balanced. We used R statistical software (version 3.4.4, R Foundation) and MedCalc (version 18.11, MedCalc Software) for statistical analyses along with the MatchIt R package for propensity score matching.

Normally distributed data were identified using the Shapiro-Wilk W test. Continuous variables are presented as the mean ± SD for normally distributed data and as the median with interquartile range for nonnormally distributed data and were compared using the independent *t* test or Mann-Whitney *U* test according to normality. When comparing the two matched groups, we used the paired *t* test for normally distributed data and the Wilcoxon signed rank test for nonnormally distributed data. We used chi-square statistics for comparing categoric variables and the McNemar test for the two matched groups. The diagnostic performance of chest CT and FDG PET/CT in the group who underwent FDG PET/CT was compared in terms of detecting LN and distant metastases; in addition, the diagnostic values of FDG PET/CT in the group who underwent FDG PET/CT and the diagnostic values of chest CT in the group who did not undergo FDG PET/CT after propensity score matching were compared using the generalized estimating equation. Subgroup analysis for comparison of diagnostic performances between chest CT and PET/CT for detecting LN and distant metastases in the group who underwent PET/CT was performed according to the solid portion diameter (SSN with no solid portion or solid portion with diameter of ≤ 1 cm and SSN with solid portion diameter of > 1 cm). To investigate the effects of clinical or lesion-related characteristics and LN or distant metastasis, we performed a logistic regression analysis. The association between variables and the rate of LN or distant metastasis is presented as an odds ratio (OR) with 95% CI. For assessing the OR of each separate category for LN metastasis, we used the Firth method to solve any biased estimate. Probability values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

The clinical and lesion characteristics are summarized in Table 1. Patients who underwent FDG PET/CT were older, had more invasive adenocarcinomas, and had more PSNs with a larger entire tumor size and larger solid portion size on CT. Two patients did not undergo surgery because disease was considered inoperable; both underwent preoperative FDG PET/CT. One patient had a primary tumor of a PSN; CT showed an entire tumor size of 32.1 mm and solid portion size of 19.5 mm, and both chest CT and FDG PET/CT showed multistation N2 LNs, which were confirmed as metastases using endobronchial ultrasound (EBUS)-guided LN biopsy. The other patient had multiple SSNs in bilateral lungs; CT showed the largest SSN to have an entire tumor size of 36.4 mm and a solid portion size of 24.4 mm. Therefore, given the possibility of multifocal lung adenocarcinomas, the patient received chemotherapy. The remaining 853 patients underwent subsequent surgery for subsolid NSCLCs.

CT Image Analysis

Among the lesions, 695 were classified as PSNs and 160 as pure GGNs. Among the 695 PSNs, 372 had a solid portion of 1 cm or smaller, 244 had a solid portion ranging from larger than 1 to 2 cm, and 79 had a solid portion ranging from larger than 2 to 3 cm. On chest CT, LN metastasis was suspected in 20 patients and liver metastasis was suspected in one patient.

FDG PET/CT for Detecting Lymph Node and Intrathoracic or Distant Metastases

Among 586 patients who underwent FDG PET/CT and subsequent surgical LN dissection or biopsy, LN metastases were present in 25 patients (N1 in nine and N2 in 16 patients), and nine had multistation N2 disease (eight

were confirmed by subsequent surgery and one was diagnosed at EBUS-guided LN biopsy). On FDG PET/CT, 115 patients were suspected of having LN metastasis. The diagnostic performance of FDG PET/CT for LN metastasis was a sensitivity of 44.0% (11/25); specificity, 81.5% (457/561); positive predictive value (PPV), 9.6% (11/115); negative predictive value (NPV), 97.0% (457/471); and accuracy, 79.9% (468/586) (Table 2 and Fig. 2). FDG PET/CT showed a significantly higher sensitivity for detecting LN metastasis than preoperative chest CT alone (44.0% vs 12.0%) but lower specificity (81.5% vs 97.5%) and accuracy (79.9% vs 93.9%) (all, $p < 0.05$). The diagnostic performance of FDG PET/CT for multistation N2 metastasis showed a sensitivity of 33.3% (3/9); specificity, 95.5% (551/577); PPV, 10.3% (3/29); NPV, 98.9% (551/557); and accuracy, 94.5% (554/586).

Regarding M category, distant metastasis was suspected on preoperative FDG PET/CT in four of 629 patients in the group who underwent PET/CT; however, all these lesions were eventually confirmed to be benign (osteoid lesion for one bone lesion diagnosed using biopsy, no change on follow-up imaging over 2 years for the other two bone lesions, and leiomyoma for the gastric LN diagnosed using surgery). One intrathoracic metastasis (pleural seeding metastasis) detected during surgery was not detected on either preoperative chest CT or FDG PET/CT. One distant metastasis was found in the skull on postoperative brain MRI performed 4 days after surgery owing to the occurrence of headache. This patient had NSCLC manifesting as PSN (entire tumor size, 20 mm; solid portion size, 14 mm) on CT and underwent preoperative FDG PET/CT, on which the skull metastasis was not detected. Therefore, among patients who underwent preoperative FDG PET/CT, the diagnostic performance of FDG PET/CT for intrathoracic or distant metastasis on a per-patient basis showed a sensitivity of 0% (0/2); specificity, 99.3% (580/584); PPV, 0% (0/4); NPV, 99.7% (580/582); and accuracy, 99.0% (580/586). No significant difference was observed between the two modalities in their diagnostic performance for detecting intrathoracic or distant metastasis (Table 2; $p > 0.05$).

LN metastasis was present in none of the 58 patients with no solid portion (pure GGN), in three of the 239 patients (1.3%) with a solid portion of 1 cm or smaller, in 12 of the 215 patients (5.6%) with the solid portion ranging from larger than 1 to 2 cm, and in 10 of the 74 patients (13.5%) with the solid portion ranging from larger than 2 to 3 cm. In SSNs with no or a solid portion of 1 cm or smaller, FDG PET/CT showed a sensitivity of 0% (0/3); specificity, 87.5% (258/295); PPV, 0% (0/37); NPV, 98.9% (258/261); and accuracy, 86.6% (258/298) for detecting LN metastasis, with significantly lower specificity (87.5% vs 97.0%) and accuracy (86.6% vs 96.0%) than did preoperative chest CT alone (all, $p < 0.05$). SSNs with a solid portion larger than 1 cm showed a sensitivity of 50.0% (11/22); specificity, 74.8% (199/266); PPV, 14.1% (11/78); NPV, 94.8% (199/210); and accuracy, 72.9% (210/288) for detecting LN metastasis, with significantly lower specificity (74.8% vs 98.1%) and accuracy (72.9% vs 91.7%) than did preoperative chest CT alone (all, $p < 0.05$). No significant differences were observed between the two modalities in their diagnostic performances for detecting intrathoracic or distant metastasis, both for SSNs with a solid portion of 1 cm or smaller and SSNs with a solid portion larger than 1 cm.

Preoperative Diagnostic Performances of FDG PET/CT in the Group Who Underwent PET/CT and of Chest CT in the Group Who Did Not Undergo FDG PET/CT for Lymph Node or Distant Metastasis

We matched 179 patients in the group who underwent PET/CT and 179 patients in the group who did not undergo PET/CT (Table 3). All covariates were well balanced (SMD < 0.2) after propensity score matching. Before matching, LN metastases were found in 25 patients (4.3%) in the group who underwent PET/CT and in none (0%) of the patients who did not undergo PET/CT ($p = 0.01$). Intrathoracic or distant metastasis was present in two patients (0.3%) in the group who underwent PET/CT. After matching, LN metastasis was present on pathologic examination in one patient (0.5%) in the group who underwent PET/CT (single-station N2 metastasis on surgery) and in no patients in the group who did not undergo PET/CT, without statistical significance ($p > 0.999$). Intrathoracic or distant metastasis was absent in both groups after matching. The diagnostic accuracy of FDG PET/CT in the group who underwent PET/CT for LN metastasis was lower than that of chest CT in the group who did not undergo PET/CT (Table 2; $p = 0.002$). Neither group showed multistation N2 metastasis after matching.

Prediction of Lymph Node Metastasis Based on Clinical and Lesion-Related Variables

For the association of clinical and lesion-related variables between the presence of LN metastasis in the pathologic specimen, a significant increase in LN metastasis was observed according to an increase in the solid portion size (adjusted OR, 1.1625; 95% CI, 1.1034–1.2248; $p < 0.0001$; Table 4). Solid portion size on CT was the only significant predictor of multistation N2 metastasis after adjusting for other variables (adjusted OR, 1.1125; 95% CI, 1.0264–1.2058; $p = 0.0095$).

Discussion

Our study shows that preoperative FDG PET/CT has lower diagnostic accuracy than chest CT for LN metastasis in patients with subsolid NSCLCs with solid portion sizes of 3 cm or smaller on CT and that preoperative FDG PET/CT has diagnostic performance similar to that of chest CT for intrathoracic and distant metastases. Solid portion size is the only significant factor associated with LN metastasis after adjusting for other clinical and lesion-related features.

Current guidelines state that preoperative NSCLC staging should include FDG PET/CT because it reduces futile thoracotomies by 20% [3, 25, 26]. However, this study shows that FDG PET/CT may have limited value in diagnosing LN, intrathoracic, and distant metastases in patients with clinical T1-category subsolid NSCLCs. Some of the reasons are as follows.

First, FDG PET/CT has limited benefits in detecting LN metastasis in clinical stage IA lung cancer because of the low prevalence of LN metastases and a high false-positive rate [27, 28]. The subsolid lesion characteristic of the primary tumor can substantially lower the utility of FDG PET/CT; a previous study reported very low sensitivity (11.1%) and low accuracy (81.9%) of preoperative FDG PET/CT for LN staging in patients with subsolid adenocarcinomas that were 3 cm or smaller in entire tumor size [15]. Our study showed similar results in the broader population of patients with NSCLC, wherein the clinical T category was changed to the T1 category according to the latest staging system, which is defined as solid portion of 3 cm or smaller. We believe our results are clinically relevant and expand the knowledge in this field. Second, FDG PET/CT could have limited diagnostic value for detecting intrathoracic and distant metastases in clinically early stage lung cancer because of the low probability of distant metastasis. Our study included four false-positive cases of distant metastasis on FDG PET/CT and only two false-negative cases.

In addition to detecting overall LN metastasis, preoperative diagnosis of multistation N2 disease remains crucial for patient

management. Unexpected N2 disease after surgery occurs in approximately 10% of surgically resected NSCLCs, negatively affecting patient prognosis; multistation N2 disease also has poorer survival rates than does single-station N2 disease [29]. In our study, except one patient who was considered to have multistation N2 disease based on EBUS-guided LN biopsy, multistation N2 disease confirmed at surgery was correctly diagnosed using preoperative FDG PET/CT in only two of eight patients.

A few studies have reported that preoperative FDG PET/CT offered little advantage in staging NSCLCs presenting as pure GGNs or ground-glass opacity (GGO)-predominant PSNs with small solid portions (> 50% GGO portion in tumor diameter on CT) because of the low incidence of LN and distant metastases [13, 14]. Our results show that the low incidence of LN and distant metastases and low diagnostic performance of preoperative FDG PET/CT were observed not only in the limited population of pure GGNs or GGO-predominant PSNs, but also in clinical T1-category subsolid NSCLCs including SSNs with a solid portion larger than 1 cm. Moreover, we found that the diagnostic performance of FDG PET/CT for LN metastasis was significantly lower than that of chest CT both for intragroup comparison within the group who underwent PET/CT and for intergroup comparison with the group who did not undergo PET/CT.

LN metastasis was significantly associated with larger solid portion size. Our results emphasize the importance of solid portion size in subsolid NSCLCs, which is consistent with subcategorization of clinical T1 category of subsolid NSCLCs according to the solid portion size on CT in the lung cancer staging system in the latest 8th edition of the TNM classification. Moreover, we suggest that careful review of preoperative chest CT for assessing solid portion size and stratifying the probability of LN or distant metastasis may be beneficial in staging disease in patients with NSCLCs presenting as SSNs with solid portions of 3 cm or smaller when deciding the need for subsequent FDG PET/CT.

Our study has several limitations. First, because this study was a nonrandomized and retrospective study, significant differences were observed in clinical and lesion characteristics among the patients who underwent PET/CT and those who did not. Generally, the use of FDG PET/CT is affected by multiple factors, such as the entire tumor size or solid portion size on CT, regional practice pattern, and patient demographics or economic status [30, 31]. To overcome this selection bias, we performed propensity score matching for adjusting multiple clinical and lesion-related variables that could affect the results and compared the diagnostic performances of PET/CT and chest CT in the group who underwent PET/CT and between the group who underwent PET/CT and the group who did not undergo PET/CT. Second, we could not use the latest lung cancer staging system from the 8th edition of the TNM classification for pathologic staging because of our retrospective study design and because our study population received treatment following the standard practices of that period. Third, we did not additionally review the individual images of PET/CT in this study, which may have affected the diagnostic performance of PET/CT.

In conclusion, preoperative FDG PET/CT has limited utility in detecting LN and distant metastases in patients with subsolid NSCLCs with a solid portion size of 3 cm or smaller. Carefully reviewing preoperative chest CT may be beneficial for the assessment of solid portion size and stratification of the probability of LN or distant metastasis.

References

1. National Comprehensive Cancer Network Guidelines, version 2.2018: non-small cell lung cancer NCCN evidence blocks. National Comprehensive Cancer Network website. www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf. Published December 20, 2017. Accessed January 29, 2018
2. Ravenel JG, Rosenzweig KE, Kirsch J, et al. ACR Appropriateness Criteria non-invasive clinical staging of bronchogenic carcinoma. *J Am Coll Radiol* 2014; 11:849–856
3. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. *N Engl J Med* 2009; 361:32–39
4. Shim SS, Lee KS, Kim BT, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. *Radiology* 2005; 236:1011–1019
5. Schrevens L, Lorent N, Dooms C, Vansteenkiste J. The role of PET scan in diagnosis, staging, and management of non-small cell lung cancer. *Oncologist* 2004; 9:633–643
6. Cheran SK, Herndon JE 2nd, Patz EF Jr. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. *Lung Cancer* 2004; 44:317–325
7. Lee HJ, Lee CH, Jeong YJ, et al. IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma: novel concepts and radiologic implications. *J Thorac Imaging* 2012; 27:340–353
8. Park CM, Goo JM, Lee HJ, Lee CH, Chun EJ, Im JG. Nodular ground-glass opacity at thin-section CT: histologic correlation and evaluation of change at follow-up. *RadioGraphics* 2007; 27:391–408
9. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6:244–285
10. Song SH, Ahn JH, Lee HY, et al. Prognostic impact of nomogram based on whole tumour size, tumour disappearance ratio on CT and SUVmax on PET in lung adenocarcinoma. *Eur Radiol* 2016; 26:1538–1546
11. Hwang EJ, Park CM, Ryu Y, et al. Pulmonary adenocarcinomas appearing as part-solid ground-glass nodules: is measuring solid component size a better prognostic indicator? *Eur Radiol* 2015; 25:558–567
12. Travis WD, Asamura H, Bankier AA, et al.; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee and Advisory Board Members. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016; 11:1204–1223
13. Cho H, Lee HY, Kim J, et al. Pure ground glass nodular adenocarcinomas: are preoperative positron emission tomography/computed tomography and brain magnetic resonance imaging useful or necessary? *J Thorac Cardiovasc Surg* 2015; 150:514–520
14. Kim TJ, Park CM, Goo JM, Lee KW. Is there a role for FDG PET in the management of lung cancer manifesting predominantly as ground-glass opacity? *AJR* 2012; 198:83–88
15. Lee SM, Park CM, Paeng JC, et al. Accuracy and predictive features of FDG-PET/CT and CT for diagnosis of lymph node metastasis of T1 non-small-cell lung cancer manifesting as a subsolid nodule. *Eur Radiol* 2012; 22:1556–1563
16. Chae HD, Park CM, Park SJ, Lee SM, Kim KG, Goo JM. Computerized texture analysis of persistent part-solid ground-glass nodules: differentiation of preinvasive lesions from invasive pulmonary adenocarcinomas. *Radiology* 2014; 273:285–293
17. Lee JH, Park CM, Lee SM, Kim H, McAdams HP, Goo JM. Persistent pulmonary subsolid nodules with solid portions of 5 mm or smaller: their natural course and predictors of interval growth. *Eur*

Radiol 2016; 26:1529–1537

18. Lee SM, Park CM, Goo JM, Lee HJ, Wi JY, Kang CH. Invasive pulmonary adenocarcinomas versus preinvasive lesions appearing as ground-glass nodules: differentiation by using CT features. *Radiology* 2013; 268:265–273
19. Yoo RE, Goo JM, Hwang EJ, et al. Retrospective assessment of interobserver agreement and accuracy in classifications and measurements in subsolid nodules with solid components less than 8 mm: which window setting is better? *Eur Radiol* 2017; 27:1369–1376
20. Lee KH, Goo JM, Park SJ, et al. Correlation between the size of the solid component on thin-section CT and the invasive component on pathology in small lung adenocarcinomas manifesting as ground-glass nodules. *J Thorac Oncol* 2014; 9:74–82
21. Goldstraw P, Chansky K, Crowley J, et al. International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11:39–51
22. Kim BT, Lee KS, Shim SS, et al. Stage T1 non-small cell lung cancer: preoperative mediastinal nodal staging with integrated FDG PET/CT—a prospective study. *Radiology* 2006; 241:501–509
23. Lee Y, Lee HJ, Kim YT, et al. Imaging characteristics of stage I non-small cell lung cancer on CT and FDG-PET: relationship with epidermal growth factor receptor protein expression status and survival. *Korean J Radiol* 2013; 14:375–383
24. Kim YK, Lee KS, Kim BT, et al. Mediastinal nodal staging of nonsmall cell lung cancer using integrated ^{18}F-FDG PET/CT in a tuberculosis-endemic country: diagnostic efficacy in 674 patients. *Cancer* 2007; 109:1068–1077
25. Reed CE, Harpole DH, Posther KE, et al.; American College of Surgeons Oncology Group Z0050 trial. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003; 126:1943–1951
26. van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002; 359:1388–1393
27. Kozower BD, Meyers BF, Reed CE, Jones DR, Decker PA, PutnAm JB Jr. Does positron emission tomography prevent nontherapeutic pulmonary resections for clinical stage IA lung cancer? *Ann Thorac Surg* 2008; 85:1166–1169; discussion, 1169–1170
28. Port JL, Andrade RS, Levin MA, et al. Positron emission tomographic scanning in the diagnosis and staging of non-small cell lung cancer 2 cm in size or less. *J Thorac Cardiovasc Surg* 2005; 130:1611–1615
29. Cho HJ, Kim SR, Kim HR, et al. Modern outcome and risk analysis of surgically resected occult N2 non-small cell lung cancer. *Ann Thorac Surg* 2014; 97:1920–1925
30. Backhus LM, Farjah F, Varghese TK, et al. Appropriateness of imaging for lung cancer staging in a national cohort. *J Clin Oncol* 2014; 32:3428–3435
31. Balekian AA, Fisher JM, Gould MK. Brain imaging for staging of patients with clinical stage IA non-small cell lung cancer in the National Lung Screening Trial: adherence with recommendations from the Choosing Wisely Campaign. *Chest* 2016; 149:943–950

FOR YOUR INFORMATION

This article has been selected for *AJR* Journal Club activity. The accompanying Journal Club Study Guide can be found on the following page.

Study Guide

Utility of FDG PET/CT for Preoperative Staging of Non–Small Cell Lung Cancers Manifesting as Subsolid Nodules With a Solid Portion of 3 cm or Smaller

Alan Mautz[1], Joseph J. Budovec[2]

[1]The Aroostook Medical Center, Presque Isle, ME.
[2]Medical College of Wisconsin, Milwaukee, WI.
*amautz@emhs.org, jbudovec@mcw.edu**

Introduction

1. What type of lung malignancy is associated with subsolid nodules? What feature of such nodules provides useful prognostic information? What is the prevalence of subsolid pulmonary nodules? What is the incidence of non–small cell lung cancer?
2. What criterion is currently used to designate subsolid lung cancers as T1-category lesions in TNM staging?
3. What clinical question does this study set out to answer? Is this question timely and relevant to current diagnosis, staging, and management of lung cancer?

Methods

4. What study design was used? What selection criteria were used? What were the exclusion criteria?
5. What categories were used to group the nodules evaluated in this study? How were lymph nodes deemed to be abnormal?
6. What rationale is provided for not evaluating interreader variability in this study?
7. What are the limitations of this study? Are these limitations adequately discussed?

Results

8. At what rates were lymph node metastases detected using PET/CT and with preoperative chest CT? Which modality was more sensitive in detecting metastatic disease in the patient population studied?
9. What factor is found in this study to be associated with lymph node metastasis in the setting of lung cancer presenting as a subsolid nodule?
10. Are current preoperative staging recommendations supported by the results of this study?

Statistics

11. In this study, performance characteristics including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy are used to discuss the diagnostic performance of PET/CT and preoperative chest CT. Briefly describe these in layperson's language such that a patient could understand why these are significant in discussing whether an imaging study is appropriate.

Discussion

12. What are the limited benefits the study ascribes to using PET/CT to stage T1-category non–small cell lung cancer?
13. Are the study results sufficiently strong that you would contact a clinical colleague ordering a PET/CT for a patient with a subsolid nodule with features of a T1-category lung cancer to discuss using only preoperative chest CT for staging?
14. The results of this study speak to the utility of decision-support systems to guide clinicians to appropriate studies and highlights how specific they may need to be. How confident are you that your clinical colleagues will follow these guidelines if adherence is not compulsory? What dilemmas may arise in decision-support systems for specific clinical situations such as the question of preoperative staging of T1-category non–small cell lung cancers?

Background Reading

1. Kim TJ, Park CM, Goo JM, Lee KW. Is there a role for FDG PET in the management of lung cancer manifesting predominantly as ground-glass opacity? *AJR* 2012; 198:83–88
2. Ravenel JG, Rosenzweig KE, Kirsch J, et al. ACR Appropriateness Criteria noninvasive clinical staging of bronchogenic carcinoma. *J Am Coll Radiol* 2014; 11:849–856

*Please note that the authors of the Study Guide are distinct from those of the companion article.