General Thoracic Surgery

Mediastinoscopy might not be necessary in patients with non–small cell lung cancer with mediastinal lymph nodes having a maximum standardized uptake value of less than 5.3

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Objective: Accurate pretreatment staging in non–small cell lung cancer remains tantamount in formulating an appropriate treatment plan. The maximum standardized uptake value obtained with integrated fluorodeoxyglucose–positron emission tomography/computed tomography has been proposed to be a predictor of malignancy in mediastinal lymph nodes. A recent study has also suggested that accuracy of integrated fluorodeoxyglucose–positron emission tomography/computed tomography might be improved by increasing the maximum standardized uptake value used for calling a lymph node positive from 2.5 to 5.3. We tested the hypotheses that the maximum standardized uptake value is a predictor of individual lymph node metastasis in non–small cell lung cancer and that pathologic staging with mediastinoscopy might not be necessary in patients with a maximum standardized uptake value of less than 5.3 in their mediastinal lymph nodes.

Methods: This is a retrospective review of 765 lymph nodes sampled from 110 patients in a single institution with biopsy-proved non–small cell lung cancer. All patients underwent integrated fluorodeoxyglucose–positron emission tomography/computed tomography before biopsy or resection of their mediastinal lymph nodes. Surgical staging was the reference standard. All N2 lymph nodes were individually assessed according to station. Data were analyzed by using the Pearson χ^2 test.

Results: Twenty-one (19%) of 110 patients had N2 disease, and a total of 765 N2 lymph nodes were pathologically examined. The mean and median maximum standardized uptake values for N2 nodes with metastatic disease were 9.2 (95% confidence interval, 7.0–11.4) and 7.2 (range, 2.2–25.8), respectively. For benign N2 nodes, the mean and median maximum standardized uptake values were 1.5 (95% confidence interval, 1.4–1.6) and 1.0 (range, 1.0–9.6), respectively ($P < .05$). When integrated fluorodeoxyglucose–positron emission tomographic/computed tomographic scans were reinterpreted by using a maximum standardized uptake value of 5.3 as a cutoff for malignancy, sensitivity decreased from 93% to 81% ($P = .15$), specificity increased from 86% to 98% ($P < .01$), positive predictive value increased from 22% to 64% ($P < .01$), negative predictive value was unchanged at 99%, and overall accuracy of integrated positron emission tomography/computed tomography increased from 87% to 97% ($P < .01$).

Conclusions: The maximum standardized uptake value is a predictor of individual lymph node metastasis in non–small cell lung cancer. Accuracy of integrated positron emission tomography/computed tomography is significantly improved by using

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a maximum standardized uptake value of 5.3 to assign malignancy, thereby dramatically decreasing the number of false-positive results. More importantly, these results suggest that some patients with non–small cell lung cancer with a maximum standardized uptake value less than 5.3 in their N2 lymph nodes might be able to forego mediastinoscopy and proceed directly to thoracotomy. This represents a significant change in the current management of standardized uptake value–positive mediastinal lymph nodes in non–small cell lung cancer.

Non–small cell lung cancer (NSCLC) remains the leading cause of cancer death in America.[1] Because treatment of NSCLC is allocated by stage, accurate pretreatment staging is an absolute necessity. Although computed tomography (CT) or standard positron emission tomography (PET) have historically been the benchmarks for noninvasive staging, multiple studies have now validated integrated PET/CT as the new gold standard in noninvasive pretreatment staging.[2-4]

The major benefit of integrated PET/CT is derived from its ability to combine form with function. Malignant cells with a high metabolic activity have a greater uptake of fluorodeoxyglucose (FDG) and can be anatomically correlated and distinguished from the surrounding tissues. However, the major pitfall of integrated PET/CT lies in its high false-positive rate because infections and other inflammatory conditions can frequently mimic malignancy.[5,6] Thus pathologic confirmation of a positive PET/CT result by means of mediastinoscopy or fine-needle aspiration (FNA) is considered mandatory.[7,8]

What remains unclear is the notion of what constitutes a positive finding on integrated PET/CT because it is not infrequent to find mediastinal regions described as having "low" or "mild" uptake. This indeterminate finding on PET/CT leaves most practitioners in a quandary as to whether pathologic confirmation is needed to verify N2/N3 disease because this might expose many patients to unnecessary invasive staging procedures, such as mediastinoscopy, which carry multiple risks, including hemorrhage or vocal cord injury.[9] Recent evidence has renewed interest in the utility of standardized uptake values in predicting malignancy.[10,11] Specifically, the maximum standardized uptake value (maxSUV) has been shown to be an independent predictor of malignancy and of lymph node metastasis. Suggestion has also been made that a defined cutoff point of 5.3 for lymph node metastases provides maximum accuracy with integrated PET/CT.[12]

We elected to test the hypotheses that the maxSUV is a predictor of individual lymph node metastasis in NSCLC and that pathologic staging with mediastinoscopy might not be necessary in patients with a maxSUV of less than 5.3 in their mediastinal lymph nodes.

Abbreviations and Acronyms

CT = computed tomography
FDG = fluorodeoxyglucose
FNA = fine-needle aspiration
maxSUV = maximum standardized uptake value
NSCLC = non–small cell lung cancer
PET = positron emission tomography

Materials and Methods

Patient Selection

A retrospective review was performed on all N2 lymph nodes sampled from patients by using cervical mediastinoscopy, anterior mediastinotomy, and/or thoracotomy between December 2003 and June 2006 on the thoracic surgery service at the University of California at Davis Cancer Center. Only N2 lymph nodes from patients with new diagnoses of biopsy-proved NSCLC and presurgical staging–integrated PET/CT scans were included. The integrated PET/CT scans were then compared with the reference standard of pathologic results to determine sensitivity, specificity, positive and negative predictive values, and accuracy. The Institutional Review Board at the University of California at Davis Medical Center approved this study.

Integrated PET/CT Imaging

All integrated PET/CT studies were performed after patient fasting for a minimum of 4 hours. PET/CT images were obtained with an integrated PET/CT scanner (Discovery LS from GE Medical Systems, Waukesha, Wis, or ECAT Reveal XVI from CTI, Knoxville, Tenn) at 2 PET imaging centers. Whole-body scans were obtained 30 to 60 minutes after intravenous injection of 10 to 20 mCi of [^{18}F] fluoro-2-deoxy-D-glucose. For PET/CT imaging, simultaneously acquired CT data were used for attenuation correction. All studies were read by dedicated nuclear medicine physicians with a specialty in interpreting PET scan images. Clinical histories and pertinent CT scans were available for review. Mediastinal lymph nodes were individually assessed and assigned maxSUVs by using software contained within the PET/CT scanner and the following formula: $MaxSUV = C(\mu Ci/mL)/ID(\mu Ci)w(kg)$, with C equal to the activity at a pixel within a region of interest and ID equal to the injected dose per kilogram of patient body weight *(w)*.[13]

Mediastinal Lymph Node Staging

Extended mediastinal lymph node staging was completed in all patients by means of cervical mediastinoscopy, anterior mediastinotomy, or thoracotomy. In patients with normal mediastinoscopic results, thoracotomy followed typically within 14 days. The results of PET and CT scanning were available to the surgeon at the time of resection. All visible and technically feasible lymph nodes were removed and were annotated according to the revised International Staging System.[14,15] Pathologic reports were reviewed to determine whether any mediastinal lymph nodes contained cancer. Only N2 lymph nodes that would have been accessible by means of mediastinoscopy (stations 2, 4, and 7), anterior mediastinotomy (stations 5 and 6), right thoracotomy (stations 2, 4, 7, 8, and 9), or left thoracotomy (4, 5, 6, 7, and 9) were considered in this study.

TABLE 1. Patient characteristics

Characteristic	Integrated PET/CT study population (n = 110)
Age (y)	
Mean	65
Range	32–86
Male sex (%)	51 (46.4)
N2/N3 mediastinal disease (%)	21 (19.1)
Primary tumor location (%)	
RUL	37 (33.6)
RML	2 (1.8)
RLL	25 (22.7)
LUL	35 (31.8)
LLL	11 (10)

PET, Positron emission tomography; *CT,* computed tomography; *RUL,* right upper lobe; *RML,* right middle lobe; *RLL,* right lower lobe; *LUL,* left upper lobe; *LLL,* left lower lobe.

Statistics

Pathologic findings served as the gold standard. Each lymph node was individually assessed both clinically and pathologically. Thus it was possible for an individual patient to have, for example, 2 true-positive, 4 true-negative, and 2 false-positive lymph nodes. Comparisons between groups were made with the χ^2 test or the Mann-Whitney test. Receiver operator characteristic curves were produced by using the SPSS Version 13.0 for Windows (SPSS, Inc, Chicago, Ill).

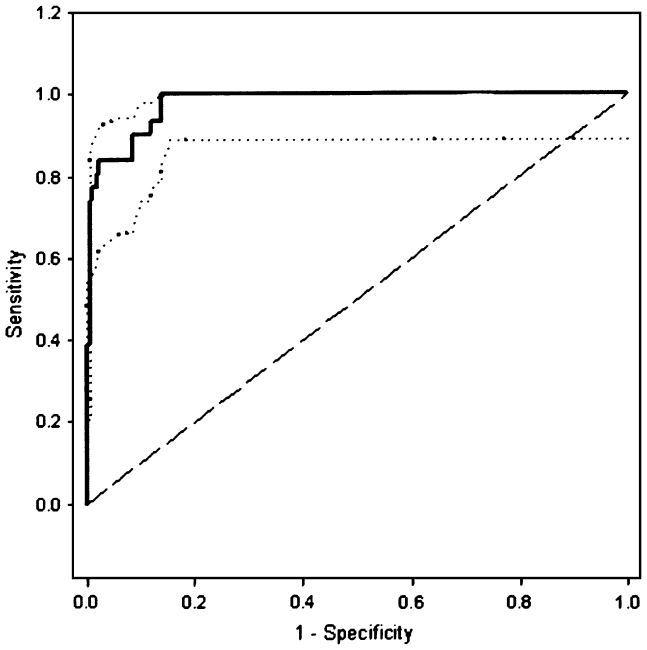

Figure 1. Receiver operating characteristic curve for N2 lymph nodes. *Dotted lines* indicate 95% confidence intervals. Optimal maximum standardized uptake value cutoff was 5.3 ($P < .001$).

Results

Between December 2003 and June 2006 at the University of California at Davis Cancer Center, a total of 142 patients underwent surgical mediastinal lymph node biopsy, with an average of 4 mediastinal lymph node stations sampled. Of the 32 patients excluded from this study, 19 either did not have an integrated PET/CT scan or did not have maxSUV values assigned, and 13 did not have a new diagnosis of NSCLC.

A total of 1311 lymph nodes were resected from the remaining 110 patients, of which 51 (46.4%) of 110 were men. Additional patient characteristics are shown in Table 1. There were 546 N1 lymph nodes and 765 N2 lymph nodes. There was pathologic evidence of metastasis in 31 (4.1%) of 765 N2 lymph nodes in 21 (19.1%) of 110 patients. Table 2 shows the distribution and median maxSUV of each mediastinal lymph node station. Station 4 was the most common location for metastatic disease. The mean and median maxSUVs for N2 nodes with metastatic disease were 9.2 (95% confidence interval, 7.0–11.4) and 7.2 (range, 2.2–25.8), respectively. For benign N2 nodes, the mean and median maxSUVs were 1.5 (95% confidence interval, 1.4–1.6) and 1.0 (range, 1.0–9.6), respectively ($P < .05$).

The optimal maxSUV cutoff for mediastinal lymph nodes was 5.3 by means of receiver operator characteristic analysis, as shown in Figure 1. When a maxSUV of 5.3 instead of 2.5 was used to assign malignancy by means of integrated PET/CT scanning, there were significant increases in overall

TABLE 2. Distribution and median maxSUV of N2 lymph nodes

	Pathologically positive nodes		Pathologically negative nodes		
Lymph node station	N	maxSUV range (median)	N	maxSUV range (median)	*P* value*
2	5	2.0–20.9 (7.2)	62	1.0–2.5 (1)	<.001
4	12	2.2–25.8 (8.1)	327	1.0–9.6 (1)	<.001
5 and 6	9	2.3–11.0 (7.1)	75	1.0–6.4 (1)	<.001
7	5	7.1–10.0 (8.5)	172	1.0–6.8 (1)	<.001
8 and 9	0		98	1.0–7.7 (1)	NA†

Note: Pathologically positive N2 lymph nodes had significantly higher median maximum standardized uptake values at each nodal station. *maxSUV,* Maximum standardized uptake value; *N,* number of lymph nodes. **P* value for Mann–Whitney test. †*P* value is unavailable because of an absence of pathologically positive lymph nodes at stations 8 or 9.

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TABLE 3. Efficacy of integrated PET/CT by using a maxSUV cutoff of 2.5 vs 5.3*

maxSUV cutoff for malignancy	2.5	5.3	P value†
Sensitivity (%)	93	81	.15
Specificity (%)	86	98	<.001
PPV (%)	22	64	<.001
NPV (%)	99	99	.34
Accuracy (%)	87	97	<.001

Note: specificity, positive predictive value, and accuracy were significantly improved when a maximum standardized uptake value cutoff of 5.3 was used. *maxSUV,* Maximum standardized uptake value; *PET,* positron emission tomography; *CT,* computed tomography; *PPV,* positive predictive value; *NPV,* negative predictive value *The efficacy of integrated positron emission tomography/computed tomography was calculated by using a maximum standardized uptake value cutoff of 2.5 and then recalculated with a maximum standardized uptake value cutoff of 5.3 for malignancy. †*P* value for χ^2 test.

accuracy (87% vs 97%, $P < .01$), specificity (86% vs 98%, $P < .01$), and positive predictive value (22% vs 64%, $P < .01$). Negative predictive value remained unchanged at 99%, and there was a trend toward decreased sensitivity, from 93% to 81% ($P = .15$, Table 3).

Furthermore, when we compared the lymph nodes that tested true positive, false positive, and false negative by using integrated PET/CT analysis, there were striking differences in the corresponding maxSUVs of both the primary lesions and the mediastinal lymph nodes (Table 4). The maxSUVs of the primary lesions in patients with either true-positive lymph nodes or false-positive lymph nodes were comparable (mean, 11.8 vs 13.6; median, 10 vs 14, respectively; $P = .145$). However, the corresponding mediastinal lymph nodes had significantly different values (mean, 11.2 vs 4.0; median, 7.6 vs 3.5, respectively; $P < .01$). On the other hand, patients with false-negative lymph nodes determined by means of integrated PET/CT analysis had significantly lower maxSUVs for both the primary lesion (mean, 5.54; median, 3.9; $P < .01$) and mediastinal lymph nodes (mean, 3.2; median, 3.3; $P < .01$).

When we examined the ratios of the maxSUVs in the lymph nodes compared with the primary tumors, we found that patients with true-positive lymph nodes had a mean and median ratio of 1.24 and 1.0, respectively. Patients with false-positive lymph nodes had mean and median ratios of 0.46 and 0.3, respectively ($P < .01$). Patients with false-negative lymph nodes had mean and median ratios of 0.75 and 0.71, respectively ($P = 0.04$).

Discussion

Our work confirms that the maxSUV with integrated PET/CT scanning is a predictor of individual lymph node metastasis in NSCLC. As suggested by previous work, lymph nodes with a higher maxSUV have a significantly higher incidence of metastatic disease.[12] The clinical importance of this study might be in redefining how integrated PET/CT scanning portends to pretreatment staging of NSCLC.

That is, with integrated PET/CT, we propose that patients with newly diagnosed NSCLC can be defined into one of 4 categories. The first are patients without mediastinal or distant uptake (maxSUV = background). Our work and multiple other studies have shown that a negative integrated PET/CT scan result does not need additional confirmation, and patients can proceed directly to surgical resection.[3-5,7]

The second category includes patients with a high uptake in both the primary tumor (maxSUV, >10) and the mediastinal lymph nodes (maxSUV, >5.3). Although this study shows that these patients have a significantly increased risk of malignancy in their mediastinal lymph nodes, pathologic confirmation is still necessary to rule out infectious or inflammatory diseases.[5,6] However, given the high likelihood of disease, successful confirmation can be achieved by using less-invasive procedures, such as FNA with endoscopic or endobronchial ultrasonographic guidance.[16-18] Moreover, this would potentially preserve the ability to perform mediastinoscopy in the posttreatment setting to determine the effectiveness of neoadjuvant therapy in patients with stage IIIA disease.[19]

The third category includes patients with high uptake in the primary tumors (maxSUV, >10) and a maxSUV of less than 5.3 in their corresponding mediastinal lymph nodes. As shown in this study, as well as in a recent study, these patients have a significantly lower median maxSUV ratio between the lymph nodes and the primary tumors and are most commonly associated with false-positive disease or micrometastatic disease.[20] Recent studies have also examined the glucose transporter as another reason for false-negative

TABLE 4. Ratios of the maxSUV in N2 lymph nodes versus the primary tumor

Integrated PET/CT result when using maxSUV cutoff of 5.3	N	Median maxSUV of N2 nodes	Median maxSUV of primary	Median ratio (range)	*P* value*
True positive	24	7.6	10	1 (0.58–2.94)	
False positive	86	3.5	14	0.3 (0.13–1.13)	<.01
False negative	7	3.3	3.9	0.71 (0.45–1.12)	.04

maxSUV, Maximum standardized uptake value; *PET,* positron emission tomography; *CT,* computed tomography; *N,* number of lymph nodes. **P* value for Mann–Whitney test. The true-positive group was used as a reference standard.

disease results; however, further studies are needed.[21] We propose that this population of patients, in the absence of other factors, such as N1 disease or central tumors, might be able to forego additional testing to rule out mediastinal disease and instead progress directly to surgical resection, thus avoiding delays in treatment and mitigating the added risks of mediastinoscopy or FNA. This would present a major deviation from the current practice of verifying all mediastinal lymph nodes with FDG uptake. Arguably, this might increase the number of false-negative results obtained by means of PET/CT scanning. However, a significant number of these patients harbor micrometastatic disease, whose benefit from neoadjuvant therapy remains to be well documented and are currently being investigated.

The final group includes patients with low uptake in both their primary tumors (maxSUV, <10) and their mediastinal lymph nodes (maxSUV, <5.3). Within our study, all of our patients with false-negative results fell into this category. However, these patients maintain a high maxSUV lymph node to primary tumor ratio, thus distinguishing them from patients with false-positive disease results who have a low maxSUV lymph node to primary tumor ratio. Accordingly, we find that this patient subpopulation might benefit from mediastinoscopy to determine the extent of disease.

One of the limitations of this study was that it was retrospective. Thus some variables, such as timing for PET/CT image acquisition and FDG injection dose, did not have a set or predefined algorithm. Moreover, the small patient population limited the ability to segregate and analyze our results by using variables such as tumor size, histology, and location. A larger prospective study would best complement this study.

In conclusion, the application of integrated PET/CT scanning continues to evolve. Although it remains the most effective noninvasive staging modality, limitations that cause false-positive (infections and inflammatory states) and false-negative (micrometastatic disease) results still hamper its overall effectiveness. However, this study provides evidence that, in the absence of other indications for mediastinoscopy, such as N1 disease, central tumors, or multiple tumors, mediastinoscopy can be omitted in patients who have a maxSUV of less than 5.3 in their N2 lymph nodes and a low maxSUV primary tumor to mediastinal lymph node ratio, as determined by using integrated PET/CT analysis. Future studies will further elucidate the role of integrated PET/CT scanning in the pretreatment staging of NSCLC.

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