View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Carolina Digital Repository

distribution to your colleagues or clients, contact us at www.rsna.org/rsnarights.

Non–Small Cell Lung Cancer: Prognostic Importance of Positive FDG PET Findings in the Mediastinum for Patients with N0–N1 Disease at Pathologic Analysis[1]

Liyi Xie, MD
Mert Saynak, MD
Nirmal K. Veeramachaneni, MD
David V. Fried, BS
Mandar R. Jagtap, MD
Wing Keung Chiu, MS
Daniel S. Higginson, MD
Michael V. Lawrence, PhD
Amir H. Khandani, MD
Bahjat F. Qaqish, MD, PhD
Ronald C. Chen, MD, MPH
Lawrence B. Marks, MD

Purpose: To assess the prognostic implications of mediastinal positron emission tomographic (PET) findings in patients undergoing curative resection of non–small cell lung cancer (NSCLC) who have histologically negative mediastinal lymph nodes (LNs), with the hypothesis that positive findings at PET are prognostic even in patients with negative histologic findings in the LNs.

Materials and Methods: Records of patients with a preoperative PET undergoing curative surgery, without adjuvant radiation, for pathologic T1–3N0–1 NSCLC at the University of North Carolina between 2000 and 2006 were reviewed as an institutional review board–approved HIPAA-compliant retrospective study. Ninety patients were evaluable (all histologically negative in mediastinum; 44 with both mediastinoscopy and surgery); 13 patients had positive mediastinal PET findings, and 77 had negative mediastinal PET findings. Local-regional and distant failure rates in patients with and those without mediastinal abnormalities at preoperative PET were compared by using logistic regression and log-rank tests.

Results: Median follow-up was 54.3 months (range, 1–99 months). There were higher rates of local-regional ($P = .001$) and distant ($P < .001$) failure as well as death ($P = .001$) in patients with postive PET findings than in patients with negative findings. In multivariable analysis (adjusting for other prognostic factors), positive PET findings in the mediastinum remained prognostic for distant failure ($P < .001$, hazard ratio = 6.9) and were marginally prognostic for local-regional failure ($P = .093$, hazard ratio = 1.9).

Conclusion: Positive findings at preoperative PET in the mediastinum appear to have prognostic implications despite the mediastinal LNs being histologically negative. The high rate of local-regional and distant failure suggests that postoperative radiation therapy and/or chemotherapy may be particularly helpful in patients with positive mediastinal findings at preoperative PET.

©RSNA, 2011

[1] From the Department of Radiation Oncology (L.X., D.V.F., D.S.H., M.V.L., R.C.C., L.B.M.), Department of Surgery (N.K.V.), Division of Nuclear Medicine, Department of Radiology (M.R.J., A.H.K.), and Department of Biostatistics (W.K.C., B.F.Q.), University of North Carolina School of Medicine, 101 Manning Dr, Box 7512, Chapel Hill, NC 27514; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China (L.X.); Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China (L.X.); and Department of Radiation Oncology, Trakya University Hospital, Edirne, Turkey (M.S.). Received January 30, 2011; revision requested March 24; revision received April 18; accepted May 17; final version accepted June 3. **Address correspondence to** L.B.M. (e-mail: *marks@med.unc.edu*).

©RSNA, 2011

Accurate staging is a cornerstone of cancer care, guiding both treatment and prognosis. For non–small cell lung cancer (NSCLC), the most commonly used staging system is adopted from TNM classification of the American Joint Committee on Cancer revised by the International Association of the Study of Lung Cancer (1). In this framework, patients with disease in the mediastinal lymph nodes (LNs) at histologic analysis are considered to be stage III and are usually treated with definitive chemotherapy and radiation therapy, while those without evidence of disease in mediastinal LNs at histologic analysis are considered to be stage I or II and are treated with surgery (2).

The routine staging of the mediastinum in patients with NSCLC includes computed tomography (CT) of the chest, mediastinoscopy, and, more recently, positron emission tomography (PET). PET can be used to identify tissues with a high metabolic rate, such as cancer. Many studies have compared the sensitivity, specificity, and positive and negative predictive values of CT versus PET versus both, with the histologic analysis essentially always used as the reference standard (3,4). The positive predictive value of PET in the mediastinum is reported to be 80%–90% (5). The remaining 10%–20% is thought to be false-positive PET findings, and treatment decisions are based on the histologic findings. Our analysis was undertaken to assess the logic of this approach. It is certainly possible that these discordant findings between PET and histologic analysis represent, in part, inaccuracies in the histologic assessment of the mediastinal LNs (eg, surgical sampling or pathologic techniques).

We herein assess the prognostic implications of mediastinal PET findings in patients undergoing curative resection of NSCLC who have a histologically negative mediastinum with the hypothesis that positive findings at PET are prognostic even in patients with negative histologic findings in the LNs.

Advances in Knowledge

- In non–small cell lung cancer, patients with positive mediastinal lymph node findings at preoperative PET have higher 5-year failure rates than those with negative findings (local-regional failure: 68.3% vs 18.6%, $P = .001$; distant failure: 66.4% vs 9.8%, $P < .001$) despite negative histologic findings.
- These patients also have a worse prognosis (5-year overall mortality: 76.9% vs 36.5%, $P = .001$); therefore, preoperative evaluation of the mediastinum with PET may complement surgical and histological findings.

Materials and Methods

The medical records of all patients who underwent surgery for lung cancer at the University of North Carolina between 2000 and 2006 were reviewed for our institutional review board–approved Health Insurance Portability and Accountability Act–compliant retrospective study. Ninety patients who met the following criteria comprised our study population: pathologic stages T1–3N0–1 NSCLC, undergoing lobectomy or pneumonectomy (wedge resection was excluded), the mediastinum was pathologically assessed, all surgical margins were negative, no neoadjuvant or adjuvant radiation therapy, no neoadjuvant chemotherapy, preoperative evaluation (typically including bronchoscopy, abdominal CT, and usually brain magnetic resonance [MR] imaging or CT, if applicable) resulted in M0 staging, had preoperative PET of the chest or whole body, and no metachronous lung cancers treated during the 2 years prior to the current resection. The study schema is shown in Figure 1. Clinical data were extracted retrospectively from the electronic medical records (eg, clinical, radiologic, and/or pathologic notes).

Implication for Patient Care

- The high rate of local-regional and distant failure suggests that postoperative radiation therapy and/or chemotherapy may be helpful in patients with a positive mediastinal findings at preoperative PET.

PET Technique

PET/CT scans with fluorine 18 fluorodeoxyglucose (FDG) were performed by using a dedicated PET scanner (Single-Slice Biograph or Biograph 40; Siemens, Knoxville, Tenn). Patients fasted for at least 6 hours before FDG injection. PET acquisition started approximately 60 minutes after the intravenous administration of approximately 444 MBq of FDG. PET/CT images were typically obtained from the base of the brain through the proximal thighs and were reconstructed in three planes. An unenhanced CT scan was obtained for attenuation correction and anatomic correlation.

Mediastinal nodal stations were defined on the basis of the International Association of the Study of Lung Cancer LN map (1). The PET findings in the mediastinum were categorized by using two methods.

Visual evaluation was the first method. Two of a group of nuclear medicine specialists (residents with 1–4 years experience, including M.R.J. with 4 years experience, and faculty with 10–40 years experience, including A.H.K. with 10 years experience) visually evaluated all PET/CT

Published online before print
10.1148/radiol.11110199 **Content codes:** NM BQ

Radiology 2011; 261:226–234

Abbreviations:
FDG = fluorine 18 fluorodeoxyglucose
NSCLC = non–small cell lung cancer
LN = lymph node
N2 = ipsilateral mediastinal LN
SUV = standardized uptake value
SUV_{max} = maximum SUV
$SUV_{max_{medLN}}$ = highest mediastinal LN SUV_{max}
VATS = video-assisted thoracoscopic surgery

Author contributions:
Guarantors of integrity of entire study, L.X., M.S., N.K.V., M.R.J., L.B.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, L.X., M.S., N.K.V., D.S.H., A.H.K., R.C.C., L.B.M.; clinical studies, M.S., M.R.J., D.S.H., A.H.K., R.C.C.; statistical analysis, L.X., M.S., D.V.F., W.K.C., D.S.H., B.F.Q.; and manuscript editing, L.X., M.S., N.K.V., D.V.F., W.K.C., D.S.H., A.H.K., B.F.Q., R.C.C., L.B.M.

Potential conflicts of interest are listed at the end of this article.

images for each patient in concert to render a consensus opinion in the clinical record. PET/CT findings of the mediastinum were recorded from the reports issued at the time of interpretation, with mediastinal LNs being broadly reported as malignant or not by using mediastinal blood pool activity as a background. Both attenuation-corrected and non–attenuation-corrected images were routinely reviewed. The findings on a PET report reflected the overall interpretation from these two sets of PET images; appearance on the CT study; and the pretest likelihood of disease in certain mediastinal nodal stations, including location (central vs peripheral) and size of the primary tumor, relative location of the nodal station to primary site, and possible false-positive conditions (eg, infection, benign inflammatory disease, rheumatoid disease).

Standardized uptake value (SUV) was the second method. SUV was defined as the activity per milliliter within the region of interest divided by the injected dose in megabecquerels per gram of body weight, and maximum SUV (SUV_{max}) was defined as the activity measured in the most intense voxel within this region of interest. The SUV calculation was done retrospectively for the purposes of our study. SUV_{max} was measured by placing a three-dimensional region of interest around each mediastinal nodal station by using the standard software provided by the manufacturer (Syngo MI Workplace; Siemens, Malvern, Pa). All measured mediastinal lesions had to be visible, and the regions of interest were selected on the basis of visibility. The highest SUV_{max} of all nodal stations in the mediastinum ($SUV_{max_{medLN}}$) for each patient was analyzed. This analysis was performed by two experienced physicians (M.R.J. and A.H.K., with 4 and 10 years experience, respectively) who were blinded to any other relevant information, including the reports issued at the time of clinical reading of the scans.

Histologic Staging of the Mediastinum

All patients underwent anatomic resection of all gross tumors with either thoracotomy or video-assisted thoracoscopic surgery (VATS). All patients had the mediastinal LNs staged at mediastinoscopy and/or mediastinal sampling during lobectomy or pneumonectomy. Nodal sampling was performed at the surgeon's discretion, but mediastinal dissection was not performed routinely. In all cases, all mediastinal nodal tissue was negative for malignancy on permanent sections, with or without frozen sections, if taken during surgery. The TNM stage was assigned according to the seventh edition of the American Joint Committee on Cancer manual (1).

End Points and Statistical Analysis

A local-regional failure was defined by using either CT progression or FDG PET avidity as a new or enlarging mass at the site of surgical resection (eg, ipsilateral lung, surgical stump, hilum, chest wall, mediastinum) that, in the patient's subsequent clinical follow-up, was consistent with disease progression. An enlarged LN or increased tissue thickening at the resection margin at CT, or an equivocal finding at PET, that failed to progress was not considered as a failure. Where possible and clinically relevant, some patients underwent biopsy of a suspected recurrence. A distant failure was a failure beyond either the surgical bed or regional LNs. Time to failure was defined as the interval from the date of surgery until failure. Patients not experiencing a failure were censored at the date of their last follow-up or at death. Follow-up survival status was obtained from the University of North Carolina registry and the Social Security death index. Overall survival time was defined as the interval from the date of surgery until the date of death due to any cause.

The goal of our study was to compare the outcomes of patients with positive mediastinum PET findings versus those with negative findings. The Fisher exact and Mann–Whitney tests were used to examine the distribution of categorical and continuous patient characteristic parameters, respectively, in the two subgroups (ie, those with positive PET mediastinal findings and those with negative findings). Binary logistic regressions of crude incidence rates of local-regional and distant failures were performed to investigate their association with PET results in the mediastinum. The Kaplan-Meier method and log-rank tests were used for the estimation and comparison of actuarial local-regional and distant failure rates and overall mortality rates between the two subgroups. Univariate and multivariate Cox proportional hazards models were used to assess the potential relationship between prognostic outcomes and potentially confounding covariates, including sex, lymphovascular space invasion, tumor histologic grade (World Health Organization classification), pleural involvement, primary tumor size, number of sampled ipsilateral mediastinal LNs (N2), histologic findings (ie, squamous vs nonsquamous carcinoma), left- versus right-sided tumor, type of surgery (lobectomy, bilobectomy, or pneumonectomy), and postoperative chemotherapy use. For SUV analysis, binary logistic regression of crude incidence rates was performed to investigate their association with the subgroups based on $SUV_{max_{medLN}}$. The overall prognostic value of the $SUV_{max_{medLN}}$ was assessed by using the area under the receiver operating characteristic curve by using the trapezoidal rule for local-regional and distant failures. Analysis was carried out by using PASW Statistics software (version 18.0; SPSS, Chicago, Ill). A P value of less than .05 was considered to indicate a significant difference without correction for multiple hypothesis testing, since this is a preliminary or exploratory study and may be considered to be hypothesis generating.

Results

Patient Characteristics

Clinical characteristics of the 90 patients included in this analysis are shown in Table 1. Median follow-up in all patients was 54.3 months (range, 1–99 months), and that in survivors was 71.7 months (range, 47–99 months). Mediastinoscopy was performed in 44 patients. The median number of total mediastinal nodal stations sampled for

Figure 1

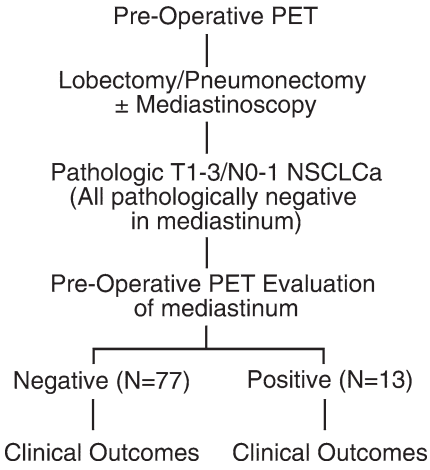

Figure 1: Study schema. *NSCLCa* = NSCLC.

each patient during mediastinal sampling procedures (ie, mediastinoscopy and/or surgery) was three (range, 1–7). One patient with negative mediastinal findings at PET had cardiac arrhythmia several days after surgery and died about one month after surgery with no sign of cancer progression.

Forty-eight patients had SUV_{max} data for mediastinal LNs available. In all patients with positive mediastinal LNs at PET, it was the surgeon's intent to sample the mediastinal nodal station with the highest SUV_{max} during subsequent surgical and histologic staging.

Analysis of Visual Assessment of PET

Thirteen patients had positive PET mediastinal findings, and 77 had negative findings (Table 2). In the entire group, the crude rates of local-regional, distant, and all failures were higher in group with positive PET findings versus the group with negative PET findings. Similar findings were seen in a subgroup of 68 patients with pathologically determined N0 disease. Actuarial estimates of local-regional and distant failures, as well as overall mortality, are shown in Figure 2.

Univariate analyses of above-mentioned covariates are shown in Table 3. The results of multivariate analyses performed to assess the association between positive PET LN findings and local-regional and distant failure, controlling for these covariates, are shown in Table 3. PET findings in the mediastinum remained prognostic for distant failure ($P < .001$, hazard ratio = 6.9) and were marginally prognostic for local-regional failure ($P = .093$, hazard ratio = 1.9).

SUV_{max} Analysis

SUV_{max} data were available in only 48 patients owing to loss of archival data (eg, drive loss). Median $SUV_{max_{medLN}}$ was 2.75 (range, 1.67–5.49). The crude rate of local-regional failure for the patients with a $SUV_{max_{medLN}}$ below the median was seven of 24 versus eight of 24 for that above the median ($P = .755$). Comparable rates of distant failure were four versus seven, respectively, both out of 24 ($P = .303$).

Table 1

Patient Demographics

Parameter	All Patients ($n = 90$)	PET Mediastinum Findings: Positive ($n = 13$)	PET Mediastinum Findings: Negative ($n = 77$)	*P* Value
Sex				.23
Female	37 (41)	3 (23)	34 (44)	
Male	53 (59)	10 (77)	43 (56)	
Median age (y)*	66 (38–88)	68 (41–81)	66 (38–88)	.69
Tumoral stage				.21
T1	32 (36)	2 (15)	30 (39)	
T2	32 (36)	5 (39)	27 (35)	
T3	26 (29)	6 (46)	20 (26)	
Nodal stage				.08
N0	68 (76)	7 (54)	61 (79)	
N1	22 (24)	6 (46)	16 (21)	
Histologic finding				.02
Squamous cell carcinoma	40 (44)	10 (77)	30 (39)	
Adenocarcinoma†	44 (49)	2 (15)	42 (55)	
Adenosquamous cell carcinoma	2 (2)	0	2 (3)	
Large-cell carcinoma	3 (3)	1 (8)	2 (3)	
Other	1 (1)	0	1 (1)	
Histologic grade				.09
1	5 (6)	0	5 (7)	
2	44 (49)	3 (23)	41 (53)	
3	39 (43)	10 (77)	29 (38)	
Lymphovascular space invasion	17 (19)	4 (31)	13 (17)	.26
Pleural involvement	13 (14)	4 (31)	9 (12)	.09
Location				.77
Right	53 (59)	7 (54)	46 (60)	
Left	37 (41)	6 (46)	31 (40)	
Bronchoscopy	55 (61)	9 (69)	46 (60)	.76
Mediastinoscopy	44 (49)	11 (85)	33 (43)	.01
Brain MR imaging and/or CT	20 (22)	2 (15)	18 (23)	.72
Type of surgery				.18
Lobectomy	71 (79)	9 (69)	62 (81)	
Bilobectomy	6 (7)	0	6 (8)	
Pneumonectomy	13 (14)	4 (31)	9 (12)	
Median no. of sampled N2 stations‡	3 (1–7)	4 (2–5)	3 (1–7)	.01
Postoperative chemotherapy	12 (13)	2 (15)	10 (13)	.68

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses.

* Data in parentheses are ranges.

† Including bronchioloalveolar carcinoma.

‡ Data are numbers of mediastinal LN stations sampled or dissected during mediastinoscopy and/or surgery, with ranges in parentheses. Individual stations defined in accordance with International Association of the Study of Lung Cancer LN map.

Table 2

End Point–related Results in PET-Positive Mediastinum versus PET-Negative Patient Groups

	All Patients		Positive PET LN Findings		Negative PET LN Findings			
Parameter	No. of Patients*	Percentage	No. of Patients*	Percentage	No. of Patients*	Percentage	*P* Value	Odds Ratio
	All Nodal Stages							
Crude incidence rates								
All failures	28/90	31.1	9/13	69.2	19/77	24.7	.003	7
Local-regional failure	22/90	24.4	7/13	53.8	15/77	19.5	.012	5
Distant failure	15/90	16.7	7/13	53.8	8/77	10.4	.001	10
5-year actuarial failure rates								
Local-regional failure	…	24.9	…	68.3	…	18.6	.001†	…
Distant failure	…	17.2	…	66.4	…	9.8	<.001†	…
5-year overall mortality rates	…	42.4	…	76.9	…	36.5	.001†	…
	Pathologically Determined N0 Stage							
Crude incidence rates								
Local-regional failure	11/68	16.2	3/7	42.9	8/61	13.1	.06	5
Distant failure	11/68	16.2	5/7	71.4	6/61	9.8	.001	23
5-year actuarial failure rates								
Local-regional failure	…	15.0	…	58.3	…	10.9	.004	…
Distant failure	…	15.9	…	82.9	…	8.8	<.001	…
5-year overall mortality rates	…	38.4	…	85.7	…	32.9	.001	…
	Pathologically Determined N1 Stage							
Crude incidence rates								
Local-regional failure	11/22	50.0	4/6	66.7	7/16	43.8	.3	…
Distant failure	4/22	18.2	2/6	33.3	2/16	12.5	.3	…
5-year actuarial failure rates								
Local-regional failure	…	55.5	…	77.8	…	48.7	.6	…
Distant failure	…	22.9	…	44.4	…	14.4	.3	…
5-year overall mortality rates	…	54.5	…	66.7	…	50.0	.3	…

* Data are numbers used to calculate percentages.

† *P* value of comparison between two curves during whole follow-up.

Receiver operating characteristic curve analyses of $SUV_{max_{medLN}}$ for local-regional and distant failure and overall mortality are shown in Figure 3. For these same three end points, there are no differences in the actuarial estimates between patients with an $SUV_{max_{medLN}}$ below the median and those with an $SUV_{max_{medLN}}$ above the median (Fig 3).

Discussion

Lung cancer is an aggressive disease that typically infiltrates local-regional LNs and also has a high propensity for a distant metastatic spread. Following resection, the risk for local-regional and distant progression is related to the pathologic stage (6,7).

Noninvasive diagnostic imaging tests, such as CT and PET, are routinely used to define the tumor extent. Inadequacies of imaging tests are widely acknowledged (3,8), and sensitivity, specificity, and positive and negative predictive values are usually used to compare the imaging findings with the reference-standard pathologic assessments. Our analysis suggests that PET might provide complementary prognostic information beyond that afforded by pathologic findings. It suggests that treatment recommendations might perhaps be influenced by the pathologic findings and the imaging results.

The two main approaches to access the mediastinum are mediastinoscopy and open thoracotomy or VATS (9). Mediastinoscopy has the advantage of allowing assessment of bilateral nodal stations, but some stations are not well accessed with the standard cervical approach (eg, levels 5 [subaortic], 6 [paraaortic], 8 [paraesophageal], and 9 [pulmonary ligament]). The sensitivity of mediastinoscopy is reported to vary from 81%–89% compared with open surgery (10–12). A recently published randomized trial (13) considered mediastinoscopy versus endoscopic ultrasonography for mediastinal staging; a false-negative rate of 10.3% (six of 58) was found in those undergoing mediastinoscopy plus endosonography at the time of thoracotomy and nodal dissection conforming to European Society for Thoracic Surgery guidelines (14). Overall, mediastinoscopy is believed to have an average false-negative rate of 11%, with histologic examination after thoracotomy as the reference standard (15).

Since ipsilateral nodal involvement is more common than contralateral nodal disease, open thoracotomy and VATS are thought to be more accurate than the mediastinoscopy. With

Figure 2

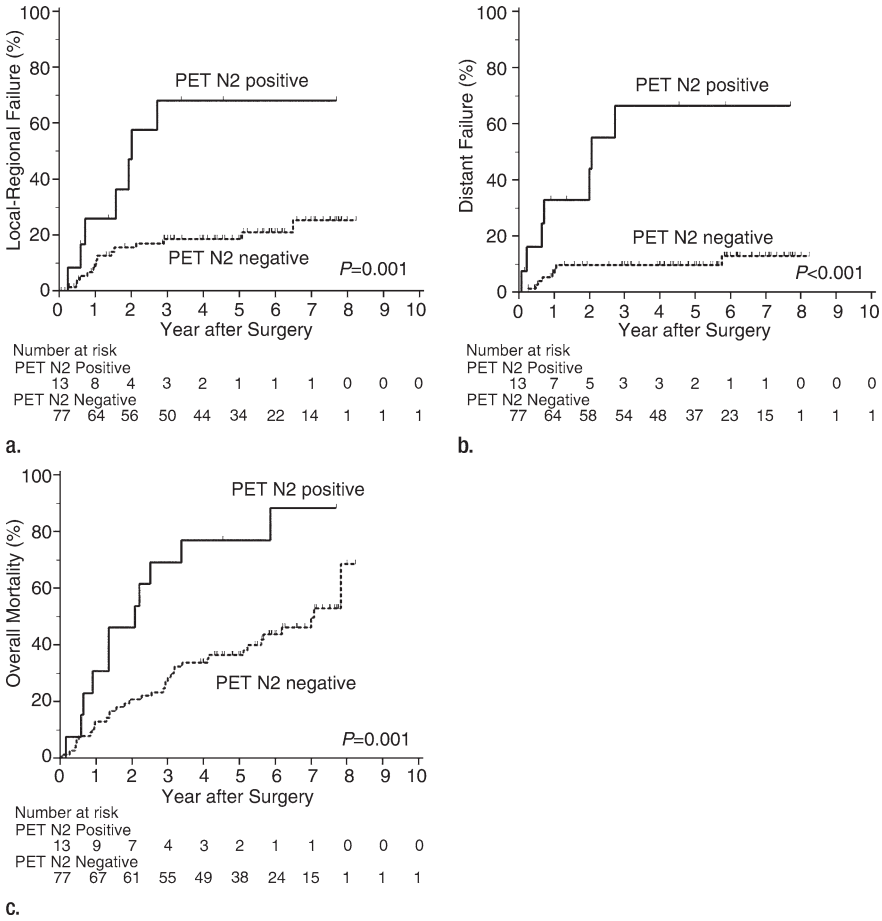

Figure 2: Comparison of actuarial **(a)** local-regional failure, **(b)** distant failure, and **(c)** overall mortality after surgery for patients with positive PET N2 findings versus those with negative findings.

thoracotomy or VATS, access to the ipsilateral mediastinum may be better than with mediastinoscopy in some settings, yet the access to the contralateral mediastinum is limited. This might be more of a factor for left lower lobe lesions that appear to have a greater propensity to metastasize to the contralateral level 2 and 4 compared with other lobes (16). The false-negative rate of VATS is reported to be approximately 7% on the basis of limited mostly retrospective data (15). These false-negative findings could be reflecting the challenging assessment of the mediastinum and/or the diligence of LN evaluation (complete dissection, systemic sampling, or selective sampling [currently the most common]) (17,18). The debatable procedure of complete nodal dissection of the mediastinum has been demonstrated to increase detection of N2 disease as well as survival by multiple authors. In the recently completed American College of Surgeons Oncology Group Z0030 trial of mediastinal dissection versus systematic sampling in patients with T1 or T2, N0 or nonhilar N1 lung cancer, 4% of patients were found to have occult N2 disease despite negative rigorous prerandomization mediastinoscopy and/or thoracotomy or VATS (19,20). A 2001 survey by the American College of Surgeons demonstrated a low rate of mediastinal evaluation in the United States: 27% of patients received preoperative mediastinoscopy, 46.6% had mediastinal LN biopsy, and 58% had mediastinal LNs sampled or removed during surgery (21). False-negative rates may be reduced with more vigorous evaluation of the mediastinum (22,23).

Beyond the surgical issues, there are uncertainties in the pathologic assessment of resected tissues. A pathologic study showed that 63% (38 of 60) of patients with NSCLC who were considered to be tumor free with hematoxylin-eosin staining had at least one positive LN detected with further immunohistologic analysis, and 10% of LNs determine to be tumor free with hematoxylin-eosin in LN-positive patients were found to be positive (24). Studies have suggested that LN micrometastases in patients with early-stage pathologic N0 NSCLC after curative surgery may be prognostic for recurrence and survival (25,26).

Therefore, it is reasonable to hypothesize that the discrepancies between PET and histologic findings reflect, at least in part, false-negative histologic findings due to insufficient evaluation of the mediastinum at surgery through sampling. PET, on the other hand, allows comprehensive evaluation of the mediastinum in a noninvasive fashion.

Most diagnostic tests, and particularly PET, have relatively high positive predictive values in the chest and mediastinum, with histologic examination as the reference standard. The positive predictive value of PET in the mediastinum in patients with NSCLC has been reported to be 87% by Fischer et al (27), 79% by Toloza et al (28), 90% by Dwamena et al (29), and 94% by Silvestri et al (8) in reviews with large populations. Factors reported to be related to false-positive PET findings are infection (eg, pneumonia), benign inflammatory disease (eg, tuberculosis), rheumatoid arthritis, non–insulin-dependent diabetes, and atypical adenomatous hyperplasia (30), most of which can be detected with routine admission tests.

Pathologic evaluation is generally considered to be the reference standard for staging many cancers. As such, treatment recommendations are widely based on the results of histologic examinations. Our analysis challenges that presumption, at least for situations when the radiologic and pathologic findings

Table 3

Univariate and Multivariate Analyses

	Univariate Analysis				Multivariate Analysis			
	Local-regional Failure		Distant Failure		Local-regional Failure		Distant Failure	
Variable	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio
Positive mediastinal PET findings	.002	4.2	<.001	7.5	.093	1.9	<.001	6.9
Lymphovascular space invasion	<.001	6.8	.001	6.5	<.001	7.1	.01	4
Higher histologic grade	.03	2.4	.3	…	.13	…	…	…
Primary tumor size	.09	…	.02	1.2	.38	…	.1	…
Male vs female sex	.16	…	.02	5.5	…	…	.14	…
Pleural involvement	.13	…	.02	3.6	…	…	.22	…
Increased no. of sampled N2 stations	.13	…	.84	…	…	…	…	…
Histologic findings*	.34	…	.33	…	…	…	…	…
Left vs right	.55	…	.28	…	…	…	…	…
Type of surgery†	.2	…	.7	…	…	…	…	…
Postoperative chemotherapy	.63	…	.44	…	…	…	…	…

* Squamous vs nonsquamous carcinoma.

† Lobectomy vs bilobectomy vs pneumonectomy.

are discordant in the mediastinum. The high rates of local-regional and distant failures in our patients who had positive PET findings in the mediastinum, despite negative histologic findings, are interesting and suggest that these patients might benefit from adjuvant postoperative therapies, such as chemo- and/or radiation therapy. In light of the generally good positive predictive value for PET imaging in the mediastinum as well as the risks of false-negative findings with surgical assessment of the LNs, the results of our analysis are not really surprising. There is ample data demonstrating the prognostic value of PET in lung cancer (31) and in other tumor sites, such as cervical cancer (24).

The broad findings of our study are roughly similar in the pathologically determined N0 and N1 subsets. For both, the rates of local-regional and distant failure are higher in the groups with positive mediastinal PET findings versus those with negative findings. Most patients with N1 disease will be recommended to receive chemotherapy. Therefore, positive preoperative PET findings in the mediastinum will likely not alter recommendations for chemotherapy. However, this is less often true for patients with N0 disease, for whom chemotherapy is generally not recommended. In these patients, the higher rate of distant failure in those with positive preoperative mediastinal PET findings might lead to the recommendation to receive chemotherapy. Since postoperative radiation therapy is generally not recommended for patients with stage N0 or N1 disease, the higher rate of local-regional failure in patients with a positive preoperative PET finding in the mediastinum might lead to consideration of postoperative radiation therapy. Thus, the potential effect of our study in altering therapy might be different between N0 and N1 groups.

The significant results in our analysis are based on visual (ie, qualitative) interpretation of PET images, taking into account both attenuation-corrected and non–attenuation-corrected PET image sets as well as the pretest likelihood of disease in certain mediastinal nodal stations as described earlier. In contrast, SUV-based (ie, quantitative) evaluation did not significantly predict outcomes. This suggests that one should be cautious when using SUV alone. While SUV may be the best method of image quantification and a strong tool in the research setting, it may not be able to replace evaluation of PET images by an experienced physician who can consider the clinical context.

Our study had several limitations. First, there are inherent inaccuracies to retrospective data collection mostly due to errors from cofounding factors to be mentioned below. PET findings and clinical outcomes were determined from records review. However, several physicians with expertise in lung cancer were involved in the record review, and records of patients suspected of having a local-regional recurrence were also reviewed by a thoracic surgeon. Second, the modest sample size limits the power of statistical analyses. Third, there are several factors that may confound one's ability to assess the independent prognostic relevance of the mediastinal PET findings. For example, tumor size, lymphovascular space invasion, and the number of sampled mediastinal nodal stations may influence the rates of local-regional or distant failure. Indeed, several of such factors were prognostic in our univariate and multivariate analyses, as well as in other reports (32). Nevertheless, in our multivariate analysis, the mediastinal PET findings remained significant. Further, the data presented represents a reasonably large group of patients treated and followed in a real-life clinical environment. Additional study involving a larger number of patients, ideally with prospective data collection, would be helpful to better understand this issue.

In conclusion, our findings suggest that, in patients with NSCLC, preoperative evaluation of the mediastinum with PET may complement the surgical and histologic findings. Among patients with a negative pathologic assessment of the mediastinum, those with an abnormality in the mediastinum at PET have a higher rate of local-regional and distant failure than do those without. Thus, positive PET findings in the face of negative histologic findings may represent a false-negative pathologic

Figure 3

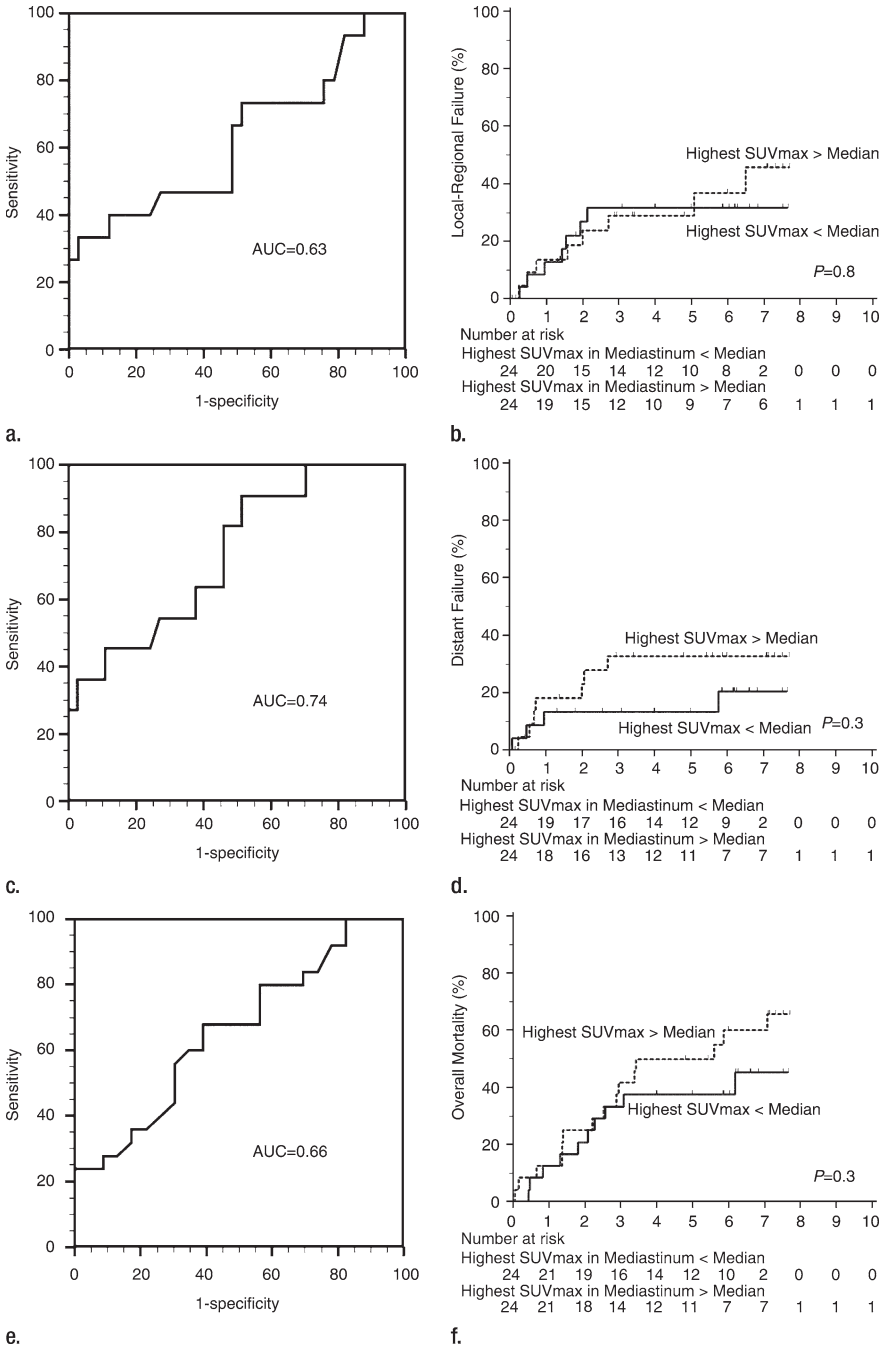

Figure 3: Receiver operating characteristic curves comparing patients with **(a)** local-regional and **(c)** distant failure as well as **(e)** overall mortality to those without in 48 patients. Comparison of **(b)** local-regional and **(d)** distant failure as well as **(f)** overall mortality after surgery for patients with $SUV_{max_{medLN}}$ below the median *(Highest SUVmax < Median)* and those with $SUV_{max_{medLN}}$ above the median *(Highest SUVmax > Median). AUC* = area under receiver operating characteristic curve.

assessment, rather than a false-positive PET finding.

Acknowledgment: The authors would like to thank Staci Hengsterman, RT(R)(N), (Department of Radiology, University of North Carolina) for technical support of the PET data.

Disclosures of Potential Conflicts of Interest: L.X. No potential conflicts of interest to disclose. **M.S.** No potential conflicts of interest to disclose. **N.K.V.** No potential conflicts of interest to disclose. **D.V.F.** No potential conflicts of interest to disclose. **M.R.J.** No potential conflicts of interest to disclose. **W.K.C.** No potential conflicts of interest to disclose. **D.S.H.** No potential conflicts of interest to disclose. **M.V.L.** No potential conflicts of interest to disclose. **A.H.K.** No potential conflicts of interest to disclose. **B.F.Q.** No potential conflicts of interest to disclose. **R.C.C.** No potential conflicts of interest to disclose. **L.B.M.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: none to disclose. Other relationships: is the recipient of a National Institutes of Health grant that broadly uses nuclear medicine imaging to assess radiation-induced cardiopulmonary injury and does not pertain to the current study.

References

1. Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York, NY: Springer, 2010.
2. NCCN clinical practice guidelines in oncology: non-small cell lung cancer, V.2.2010. National Comprehensive Cancer Network Web site. http://www.nccn.org/. Published 2010. Accessed January 30, 2011.
3. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. N Engl J Med 2006;354(5):496–507.
4. Pozo-Rodríguez F, Martín de Nicolás JL, Sánchez-Nistal MA, et al. Accuracy of helical computed tomography and [18F] fluorodeoxyglucose positron emission tomography for identifying lymph node mediastinal metastases in potentially resectable non-small-cell lung cancer. J Clin Oncol 2005;23(33):8348–8356.
5. Kelsey CR, Marks LB. Oncologic imaging/oncologic anatomy. In: Halperin EC, Perez CA, Brady LW, eds. Perez and Brady's principles and practice of radiation oncology. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2008; 620–636.
6. Varlotto JM, Recht A, Flickinger JC, Medford-Davis LN, Dyer AM, Decamp MM. Factors associated with local and distant recurrence and survival in patients with resected nonsmall cell lung cancer. Cancer 2009;115(5):1059–1069.
7. Sawyer TE, Bonner JA, Gould PM, Deschamps C, Lange CM, Li H. Patients with stage I non-small cell lung carcinoma at

postoperative risk for local recurrence, distant metastasis, and death: implications related to the design of clinical trials. Int J Radiat Oncol Biol Phys 1999;45(2):315–321.

8. Silvestri GA, Gould MK, Margolis ML, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007; 132(3 Suppl):178S–201S.
9. Detterbeck FC. Surgical evaluation of the mediastinum. In: Pass HI, Carbone DP, Johnson DH, et al, eds. Principles and practice of lung cancer: the official reference text of the IASLC. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2010; 425–435.
10. Funatsu T, Matsubara Y, Ikeda S, Hatakenaka R, Hanawa T, Ishida H. Preoperative mediastinoscopic assessment of N factors and the need for mediastinal lymph node dissection in T1 lung cancer. J Thorac Cardiovasc Surg 1994;108(2):321–328.
11. Gdeedo A, Van Schil P, Corthouts B, Van Mieghem F, Van Meerbeeck J, Van Marck E. Prospective evaluation of computed tomography and mediastinoscopy in mediastinal lymph node staging. Eur Respir J 1997;10(7):1547–1551.
12. Leschber G, Holinka G, Freitag L, Linder A. Mediastinoscopy in the staging of bronchial carcinoma: a critical assessment [in German]. Pneumologie 2000;54(11):489–493.
13. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. JAMA 2010;304(20):2245–2252.
14. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006;30(5):787–792.
15. Detterbeck FC, Jantz MA, Wallace M, et al. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132(3 Suppl): 202S–220S.
16. Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006;65(4):1097–1105.
17. Shields TW. Mediastinal surgery. Philadelphia, Pa: Lea & Febiger, 1991.
18. Whitson BA, Groth SS, Maddaus MA. Surgical assessment and intraoperative management of mediastinal lymph nodes in non-small cell lung cancer. Ann Thorac Surg 2007;84(3):1059–1065.
19. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group z0030 trial. Chest 2011;139(5):1124–1129.
20. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81(3):1013–1019; discussion 1019–1020.
21. Little AG, Rusch VW, Bonner JA, et al. Patterns of surgical care of lung cancer patients. Ann Thorac Surg 2005;80(6):2051–2056.
22. Anraku M, Miyata R, Compeau C, Shargall Y. Video-assisted mediastinoscopy compared with conventional mediastinoscopy: are we doing better? Ann Thorac Surg 2010;89(5): 1577–1581.
23. Witte B, Hürtgen M. Video-assisted mediastinoscopic lymphadenectomy (VAMLA). J Thorac Oncol 2007;2(4):367–369.
24. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. J Clin Oncol 2010;28(12):2108–2113.
25. Osaki T, Oyama T, Gu CD, et al. Prognostic impact of micrometastatic tumor cells in the lymph nodes and bone marrow of patients with completely resected stage I non-small-cell lung cancer. J Clin Oncol 2002; 20(13):2930–2936.
26. Maruyama R, Sugio K, Mitsudomi T, Saitoh G, Ishida T, Sugimachi K. Relationship between early recurrence and micrometastases in the lymph nodes of patients with stage I non-small-cell lung cancer. J Thorac Cardiovasc Surg 1997;114(4):535–543.
27. Fischer BM, Mortensen J, Højgaard L. Positron emission tomography in the diagnosis and staging of lung cancer: a systematic, quantitative review. Lancet Oncol 2001;2(11): 659–666.
28. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. Chest 2003;123(1 Suppl):137S–146S.
29. Dwamena BA, Sonnad SS, Angobaldo JO, et al. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s—meta-analytic comparison of PET and CT. Radiology 1999;213(2):530–536.
30. Al-Sarraf N, Aziz R, Doddakula K, et al. Factors causing inaccurate staging of mediastinal nodal involvement in non-small cell lung cancer patients staged by positron emission tomography. Interact Cardiovasc Thorac Surg 2007;6(3):350–353.
31. Vansteenkiste J, Fischer BM, Dooms C, Mortensen J. Positron-emission tomography in prognostic and therapeutic assessment of lung cancer: systematic review. Lancet Oncol 2004;5(9):531–540.
32. Kelsey CR, Marks LB, Hollis D, et al. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. Cancer 2009;115(22):5218–5227.