

Clinical application of positron emission tomography in designing radiation fields in non-small cell lung cancer patients

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Abstract. There is significant interest in incorporating positron emission tomography (PET) into radiation therapy planning, although limited data exist that separately consider its diagnostic accuracy with respect to the primary tumor, hilum and mediastinum. This study evaluates the accuracy of PET planning by region of interest. Between January 2003 and July 2005, 351 patients with a pre-operative PET study underwent surgical resection. Of this population, 257 (73%) patients with a diagnosis of non-small cell lung cancer were evaluated. PET study findings regarding the suspected primary tumor site, ipsilateral hilum and mediastinum were correlated with surgical pathology for determination of accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The accuracy of the primary site (95%), ipsilateral hilum (80%) and mediastinum (84%) was relatively high. The NPV of the ipsilateral hilum and mediastinum was also high (92 and 86%, respectively). However, the PPV of the ipsilateral hilum (31%) and mediastinum (75%) was lower. PET accuracy evaluating bronchoalveolar primary tumors was lower vs. other histologies (86 vs. 96%, $p=0.02$), although there was no difference with regard to the hilum or mediastinum. PET scanning may be an important tool in designing radiation treatment fields for lung cancer when combined with other imaging modalities. However, caution must be exercised when evaluating lymph node regions, as the PPV is not as high for the ipsilateral hilum and mediastinum as for the primary tumor. The NPV is high for nodal regions and may help with the exclusion of large treatment volumes in selected cases.

Introduction

Positron emission tomography (PET) continues to gain acceptance as a valuable tool in the diagnosis and staging of non-small cell lung cancer (NSCLC) (1-4). Its sensitivity and specificity with respect to the detection of malignancy in solitary pulmonary nodules have been estimated at 97 and 78%, respectively (5), and PET has been shown to be superior to computed tomography (CT) in staging of the mediastinum (6-21). There has also been much interest in the incorporation of PET into radiation treatment planning, particularly with the opportunities afforded by 3-D conformal radiation therapy and intensity-modulated radiation therapy, which improve dose conformality and allow for dose escalation. The utilization of PET imaging in treatment planning could conceivably alter target volumes in two ways: exclusion of suspicious, but PET-negative, tissue volumes and inclusion of previously undetected tumor burden (22). Classically, target volumes in NSCLC include a combination of the primary site, with or without the ipsilateral hilum and/or mediastinum. While many studies have been conducted which evaluate the accuracy of PET in lung cancer, few have separated the data with respect to these areas, limiting the confidence with which PET can be employed in radiation planning. For this reason, this study was performed to evaluate the accuracy of PET imaging according to these regions of interest.

Materials and methods

A University of Pennsylvania Institutional Review Board-approved retrospective study was undertaken to assess the diagnostic accuracy of PET based on surgical pathology confirmation. Between January 2003 and July 2005, 351 patients with suspicion of lung cancer underwent pre-operative PET imaging followed by surgical resection. The dates listed were based on the date of surgery, and all surgical procedures were performed at the Hospital of the University of Pennsylvania. From this population, 257 (73%) patients with a pathologic diagnosis of NSCLC who did not undergo neoadjuvant therapy were assessed. Pre-operative clinical stage was estimated based on pre-operative PET and CT

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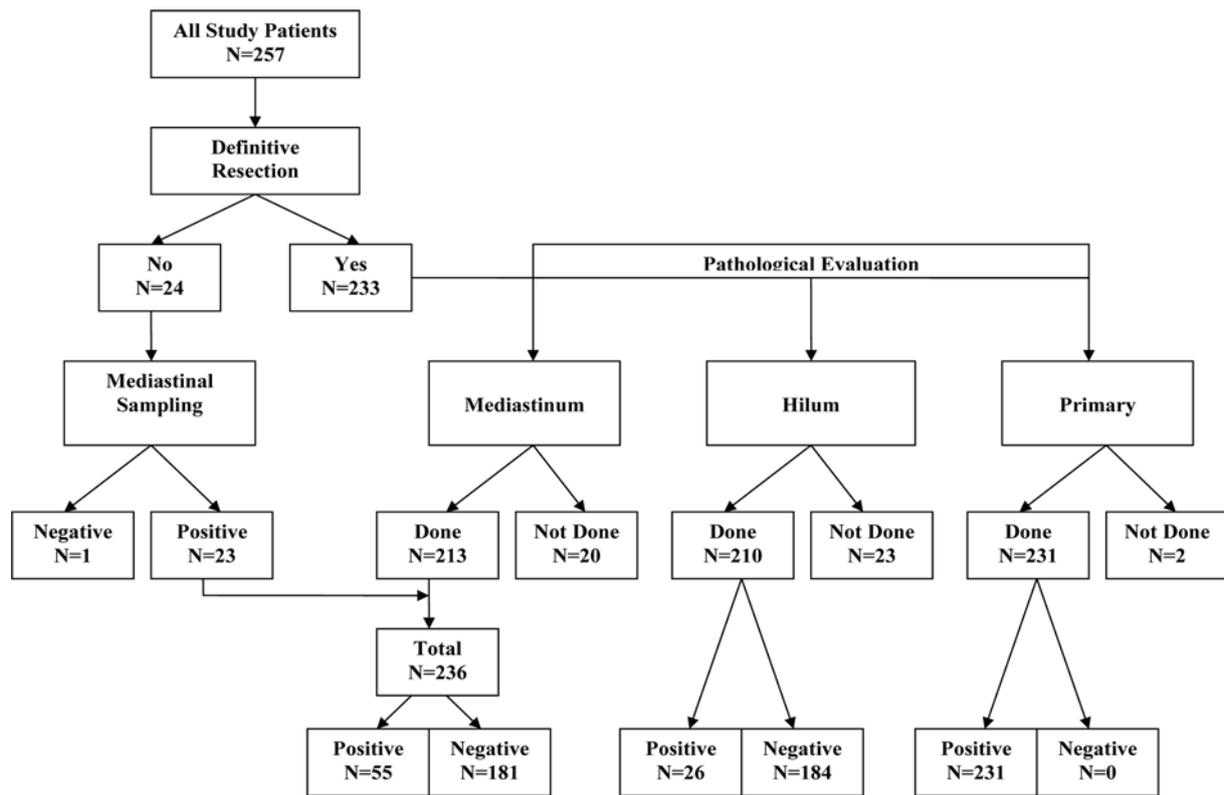


Figure 1. Pathology evaluation and findings.

imaging via the American Joint Committee on Cancer Staging System (6th edition) (23). Postoperative pathologic stage was based on surgical pathologic findings.

PET findings were documented separately with respect to the primary site, ipsilateral hilum and mediastinum. The PET results were then correlated with surgical pathology at the time of resection. Measures, including accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), were determined. PET findings were scored as positive, suspicious or negative based solely on the original radiology report, and suspicious findings were ultimately considered positive as there would be a tendency to treat those regions of suspicion. A secondary radiology review of the original PET films was not conducted by the investigators, as it was decided to reflect utilization of PET reports and films in a typical radiation oncology clinic. PET studies were performed at both academic (30%) and community (70%) centers, and patients did not undergo combined PET/CT studies.

Statistical analysis. The χ^2 (24) and Fisher's exact (24) tests were employed to test for associations of PET accuracy with clinical and surgical factors. All tests were two-sided, and statistical significance was defined as $p \leq 0.05$. Concordance between clinical staging and pathologic staging was determined via a weighted Kappa statistic (24). Statistical analyses were performed with Statistical Package for Social Sciences statistical software (version 11.5 for Windows; SPSS Inc., Chicago, IL, USA) and StatXact statistical software (version 5.0 for Windows; Cytel Software Corporation, Cambridge, MA, USA).

Results

The characteristics of the patients included in the study are summarized in Table I. The median patient age was 68 years (range 35-86), and most presented with early clinical stage disease (63% stage I and 14% stage II). Similar numbers of males and females were included, and the majority of patients were Caucasian (90%).

A diagram demonstrating the pathologic evaluation of the study patients is listed in Fig. 1. Nearly all patients underwent definitive surgical resection (91%), with the remainder undergoing mediastinal sampling alone. The characteristics of the patients who underwent definitive resection are summarized in Table II. The median time between pre-operative PET and definitive resection was 41 days (range 2-333), and a majority of patients underwent lobectomy (77%). Most tumors were either adenocarcinoma (45%) or squamous cell carcinoma (30%), and 92% of resected primary tumors were >1 cm on pathologic measurement. Pre-operative clinical measurement of tumor diameter could not be documented, as primary tumor size was not always noted on the original radiology report.

The accuracy and prediction measures for the study patients with respect to PET imaging are shown in Table III. The accuracy of PET imaging was relatively high at the primary site (95%), ipsilateral hilum (80%) and mediastinum (84%). Although the specificity of the hilum (84%) and mediastinum (95%) was likewise high, the sensitivity with regard to both was lower than the primary site (50 and 49%, respectively, vs. 95%). The specificity of the primary site was not evaluated, as all patients had pathologic evidence of

Table I. Baseline clinical factors of all study patients (n=257).

Clinical factor	No.	%
Gender		
Male	131	51
Female	126	49
Age (years)		
≤65	105	41
>65	152	59
Median (range)	68 (35-86)	
Race		
Caucasian	232	90
Non-caucasian	21	8
Unknown	4	2
Clinical T stage		
T0	3	1
T1	154	60
T2	78	30
T3	3	1
T4	19	7
Clinical N stage		
N0	182	71
N1	34	13
N2	33	13
N3	8	3
Clinical stage		
IA	118	46
IB	43	17
IIA	17	7
IIB	17	7
IIIA	24	9
IIIB	22	9
IV	16	6
Primary tumor location		
Left lung	104	40
Right lung	146	57
Not applicable/unknown	7	3

disease at the primary site. The negative prediction measures of the ipsilateral hilum (92%) and mediastinum (86%) were again high, but, as with sensitivity, the positive prediction measures of the ipsilateral hilum and mediastinum were lower (31 and 75%, respectively). The PPV and NPV of the primary site were not calculated, as all patients had pathologic evidence of disease at the primary site.

Additionally, association tests were performed between PET accuracy and various clinical and pathologic factors. A comparison of PET accuracy with respect to bronchoalveolar tumors is shown in Table IV. There was decreased PET accuracy for bronchoalveolar primary tumors vs. other histologies (86 vs. 96%, $p=0.02$), but no difference was noted with regards to accuracy within the ipsilateral hilum (85 vs. 79%, $p=0.64$) or mediastinum (94 vs. 85%, $p=0.27$).

PET accuracy within the ipsilateral hilum and mediastinum in patients in whom PET accurately evaluated the primary tumor was compared to those in whom the primary

Table II. Characteristics of definitive resection patients (n=233).

	No.	%
Time from CT/PET to surgery (days)		
≤30	95	41
>30	138	59
Median (range)	41 (2-333)	
Surgical procedure		
Pneumonectomy	9	4
Bilobectomy	7	3
Lobectomy	180	77
Wedge resection	30	13
Other	7	3
Pathologic primary tumor size (cm)		
≤1	19	8
>1	214	92
Median (range)	2.5 (0.5-13.5)	
Histology		
Squamous	70	30
Adenocarcinoma	105	45
Large cell	9	4
Bronchoalveolar	36	16
Poorly differentiated	12	5
Non-small cell	1	<1

tumor was inaccurately evaluated. No difference was found in accuracy at either site. In the ipsilateral hilum, PET was accurate in 79% of patients with accurate PET at the primary site vs. 100% in those with false negative PET of the primary site ($p=0.36$). In the mediastinum, PET was accurate in 86% of patients with accurate PET at the primary site vs. 100% in those with false negative PET of the primary site ($p=0.61$).

PET accuracy at the primary site was decreased in primary tumors ≤1 cm on pathologic evaluation vs. those >1 cm (78 vs. 96%, $p=0.01$), and there was no difference in PET accuracy at either the primary site (93 vs. 96%, $p=0.44$), ipsilateral hilum (75 vs. 81%, $p=0.44$) or mediastinum (82 vs. 85%, $p=0.73$) when comparing studies interpreted at academic centers ($n=42$) vs. those interpreted at community facilities ($n=215$).

Table V depicts concordance between clinical and pathologic staging of patients in the study. Thirty-five percent of patients were upstaged at surgery, 51% had no change in stage at surgery and 14% were downstaged at surgery. A weighted Kappa analysis demonstrated statistical concordance between clinical and pathologic staging ($p<0.0001$).

Discussion

Radiation treatment planning for lung cancer has evolved with the introduction of new diagnostic and imaging modalities and with increasing capacity for delivering conformal radiotherapy. Traditional radiation portals typically included the mediastinum and ipsilateral hilum electively, in addition to the primary tumor. Newer techniques omit elective coverage of the entire mediastinum and ipsilateral hilum, treating instead an 'involved field', which limits the treatment portals to only

Table III. Accuracy and prediction measures of PET findings vs. pathology findings.

A, Correlation of PET to pathology findings by subsite.				
	Pathology finding		Total	
	+	-		
Primary				
PET finding				
+	219	0	219	
-	12	0	12	
Total	231	0	231	
Hilum				
PET finding				
+	13	29	42	
-	13	155	168	
Total	26	184	210	
Mediastinum				
PET finding				
+	27	9	36	
-	28	172	200	
Total	55	181	236	
B, Accuracy of PET by subsite.				
Site	PET accuracy measure	No. with finding	Total no.	%
Primary (n=231)				
	Sensitivity	219	231	94.8
	Specificity	0	0	NE ^a
	Overall accuracy	219	231	94.8
Hilum (n=210)				
	Sensitivity	13	26	50.0
	Specificity	155	184	84.2
	Overall accuracy	168	210	80.0
Mediastinum (n=236)				
	Sensitivity	27	55	49.1
	Specificity	172	181	95.0
	Overall accuracy	199	236	84.3
C, Predictive value of PET by subsite.				
Site	PET prediction measure	No. with finding	Total no.	%
Primary (n=231)				
	PPV	219	219	NE ^a
	NPV	0	12	NE ^b
Hilum (n=210)				
	PPV	13	42	31.0
	NPV	155	168	92.3
Mediastinum (n=236)				
	PPV	27	36	75.0
	NPV	172	200	86.0

^aAll cases were positive; ^bNo cases were negative. NE, not evaluated.

the primary tumor and nodal areas deemed to be positive on pre-treatment staging and evaluation. Single institution studies of involved field radiation suggest that elective nodal failures are rare, occurring in approximately 6% of patients (25,26); this may lead to the underestimation of the true incidence of elective nodal relapse, as isolated nodal relapses are rare and nodal relapses in the setting of hematogenous metastases are typically excluded. A phase III randomized trial of 200 patients (in whom staging did not include PET) comparing elective nodal radiation and involved field radiation demonstrated no difference in overall survival between the groups at 5 years (27). However, a potential limitation of involved field radiation is in the accuracy of staging and diagnostic studies to detect pathologic disease. PET is a modality which might provide such enhanced target delineation. While the role of PET or PET/CT in addition to conventional workup to prevent unnecessary surgery has been previously studied in randomized trials (28-30), the role of PET in radiation field design is an equally relevant, yet less examined, issue. This study sought to evaluate PET imaging by region of interest as it applies to radiation treatment planning in NSCLC.

To our knowledge, the present study constitutes one of the largest published series comparing PET to surgical pathologic data. We analyzed PET accuracy at several distinct sites relevant for radiation treatment planning: primary tumor, ipsilateral hilum and mediastinum. We found a relatively high overall accuracy of PET with regard to staging of the primary site (95%), ipsilateral hilum (80%) and mediastinum (84%), which is similar to other published series investigating PET-based staging and higher than the accuracy rates obtained with CT staging (17,18,20,21). Even with bronchoalveolar tumors, where PET demonstrated decreased accuracy and instances where the primary site was inaccurately evaluated, PET retained a high accuracy in the ipsilateral hilum and mediastinum. This supports the use of PET in combination with other imaging and staging modalities as a potentially important tool for radiation field design.

The specificity and negative predictive values associated with PET evaluation of nodal regions from our study were relatively high. These findings could be utilized in deciding to treat with involved field radiation techniques, excluding large, elective treatment volumes in selected cases. Conversely, the sensitivity and positive predictive values noted in our study were relatively low; however, these results should be interpreted with caution and may simply reflect the smaller numbers of patients with positive hilar and mediastinal disease, as the majority had early stage disease.

It is important to note that clinical and pathologic stage were in agreement only half of the time, with 35% of patients being upstaged at the time of surgery. Previous studies have reported a level of agreement between 35 and 55% for clinical and pathologic staging (31-35), with deterioration in agreement as stage increases (31). Subclinical, microscopic disease, not visualized on CT or PET, often accounts for this upstaging. Nomori *et al.* (16), in a study of 80 patients comparing pre-operative PET and CT vs. surgical pathology, found that PET was unable to distinguish foci of disease less than 4 mm and that 32% of all resected lymph nodes with disease involvement had foci of disease less than 4 mm. The presence of subclinical disease involvement illustrates the limitations of clinical

Table IV. PET overall accuracy for bronchoalveolar tumors vs. other histologies.

Site	Brochoalveolar		Other histologies		P-value
	Pathology		Pathology		
	+	-	+	-	
Primary					
PET ⁺	31	0	188	0	
PET ⁻	5	0	7	0	
Accuracy	31/36 (86%)		188/195 (96%)		0.02
Hilum					
PET ⁺	0	4	13	25	
PET ⁻	1	28	12	127	
Accuracy	28/33 (85%)		140/177 (79%)		0.64
Mediastinum					
PET ⁺	0	1	12	8	
PET ⁻	1	30	19	142	
Accuracy	30/32 (94%)		154/181 (85%)		0.27

Table V. Concordance between clinical and pathologic staging.

A, Comparison between clinical and pathologic stage.

Clinical stage	Pathologic stage					
	IA (n=67)	IB (n=57)	IIA + IB (n=34)	IIIA (n=27)	IIIB (n=18)	IV (n=12)
IA (n=108)	56	19	15	3	9	6
IB (n=42)	2	26	5	6	3	0
IIA + IIB (n=31)	5	7	12	7	0	0
IIIA (n=13)	0	3	0	7	1	2
IIIB (n=13)	3	1	2	3	4	0
IV (n=8)	1	1	0	1	1	4

B, Change in staging based on operative findings.

Pathologic vs. clinical staging	No.	%
↑ Stage Pathologic stage > clinical stage (to the right of the bold area)	76	35
= Stage Pathologic stage = clinical stage (bold area)	109	51
↓ Stage Pathologic stage < clinical stage (below bold area)	30	14

Weighted Kappa = 0.36 (95% CI 0.21-0.50); p<0.0001.

staging in NSCLC, especially in those treated with definitive radiation therapy. The use of involved field radiation, with target delineation based on PET and CT alone, could therefore potentially lead to erroneous underdosing or non-treatment of microscopic disease foci. Incorporation of pathologic assessment of lymph nodes, via mediastinoscopy or endobronchial ultrasound, in addition to conventional staging with imaging

and PET, may improve the overall accuracy of staging and further assist in radiation treatment planning.

There are strengths and limitations to the present study. More than three-quarters of the patients had clinical stage I or II disease, which may account for the lower than expected sensitivity and PPV for PET detection of lymph node involvement. Further evaluation of PET accuracy in more advanced

stage patients is warranted, as this would better reflect the typical lung cancer patient referred for definitive radiation therapy. Additionally, this study focused specifically on the role of PET alone, whereas PET/CT is now more commonly used for staging. Despite these limitations, our results constitute one of the largest collected series on PET staging, and the study presented here is one of the few examining accuracy by specific disease subsites. In addition, our findings that there was no compromise in accuracy of lymph node staging, even with bronchoalveolar histology or when PET inaccurately staged the primary site, are novel to our knowledge.

In conclusion, PET is a useful tool in the clinical assessment and staging of lung cancer, and should be incorporated as part of standard staging. With respect to radiation treatment planning, it is helpful in delineating disease-affected sites and in determining which areas to incorporate and which to exclude in the radiation portals. However, given the rates of upstaging observed between clinical and pathologic staging and the risk of subclinical disease involvement, caution must be exercised during the delineation of limited fields, and pathologic assessment of nodes should be performed whenever possible. Lung cancer remains one of the most common causes of cancer-related death in both men and women, and local failure is a common occurrence. Refinements in target delineation, radiation planning and delivery are potential avenues by which outcomes may be improved, which will ultimately require the incorporation of multimodal staging evaluations, including PET.

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