Positron Emission Tomography-Computed Tomography Compared with Invasive Mediastinal Staging in Non-small Cell Lung Cancer

Results of Mediastinal Staging in the Early Lung Positron Emission Tomography Trial

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Introduction: Patients with non-small cell lung cancer (NSCLC) require careful preoperative staging to define resectability for potential cure. [18]Fluorodeoxyglucose positron emission tomography combined with computed tomography ([18]FDG PET-CT) is widely used to stage NSCLC. If the mediastinum is positive on PET-CT examination, some practitioners conclude that the patient is inoperable and refer the patient for nonsurgical treatment.

Methods: In this analysis of a previously reported trial comparing PET-CT with conventional imaging in the diagnostic work-up of patients with clinical stage I, II, or IIIA NSCLC, we determined the accuracy of PET-CT in mediastinal staging compared with invasive mediastinal staging either by mediastinoscopy alone or by mediastinoscopy combined with thoracotomy.

Results: All 149 patients had mediastinal nodal staging at mediastinoscopy alone (14), thoracotomy alone (64), or both (71). The sensitivity of PET-CT was 70% (95% confidence interval [CI], 48–85%), and specificity was 94% (95% CI, 88–97%). Of 22 patients with a PET-CT interpreted as positive for mediastinal nodes, 8 did not have tumor. The positive predictive value and negative predictive value were 64% (95% CI, 43–80%) and 95% (95% CI, 90–98%), respectively. Based on PET-CT alone, eight patients would have been denied potentially curative surgery if the mediastinal abnormalities detected by PET-CT had not been evaluated with an invasive mediastinal procedure.

Conclusions: PET-CT assessment of the mediastinum is associated with a clinically relevant false-positive result. Our study confirms the need for pathologic confirmation of mediastinal lymph node abnormalities detected by PET-CT.

Key Words: Non-small cell lung cancer, Mediastinum, PET-CT, Staging

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Lung cancer is the leading cause of cancer-related mortality in North America. It was estimated that in 2010, approximately 157,300 persons died of this disease in the United States,[1] with the corresponding number in Canada being 20,600.[2] Non-small cell lung cancer (NSCLC) makes up 80% of all lung cancers. Unfortunately, only 25% of patients will have resectable disease at presentation. Of those with stage I and II disease, 20 and 40%, respectively, will ultimately relapse with metastatic disease that was occult at the time of presentation.[3] These statistics underscore the need for both more precise staging and more effective stage-specific therapies.

In the absence of distant metastatic disease, the status of the mediastinal lymph nodes determines the therapeutic approach in NSCLC. Patients without mediastinal lymph node involvement are considered candidates for potentially curative surgical resection. In contrast, those with tumor in the mediastinal lymph nodes are not candidates for primary surgery and are offered other forms of therapy depending on performance status and other clinical factors.[4,5]

Mediastinal staging includes both noninvasive techniques such as computed tomography (CT), and invasive methods such as mediastinoscopy, endobronchial ultrasound with transbronchial needle aspiration, and endoscopic ultrasound fine needle aspiration. Although CT provides anatomic information, it has poor sensitivity (approximately 50%) and

specificity (approximately 85%) for detecting mediastinal tumor.[6] Mediastinoscopy, which has been considered the reference standard for staging mediastinal lymph nodes, has a false-negative rate (i.e. 1-negative predictive value [NPV]) of approximately 10%.[7]

[18]Fluorodeoxyglucose positron emission tomography (PET) is a functional imaging modality that can potentially detect tumor activity in nonenlarged structures and allow earlier detection of metastatic disease.[8] Based on a number of trials, PET-CT is now widely used for the staging of NSCLC[9–13] and offers some advantage over CT alone in assessing the mediastinal nodes.[14]

The purpose of the current study was to determine the accuracy of PET-CT in staging the mediastinum compared with pathological staging based on observations made during a previously reported randomized trial of conventional staging versus PET-based staging.[13] Pathological staging was determined surgically with mediastinoscopy, node sampling at thoracotomy, or both.

PATIENTS AND METHODS

Population

The Early Lung PET trial (ELPET) randomized patients who had a chest CT scan and proven NSCLC to conventional staging with bone scan, CT abdomen and brain imaging, or PET-CT and brain imaging. Those patients who were randomized to the PET-CT arm of the trial are the subjects of this study. Details of the trial design and procedures have been published previously.[13] Eligible patients had histologically or cytologically proven NSCLC; clinical stage I, II, or IIIA disease based on CT chest; and were considered candidates for surgical resection. Staging was based on the 6th edition of the American Joint Committee on Cancer (AJCC)/Union Internationale Contre le Cancer (UICC) Tumor, Node, Metastasis Staging Manual. Consenting patients from four academic metropolitan tertiary centers and four community hospitals in Ontario, Canada, were enrolled into ELPET between 2004 and 2007.

This study was supported through grants from the Ontario Ministry of Health and Long-Term Care and the Canadian Institutes of Health Research and was coordinated by the Ontario Clinical Oncology Group. The study protocol was approved by the local Institutional Review Board at each clinical center.

Imaging

All patients had a CT scan of the chest before study entry. Patients who were randomized to PET staging underwent whole body [18]fluorodeoxyglucose PET-CT and cranial imaging using either CT or magnetic resonance imaging. Details of imaging procedures have been published previously.[13]

Interpretation of all PET-CT images occurred at the locations where the PET study was done. A 5-point ordinal scale was used to record the interpreter's degree of suspicion for an abnormality. This scale consisted of the following categories: 0, normal; 1, probably normal; 2, equivocal; 3, probably abnormal; and 4, definitely abnormal.[15] The stan-

dardized uptake value was determined and was used to aid in grading the identified abnormalities. A specific cutoff uptake value for the determination of the presence or absence of cancer was not provided to readers of the scans. If the PET-CT or CT suggested the presence of metastatic disease, confirmation by biopsy or further diagnostic imaging modalities was required.

Invasive Mediastinal Staging

In patients whose PET-CT was negative for mediastinal disease, surgeons had the option of performing cervical mediastinoscopy, anterior mediastinotomy, or both, or proceeding directly to thoracotomy. If mediastinoscopy was performed, it was recommended that stations 2 R/L, 4 R/L, and 7 should be explored and nodes sampled if present.

Because of the 10% false-negative rate (1-NPV) for mediastinoscopy, all patients were required by protocol to have detailed lymph node sampling at thoracotomy even if they had mediastinal node sampling by mediastinoscopy.[7] On the right side, this consisted of removing one or two lymph nodes, if present, from each of the following lymph node stations: 2R (upper paratracheal), 4R (lower paratracheal), 7 (subcarinal), and 10R (tracheobronchial angle). For left-sided tumors, sampling consisted of removing one or two lymph nodes from each of station 2L (upper paratracheal), 4L (lower paratracheal), station 5 (aortopulmonary window), 6 (para-aortic anterior mediastinal), 7 (subcarinal), and 10L (tracheobronchial angle), if present. Any other suspicious nodes were sampled. However, all protocol-specified lymph node stations sampled at mediastinoscopy were resampled at thoracotomy.

If a CT of the chest or the PET-CT demonstrated suspicious mediastinal adenopathy based on either size criteria (>1 cm) or increased uptake on PET-CT, mediastinoscopy was required before proceeding to thoracotomy. Patients with proven N2- or N3-positive stage IIIA/B disease on mediastinoscopy were declined thoracotomy and received stage-appropriate therapy. If mediastinoscopy was negative, patients underwent thoracotomy and resampling of mediastinal nodes as per the protocol outlined above.

Surgery

Anatomic lobectomy or pneumonectomy was performed for stage I and II disease, as appropriate, by a posterolateral thoracotomy or video-assisted thoracotomy. Patients with stage IIIA disease were resected after neoadjuvant therapy if deemed resectable by the treating surgeon. Adjuvant therapy (stage II or IIIA) was permitted.

Study Outcomes

The primary goal of this study was the estimation of the diagnostic accuracy parameters: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PET-CT in staging the mediastinum in comparison with the reference standard of pathology by surgical staging with node sampling by mediastinoscopy or thoracotomy or both (in this case, the worst result was used). A secondary outcome was the estimation of test characteristics of PET-CT in comparison with pathologic staging by mediastinoscopy only as the reference standard.

Statistical Considerations

For the purpose of the primary analysis, it was decided a priori to distinguish between N0/N1 and N2/N3 nodes, as the former group would be candidates for surgical management, whereas the latter group would generally not be managed surgically.[5]

The gold standard for the calculation of the test characteristics (sensitivity, specificity, PPV, and NPV) was the presence (or absence) of tumor in lymph nodes sampled at mediastinoscopy and/or thoracotomy. The confidence intervals (CIs) for the estimates of the diagnostic accuracy parameters were obtained using the Wilson Score method for single proportions.

RESULTS

Between June 2004 and August 2007, 589 patients were assessed for eligibility, of whom 380 met the eligibility criteria of the study and were approached for consent. Of these, 337 agreed to participate and 170 were randomized to the PET-CT arm. One subject refused study investigations after randomization and was, therefore, excluded.

Of the 114 patients with a negative PET-CT, 58 (51%) had a mediastinoscopy attempted. This compares to 27 (77%) of 35 patients with a positive PET-CT, $p = 0.006$.

Mediastinoscopy was performed in 85 patients in the PET-CT arm (and in one of these patients, nodal sampling was unsuccessful because of the presence of calcified plaque in the innominate artery). In 12 patients, mediastinoscopy was positive for N2 or N3 disease. The remaining 73 patients went on to thoracotomy with nodal sampling. However, two patients did not undergo nodal sampling at thoracotomy. Of the 84 patients who did not have mediastinoscopy, 19 did not undergo thoracotomy: 17 upstaged with metastases, one with rectal cancer detected by PET, and one who refused invasive treatment. Sixty-five patients had thoracotomy, and one of them did not have node sampling because the tumor was unresectable at thoracotomy. In total, 149 patients had mediastinal node sampling at mediastinoscopy or thoracotomy or both (Figure 1). The baseline characteristics of the population that underwent mediastinal nodal sampling either at mediastinoscopy or thoracotomy are presented in Table 1.
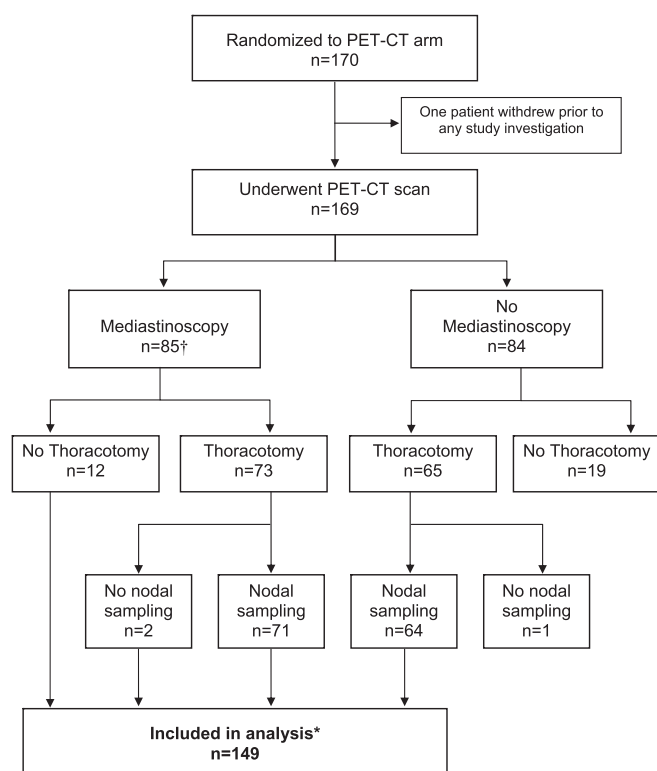
Using mediastinoscopy and/or thoracotomy as the reference standard, PET-CT detected disease in 14 of 20 patients with pathologically proven N2/N3 disease. The scan was negative in 121 of 129 patients who did not have N2/N3 disease on pathology (Table 2). Hence, the sensitivity of PET-CT was 70% (95% CI, 48–85%) and specificity was 94% (95% CI, 88–97%). Of the 22 patients with a positive

† One subject had unsuccessful nodal sampling at mediastinoscopy

* Subjects with nodal sampling at mediastinoscopy, thoracotomy or both

FIGURE 1. Study flow diagram. PET-CT, positron emission tomography combined with computed tomography.

TABLE 1. Baseline Characteristics of Analyzable PET-CT Patients

Characteristic	PET-CT, $n = 149$
Age (yr), median (minimum to maximum)	67 (41–86)
Gender, n (%)	
Female	73 (49)
Male	76 (51)
Smoking, n (%)	
Never	9 (6)
Ex-smoker	99 (66)
Current smoker	41 (28)
ECOG performance status, n (%)	
0	91 (61)
1	55 (37)
2	3 (2)
Primary tumor size (cm), median (minimum to maximum)	3.1 (0.8–8.7)
Tumor location—right, n (%)	90 (60)
Clinical stage, n (%)	
IA	78 (52)
IB	41 (28)
IIA	5 (3)
IIB	11 (7)
IIIA[a]	14 (9)
Histological/cytological diagnosis, n (%)	
Adenocarcinoma	64 (43)
Squamous	24 (16)
Large cell	5 (3)
NSCLC	53 (36)
Suspicious for NSCLC	3 (2)

[a] Includes one IIIB patient who was $T_4N_0M_0$ at baseline but assessed as resectable.

PET-CT, positron emission tomography and computed tomography; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

TABLE 2. Comparison of PET-CT and the Composite Reference Standard

| PET-CT | Composite Reference Standard Mediastinoscopy and Thoracotomy | | | | |
	N0	N1	N2	N3	Total
N0	101	11	2	0	114
N1	1	8	4	0	13
N2	7	0	10	1	18
N3	1	0	2	1	4
Total	110	19	18	2	149
	N0 + N1		N2 + N3		
N0 + N1	121		6		127
N2 + N3	8		14		22
Total	129		20		149

PET-CT, positron emission tomography and computed tomography; N, node.

PET-CT in N2 and N3 nodes, 8 did not have tumor in mediastinal nodes on invasive staging. Of the four patients whose PET-CT was positive in N3 nodes, only one was positive on invasive staging. The PPV and NPV were 64% (95% CI, 43–80%) and 95% (95% CI, 90–98%), respectively (Table 3). In the eight patients with a false-positive PET-CT result, no underlying conditions (e.g., granulomatous disease, active infection, or inflammation) were identified. Furthermore, although pathology reported associated findings in the lymph nodes of four patients (e.g., anthracosis, histiocytosis, adhesions, and lymphoid hyperplasia), no consistent patterns were identifiable to explain the false-positivity.

Separate analysis by clinical stage determined by CT scan (clinical stages IA and IB versus IIA, IIB, and IIIA) was performed (Table 3). The sensitivity and PPV for clinical stages II and IIIA were larger than they were for stage I, whereas the specificity and NPV were lower for the higher stages. Similarly, separate analysis by clinical nodal stage determined by CT scan is listed in Table 4.

At mediastinoscopy, the four most common nodal stations biopsied were 2R, 4R, 4L, and 7. The corresponding proportions of patients who had these stations biopsied were 47.6, 86.9, 56.0, and 77.4%. Using only mediastinoscopy as the reference standard, 12 patients were noted to have N2 or N3 disease, and all of these were found to be positive by PET-CT. However, of the 21 patients identified as having N2 or N3 disease by PET-CT, 9 patients were determined to be N0 by mediastinoscopy (Table 5). The accuracy estimates for the comparison of PET-CT versus mediastinoscopy alone

were sensitivity 100% (95% CI, 76–100%); specificity 88% (95% CI, 78–93%); PPV 57% (95% CI, 37–76%); and NPV 100% (95% CI, 94–100%).

DISCUSSION

The determination of mediastinal lymph node status is an essential part of staging NSCLC. Medically fit patients will be offered potentially curative surgery if mediastinal nodes are not involved. If mediastinal lymph nodes are involved by tumor, primary surgery is not recommended and such patients are commonly treated with radiation therapy with or without chemotherapy or supportive care alone, depending on performance status and other clinical factors. In highly selected patients with N2 disease, surgery may be part of multimodality therapy. Imaging with PET-CT is now widely used for the staging of NSCLC.[12,13,16]

In our study, the sensitivity and PPV of PET-CT when compared with the composite reference standard of mediastinoscopy and thoracotomy were 70 and 64%, respectively. These results highlight the issue of false-negative test results, which may result from a small volume of metastatic disease being present or relatively low metabolic activity or both. A wide range of sensitivities for PET-CT have been reported in the literature.[17–22] There are limitations in comparing sensitivities and other accuracy parameters between studies because the studies may differ in the prevalence of malignancies, size of nodes, tumor histology, study size, and standardized uptake value used.[17–22]

In our study, the specificity and NPV of PET-CT were over 90%, which is similar to results reported by others.[18,19] In the group that tested positive with PET-CT, the percentage of false-positives (i.e., 1-PPV) was 36%. The corresponding data for the studies reported by Lee,[19] Hwangbo,[17] and Sanli[18] were 44, 62, and 44 %, respectively. Conditions such as granulomatous inflammation may cause enlarged nodes. The prevalence of tuberculosis, or histoplasmosis may increase the rate of false-positive PET-CT. However, we were unable to explain the false-positive imaging in our patients.

In our study, we did not assess the size of the nodes. In other studies in NSCLC, centrally located tumors have been found to be significantly associated with occult N2 disease. We did not assess the location of tumors. Our evaluation of the diagnostic accuracy of PET-CT by lymph node station was limited by the small number of nodes examined by station (data not reported).

TABLE 3. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value by Clinical Stage at Baseline

| Clinical Stage | Sensitivity (%) | | Specificity (%) | | PPV (%) | | NPV (%) | |
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
IA, IB	57 (4/7)	25–84	96 (108/112)	91–99	50 (4/8)	22–78	97 (108/111)	92–99
IIA, IIB, IIIA[a]	77 (10/13)	50–92	76 (13/17)	53–90	71 (10/14)	45–88	81 (13/16)	57–93
All subjects	70 (14/20)	48–85	94 (121/129)	88–97	64 (14/22)	43–80	95 (121/127)	90–98

[a] Includes one IIIB patient who was $T_4N_0M_0$ at baseline but assessed as resectable.
PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

TABLE 4. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value by Nodal Stage at Baseline

Nodal Stage	Sensitivity %		Specificity %		PPV %		NPV %	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
N0	63 (5/8)	31–86	96 (111/116)	90–98	50 (5/10)	24–76	97 (111/114)	93–99
N1	67 (4/6)	30–90	88 (7/8)	53–98	80 (4/5)	38–96	78 (7/9)	45–94
N2	83 (5/6)	44–97	60 (3/5)	23–88	71 (5/7)	36–92	75 (3/4)	30–95
All subjects	70 (14/20)	48–85	94 (121/129)	88–97	64 (14/22)	43–80	95 (121/127)	90–98

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; N, node.

TABLE 5. Nodal Staging by PET-CT and Mediastinoscopy

	Reference Standard Mediastinoscopy Alone				
PET-CT	N0	N1	N2	N3	Total
N0	57	0	0	0	57
N1	6	0	0	0	6
N2	9	0	8	1	18
N3	0	0	2	1	3
Total	72	0	10	2	84
	N0 + N1		N2 + N3		
N0 + N1	63		0		63
N2 + N3	9		12		21
Total	72		12		84

PET-CT, positron emission tomography and computed tomography; N, node.

Although mediastinoscopy improves the accuracy of preresection staging,[23] it is invasive, requires general anesthesia, and may be falsely negative.[7] We chose to compare PET-CT with mediastinoscopy because some surgeons do not resample mediastinal nodes at the time of thoracotomy if a previous mediastinoscopy has been performed. Mediastinoscopy does not detect N1 nodes in comparison with node sampling at thoracotomy. Although the estimate of sensitivity for PET-CT when compared with mediastinoscopy alone was 100% (95% CI, 76–100%), this likely represents an overestimate in light of the relatively small number of lymph nodes sampled and the prevalence of disease.

The current analysis is based on patients assessed prospectively in one arm of a randomized controlled trial. The relatively few participating PET-CT centers allowed for a high level of adherence to quality control measures, and all of the thoracic surgeons were experienced in the conduct of clinical trials. As the patient, rather than the lymph node, is the more clinically appropriate unit of analysis, we chose to use patient-level data as the unit of our analyses. An important strength of our study was that all but two patients who were candidates for surgery had mediastinal nodes sampled systematically at thoracotomy, whether or not they had been sampled previously by mediastinoscopy.

Although the size of the PET-CT arm was larger than three previous randomized controlled trials,[9,10,12] the sample size and the number of lymph nodes sampled per region were still relatively limited, especially when imaging was compared with mediastinoscopy. The high prevalence of clinical stage I disease at baseline (80%) within the PET-CT cohort is not typical of the usual stage distribution at diagnosis for NSCLC and could impact the generalizability of our results.[24]

In our study, PET-CT erroneously staged 29 of 149 patients. Of these, 14 could be considered as clinically relevant: 8 of 11 who were overstaged and 6 of the 18 patients who were understaged. Importantly, based on PET-CT alone, eight patients would have been denied potentially curative surgery. If the results of our study were to be extrapolated to the incidence and stage-specific prevalence data available through the SEER database, noninvasive staging by PET-CT alone could result in inaccurate staging in 12,844 of the NSCLC patients diagnosed in the United States in 2010.[1,3,24] Of these, incorrect staging would alter treatment in 6191 patients. Importantly, approximately 3500 patients in the United States and 385 patients in Canada would be denied potentially curative resection based on noninvasive staging with PET-CT this year alone.[2]

In conclusion, a positive PET in the mediastinum must be confirmed by biopsy in patients who are potentially operable. This is true regardless of the clinical stage by CT because, in our study, the false-positive rates (1-PPV) for PET were 50, 20, and 29% for cN0, cN1, and cN2 patients, respectively. A negative PET in the mediastinum is reliable for cN0 patients (false-negative rate [1-NPV] of 3%). However, a negative PET in the mediastinum must be confirmed by biopsy for cN1 and cN2 patients by CT as the false negative rates (1-NPV) of PET in our study were 22 and 25%, respectively.

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