Technology in Cancer Research & Treatment
2017, Vol. 16(1) 15–21

DOI: 10.1177/1533034615624045
journals.sagepub.com/home/tct
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# Limitations of PET/CT in the Detection of Occult N1 Metastasis in Clinical Stage I(T1-2aN0) Non-Small Cell Lung Cancer for Staging Prior to Stereotactic Body Radiotherapy

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## Abstract

**Purpose/Objectives:** Patients receiving stereotactic body radiotherapy for stage I non-small cell lung cancer are typically staged clinically with positron emission tomography–computed tomography. Currently, limited data exist for the detection of occult hilar/peribronchial (N1) disease. We hypothesize that positron emission tomography–computed tomography underestimates spread of cancer to N1 lymph nodes and that future stereotactic body radiotherapy patients may benefit from increased pathologic evaluation of N1 nodal stations in addition to N2 nodes. **Materials/Methods:** A retrospective study was performed of all patients with clinical stage I (T1-2aN0) non-small cell lung cancer (American Joint Committee on Cancer, 7th edition) by positron emission tomography–computed tomography at our institution from 2003 to 2011, with subsequent surgical resection and lymph node staging. Findings on positron emission tomography–computed tomography were compared to pathologic nodal involvement to determine the negative predictive value of positron emission tomography–computed tomography for the detection of N1 nodal disease. An analysis was conducted to identify predictors of occult spread. **Results:** A total of 105 patients with clinical stage I non-small cell lung cancer were included in this study, of which 8 (7.6%) patients were found to have occult N1 metastasis on pathologic review yielding a negative predictive value for N1 disease of 92.4%. No patients had occult mediastinal nodes. The negative predictive value for positron emission tomography–computed tomography in patients with clinical stage T1 versus T2 tumors was 72 (96%) of 75 versus 25 (83%) of 30, respectively ($P = .03$), and for peripheral versus central tumor location was 77 (98%) of 78 versus 20 (74%) of 27, respectively ($P = .0001$). The negative predictive values for peripheral T1 and T2 tumors were 98% and 100%, respectively; while for central T1 and T2 tumors, the rates were 85% and 64%, respectively. Occult lymph node involvement was not associated with primary tumor maximum standard uptake value, histology, grade, or interval between positron emission tomography–computed tomography and surgery. **Conclusion:** Our results support pathologic assessment of N1 lymph nodes in patients with stage Inon-small cell lung cancer considered for stereotactic body radiotherapy, with the greatest benefit in patients with central and T2 tumors. Diagnostic evaluation with endoscopic bronchial ultrasound should be considered in the evaluation of stereotactic body radiotherapy candidates.

## Keywords

positron emission tomography–computed tomography (PET/CT), negative predictive value (NPV), N1, clinical stage I, non-small cell lung cancer (NSCLC), stereotactic body radiotherapy (SBRT)

## Abbreviations

CT, computed tomography; EBUS, endobronchial ultrasound; N0, no regional lymph node metastasis; N1, metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension; N2,

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metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s); NSCLC, non-small cell lung cancer; PET/CT, positron emission tomography–computed tomography; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiotherapy; SUV, standard uptake value; NPV, negative predictive value

Received: September 07, 2015; Revised: November 04, 2015; Accepted: December 02, 2015.

## Introduction

Lung cancer is the leading cause of cancer mortality in the United States with 158, 000 deaths projected to occur during 2015.[1] Approximately 15% of patients present with stage I disease at the time of diagnosis, defined as tumor confined to the lung without any regional extension or lymph node metastasis.[1,2]

Standard treatment for patients with stage I non-small cell lung cancer (NSCLC) having normal cardiopulmonary function is surgical resection.[3,4] Patients with compromised cardiopulmonary reserve are considered ''high risk'' and may be considered for sublobar resection.[5]

A third group of stage I patients includes those who are medically inoperable due to comorbidities. Standard treatment for this population is stereotactic body radiotherapy (SBRT). This treatment modality delivers ablative doses of radiation to the tumor site with high conformality. Use of SBRT for high risk and operable candidates is more controversial. Randomized trials investigating its use in each setting have closed early due to poor accrual, however, a recent pooled analysis of two of these trials investigating SBRT in healthy operable candidates suggests SBRT may be better tolerated and confer improved survival when compared to surgery.[6]

Patients who undergo SBRT are usually staged clinically on the basis of positron emission tomography–computed tomography (PET/CT) findings.[7] Confirmatory staging of the mediastinum or hilum with invasive modalities such as mediastinoscopy and endobronchial ultrasound (EBUS) is not routinely performed in peripheral lung tumors with no suggestion of nodal involvement on imaging due to data focused on the detection of N2 (mediastinal) nodes reporting high sensitivity of imaging alone, relative low prevalence of occult N2 nodal disease in PET-negative patients, and low cost effectiveness.[8,9]

However, accurate exclusion of N1 (hilar) nodal disease is also important for patients undergoing SBRT since ablative radiation doses are directed only at the primary tumor, with no elective coverage of at-risk nodal regions. Although current SBRT series report low regional failure rates of approximately 10% or less, these failure rates may be offset by competing rates of intercurrent mortality in the medically inoperable population.[7,10-13] As investigations of SBRT are performed in high-risk and operable patients, the significance of occult nodal disease may be greater and further investigation of appropriate staging techniques is critical.[14,15] Currently, limited data exist on the role of PET/CT in specifically identifying isolated N1 disease for patients with clinically staged I NSCLC who would be considered for SBRT.

We hypothesized that the use of PET/CT underestimates the presence of N1 lymph node metastasis in patients determined to have clinical stage I NSCLC. The primary aim of this study was to report the negative predictive value (NPV) of PET/CT for N1 nodal metastasis. A secondary aim of this study was to identify predictors of occult nodal spread.

## Materials and Methods

A retrospective study was performed of all patients with clinical stage I NSCLC (cT1-2aN0M0) at the University of Chicago Medical Center from 2003 to 2011 with subsequent surgical resection. All patients received a dedicated CT and PET/CT within 3 months of surgical resection. Clinical tumor size was restricted to $\leq$5 cm in order to include only patients who would have met size criteria for SBRT as per the Radiation Therapy Oncology Group (RTOG) 0236 trial.[12] Clinical N0 disease was defined as mediastinal or hilar nodes measuring <1 cm in short-axis diameter on CT and demonstrating maximum standard uptake value ($SUV_{max}$) of <2.5 on PET/CT. Exclusion criteria included patients with scans identifying nodes as suspicious, indeterminate, or equivocal. In addition, patients who received imaging at outside institution were excluded in order to ensure standardization of imaging technique and availability of images for review. Select patients in this series received mediastinoscopy as part of the staging process, and no patients received EBUS. All patients underwent resection with hilar and mediastinal lymph node staging by a board-certified cardiothoracic surgeon. Pathology review was conducted at a multidisciplinary tumor oncology conference.

For the current analysis, demographic data were obtained including age, gender, race, and history of cancer. The PET/CT images and reports were reviewed for tumor size, location, $SUV_{max}$, and lymph node involvement. Tumors were considered central if located within 2 cm of the proximal bronchial tree (trachea, carina, and major lobar bronchi up to their first bifurcation).[12] Operative details analyzed included extent of resection and number and location of lymph nodes sampled. Pathology reports were assessed for tumor size, histology, grade, lymphovascular invasion, and margin status.

Findings on PET/CT were compared to findings at the time of surgery as the criterion standard to calculate NPV. Tumor characteristics for patients found to have occult disease were then reviewed including size, location, histology, grade, $SUV_{max}$, and time between PET/CT and surgery.

Descriptive statistics were generated in Microsoft Excel based on data collected from each patient. JMP 12 (SAS, Cary, North Carolina) statistical software was used to analyze the presence of occult lymph node involvement against T stage, tumor location, primary $SUV_{max} \geq$ versus < median, interval between PET/CT and surgery $\leq$ versus >4 weeks, tumor histology, and grade using the $\chi^2$ test. Statistical significance was set at $P < .05$. This study was approved by our institutional review board (protocol 16057A), and the need for patient consent was waived.

## Results

A total of 105 patients were analyzed in this study (Table 1). The median age at operation was 68 years (range: 43-87 years). Males represented 42% of the entire cohort. Race included 53% Caucasian, 45% African American, and 2% other. Twenty-two (21%) patients had a history of cancer, 4 of whom had previous primary lung cancers. Those with previous lung malignancies were determined to have a new primary cancer rather than recurrence by pathologic review and were therefore included in our study.

Clinical T-stage distribution included T1a (43%), T1b (28.5%), and T2a (28.5%). The median clinical tumor size was 2.2 cm (range: 0.4-5.0 cm). Tumors were central in location in 27 (26%) of the patients. The median time from PET/CT scan to operation was 4 weeks (range: 0.5-12 weeks). The $SUV_{max}$ of the primary tumor was reported in 79 (75%) patients, with a median value of 5.2 (range 0.7-33.6).

A total of 11 (10%) patients underwent mediastinoscopy before resection. Nodal stations sampled in these patients included level 4 (11 of the 11), level 5 (1 of the 11), and level 7 (7 of the 11). Over half (53%) of the patients underwent open thoracotomy versus video-assisted thoracoscopic surgery (47%). Extent of resection included lobectomy (94%), bilobectomy (4%), and wedge resection (2%). The median number of N1 nodes sampled was 5 (range: 1-19), and the median number of N2 nodes sampled was 5 (range: 1-27).

The mean pathologic tumor size was 2.62 cm (range: 0.5-8.0 cm; Table 2). Pathologic T-stage distribution was as follows: T1a (35%), T1b (12%), T2a (43%), T2b (6%), and T3 (4%). Histologies included adenocarcinoma (52%), squamous (33%), large cell (10%), and adenosquamous (5%). Tumor grade was as follows: grade 1 (13%), grade 2 (42%), grade 3 (39%), and not reported (6%). A total of 25 (24%) patients had lymphovascular invasion. Six (6%) patients had positive margins including 2 bronchial margins, 3 staple line/parenchymal margins, and 1 vascular margin.

A total of 8 (7.6%) of the 105 patients were found to have occult N1 metastasis on pathologic review (Table 3). No patients had occult mediastinal nodes. Based on these findings, the NPV of PET/CT for N1 disease among all clinical stage I patients was 92.4%. Five of the 8 patients with occult N1 disease had T2 tumors. The NPV in patients with clinically staged T1 versus T2 tumors was 72 (96%) of 75 versus 25 (83%) of 30, respectively ($P = .03$). The NPV of peripheral versus central tumor location was 77 of 78 (98%) versus 20 of 27 (74%), respectively ($P = .0001$). The NPV rates for the following groups were as follows: peripheral T1: (98%), peripheral T2 (100%), central T1 (85%), and central T2 (64%; Table 4). There was no association between occult lymph node involvement and the following clinical and pathologic features: primary tumors with $\geq$ versus < median $SUV_{max}$, time between PET/CT and surgery $\leq$ versus > 4 weeks, tumor histology, and tumor grade.

**Table 1.** Clinical Features of All Patients With Stage I NSCLC.[a]

| | |
|---|---|
| Patient Characteristics | |
| Age, years | |
| Median | 68 |
| Range | 43-87 |
| Gender | |
| Male | 44 (42%) |
| Female | 61 (58%) |
| Race | |
| Caucasian | 56 (53%) |
| African American | 47 (45%) |
| Other | 2 (2%) |
| Cancer history | |
| Present | 22 (21%) |
| NSCLC | 4 |
| Other | 18 |
| Absent | 83 (79%) |
| Imaging | |
| Clinical tumor size, cm | |
| Median | 2.2 |
| Range | 0.4-5.0 |
| Clinical T stage | |
| cT1a | 45 (43%) |
| cT1b | 30 (28.5%) |
| cT2a | 30 (28.5%) |
| $SUV_{max}$ (N = 79) | |
| Median | 5.2 |
| Range | 0.7-33.6 |
| Location | |
| Central | 27 (26%) |
| Peripheral | 78 (74%) |
| Operative details | |
| Preoperative mediastinoscopy | |
| Yes | 11 (10%) |
| No | 94 (90%) |
| Resection type | |
| Open | 56 (53%) |
| VATS | 49 (47%) |
| Lobectomy | 99 (94%) |
| Bilobectomy | 4 (4%) |
| Wedge | 2 (2%) |
| N1 lymph nodes sampled | |
| Median | 5 |
| Range | 1-19 |
| N2 lymph nodes sampled | |
| Median | 5 |
| Range | 1-25 |

Abbreviations: NSCLC, non-small cell lung cancer; SUV, standard uptake value; VATS, video-assisted thoracoscopic surgery.
[a]N = 105.

**Table 2.** Pathologic Features of All Patients With Stage I NSCLC.[a]

| Pathology | |
|---|---|
| Pathologic tumor size, cm | |
| Mean | 2.62 |
| Range | 0.5-8.0 |
| Pathologic T stage | |
| pT1a | 37 (35%) |
| pT1b | 13 (12%) |
| pT2a | 45 (43%) |
| pT2b | 6 (6%) |
| pT3 | 4 (4%) |
| Pathologic N stage | |
| pN0 | 97 (92%) |
| pN1 | 8 (8%) |
| pN2 | 0 |
| Histology | |
| Adenocarcinoma | 55 (52%) |
| Squamous | 35 (33%) |
| Large cell | 10 (10%) |
| Adenosquamous | 5 (5%) |
| Grade | |
| G1 | 14 (13%) |
| G2 | 44 (42%) |
| G3 | 41 (39%) |
| Not reported | (6%) |
| Lymphovascular invasion | |
| Present | 25 (24%) |
| Absent | 80 (76%) |
| Margin status | |
| Positive | 6 (6%) |
| Negative | 96 (91%) |
| Not reported | 3 (3%) |

Abbreviation: NSCLC, non-small cell lung cancer.
[a]N = 105.

## Discussion

Stereotactic body radiotherapy is considered a standard treatment for patients with medically inoperable stage I NSCLC having favorable outcomes including a 3-year local control, cause-specific survival, and overall survival rate of 90%, 75% to 80%, and 50% to 60%, respectively.[7,10-13] Clinical staging by PET/CT alone is routine in patients being considered for SBRT as opposed to the use of both imaging and confirmatory methods such as mediastinoscopy and EBUS for staging of the mediastinum and hilum, respectively.[7] This series identifies a subgroup of patients who harbor occult N1 nodal disease and would therefore receive suboptimal treatment if undergoing SBRT after clinical staging alone as opposed to further nodal evaluation.

Most prior investigations have focused on NPV rates of PET/CT for N2 (mediastinal) nodal disease since its presence distinguishes resectable disease from disease requiring combined modality treatment and report an NPV of 83% to 99%.[16-22] These investigations do not report NPV rates for N1 nodal disease or do not include only clinical stage I patients.

The purpose of our study was to determine the NPV of PET/CT for N1 nodal disease in patients with clinical stage I (cT1-2aN0) NSCLC. Our unique focus on the first echelon N1 nodal stations distinguishes this study from numerous prior studies focusing on isolated N2 or combined N1 and N2 nodal metastases. In this patient population, we report an occult N1 nodal rate of 8 (7.6%) of the 105 and PET/CT NPV of 92.4% for N1 nodal disease among all clinical stage I patients. This study identifies tumor size and central location to be predictors of occult N1 nodal metastasis with a NPV rates in clinically staged T1 versus T2 tumors of 96% and 83%, respectively ($P = 0.03$), and a NPV of peripheral versus central tumors to be 98% versus 74%, respectively ($P = .0001$). These findings are consistent with previous risk factors reported for overall occult nodal spread and specifically N2 nodal spread in patients with clinical N0 NSCLC.[23,24] A high $SUV_{max}$ was not associated with occult nodal metastasis in the current series, despite prior reports of this metric as a predictive feature.[23,25] There was also no association of occult spread with tumor histology or tumor grade. Overall, these findings suggest that patients with central and/or T2 tumors deserve greatest consideration of pathologic evaluation with hilar node sampling before undergoing treatment with SBRT.

Our findings are comparable to the limited amount of previous studies that investigate the NPV of N1 disease in patients with clinical stage I NSCLC. These studies were designed to look at overall (N1 and N2) rates of occult disease and report occult N1 rates of 9.5% to 27.2%.[21,23,26] The findings of this study are also in concordance with recent investigations, which investigate the incidence of occult N1 disease in the context of SBRT patient selection. The first of these studies reports an NPV of 86% for N1 disease but includes all patients with NSCLC who underwent surgical resection in the analysis including clinical N1 patients.[27] The second study reports an NPV of 90% for N1 disease in cT1-2aN0 patients and identifies tumor size, central tumor location, and age at surgery as predictors of occult spread.[28] These studies along with the current series demonstrate the growing interest in characterizing the risk of occult nodal disease in the context of SBRT patient selection.

An important clinical question is how to best implement diagnostic evaluation of the hilum in selected SBRT patients. There is a large need for minimally invasive pathologic sampling techniques given that SBRT is often performed in patients with several medical comorbidities. One technique with encouraging results includes EBUS with transbronchial needle aspiration. Although the technique is most commonly used to sample enlarged mediastinal nodes seen on imaging, investigation of hilar lymph node sampling in patients with enlarged (>1 cm) or PET-positive hilar nodes has reported a diagnostic sensitivity, specificity, and positive predictive value of 91%, 100%, and 92.4%, respectively.[29]

One group has specifically examined the role of EBUS for nodal staging in the SBRT population. This study included patients undergoing EBUS-directed fiducial marker placement and mediastinal lymph node sampling prior to Cyberknife.[30] In this study, 4 (8%) of 50 patients had negative CT and PET imaging but were found to have positive mediastinal and/or

**Table 3.** Tumor Characteristics of Patients With Occult N1 Node.[a]

| Patient | Clinical T Stage | Location | Histology | Grade | LVI | Margin Status | Location of Positive N1 Node(s) |
|---|---|---|---|---|---|---|---|
| 1 | 1b | C | Adeno | 3 | P | N | Peribronchial/hilar |
| 2 | 1b | PR | Adenosquamous | 2 | N | N | Peribronchial/hilar |
| 3 | 1b | C | Adenosquamous | NR | P | N | Peribronchial/hilar |
| 4 | 2a | C | Squamous | 2 | P | N | Peribronchial/hilar |
| 5 | 2a | C | Adeno | 2 | N | P | Peribronchial/hilar |
| 6 | 2a | C | Adeno | 2 | P | N | Perihilar and intraparenchymal |
| 7 | 2a | C | Adeno | 3 | P | N | Peribronchial/hilar |
| 8 | 2a | C | Squamous | 3 | N | N | Peribronchial/hilar |

Abbreviations: C, central; LVI, lymphovascular invasion; N, negative; NR, not reported; PR, peripheral; P, positive.
[a]N = 8.

**Table 4.** NPV of PET/CT for Occult N1 Disease by Clinical Stage and Location.

| Patient Group | NPV |
|---|---|
| T1 + peripheral | 61/62 (98%) |
| T1 + central | 11/13 (85%) |
| T2 + peripheral | 16/16 (100%) |
| T2 + central | 9/14 (64%) |

Abbreviations: NPV, negative predictive value; PET/CT, positron emission tomography–computed tomography.

hilar lymph nodes with EBUS-directed biopsies. All patients tolerated the procedure well with no reported cases of anesthesia-related complications, hospital readmissions, or pneumothoraces. The authors of this study supported consideration of EBUS for all patients with stage I NSCLC managed with SBRT in order to maximize detection of both occult mediastinal and hilar nodal disease. Furthermore, these findings suggest EBUS is well tolerated as a staging procedure in the medically inoperable population. A systematic review of the literature, although not limited to medically inoperable patients, further supports the safety of EBUS reporting no serious complications and minor complications consisting of agitation, cough, and blood at the puncture site.[31]

Before applying the work of previous investigators and the findings reported here to clinical practice, there are several limitations of our study worth noting including a limited sample size treated at a single institution. Furthermore, certain clinical and pathologic information was not available for select patients due to the retrospective nature of this study and incomplete previously recorded data. Despite these limitations, the authors of this study believe that the demonstrated rate of occult N1 nodal disease, particularly in patients with clinical T2 and/or central tumors, and the diagnostic efficacy of EBUS make a compelling argument for the routine use of EBUS in medically appropriate patients considered for SBRT.

Increased use of EBUS in this setting will ideally allow clinicians to identify subclinical disease, optimize treatment selection, and ultimately improve clinical outcomes. These goals are becoming increasingly relevant as SBRT is being considered for a healthier population including high-risk and operable candidates. These patients have less competing mortality risks and the potential to live longer. Focusing on appropriate staging techniques to accurately exclude nodal disease will provide additional benefit to this population.

## Conclusion

In conclusion, we report a PET/CT NPV rate for N1 disease in patients with clinical stage I NSCLC to be 92.4%. The NPV rates in patients with clinically-staged T1 and T2 tumors was 96% and 83%, respectively ($P = .03$), and the NPV of peripheral versus central tumor location was 98% versus 74%, respectively ($P = .0001$). Our findings suggest that patients with central and T2 tumors are at greatest risk for occult metastasis to N1 nodal stations. With these findings, we recommend that patients being considered for SBRT be increasingly considered for diagnostic staging with EBUS.

### Author's note

At the time of this research the author Wickii T. Vigneswaran was affiliated to Department of Surgery, The University of Chicago, Chicago, IL, USA and now the author is associated with Department of Thoracic and Cardiovascular Surgery, Loyola University Health System, Maywood, IL, USA.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This project was awarded the 2013 Carolyn L. Kuckein Student Research Fellowship by the Alpha Omega Alpha Honor Society.

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