# Improving the Inaccuracies of Clinical Staging of Patients with NSCLC: A Prospective Trial

Robert James Cerfolio, MD, FACS, Ayesha S. Bryant, MD, MSPH, Buddhiwardhan Ojha, MD, MPH, and Mohammad Eloubeidi, MD

Section of Thoracic Surgery, University of Alabama at Birmingham and Division of Cardiothoracic Surgery, Department of Surgery, Birmingham Veterans Administration Hospital, Department of Epidemiology, University of Alabama at Birmingham School of Public Health, Divisions of Nuclear Radiology and Gastroenterology, University of Alabama at Birmingham, Birmingham, Alabama

*Background.* **Clinical stage affects the care of patients with nonsmall cell lung cancer.**

*Methods.* **This is a prospective trial on patients with suspected resectable nonsmall cell lung cancer. All patients underwent integrated positron emission tomographic scanning and computed tomographic scanning, and all suspicious metastatic sites were investigated. A, T, N, and M status was assigned. If N2, N3 and M1 were negative, patients underwent thoracotomy and complete thoracic lymphadenectomy.**

*Results.* **There were 383 patients. The accuracy of clinical staging using positron emission tomographic scanning and computed tomographic scanning was 68% and 66% for stage I, 84% and 82% for stage II, 74% and 69% for stage III, and 93% and 92% for stage IV, respectively. N2 disease was discovered in 115 patients (30%) and was most common in the subcarinal lymph node (30%). Unsuspected N2 disease occurred in 28 patients (14%) and was most common in the posterior mediastinal lymph nodes (subcarinal, 38%; posterior aortopulmonary, 15%). It was found in 9% of patients who were clinically staged I (58% in the posterior mediastinal lymph nodes) and in 26% of patients clinically staged II (86% in posterior mediastinal lymph nodes).**

*Conclusions.* **Despite integrated positron emission tomographic scanning and computed tomographic scanning, clinical staging remains relatively inaccurate for patients with nonsmall cell lung cancer. Recent studies suggest adjuvant therapy for stage Ib and II nonsmall cell lung cancer; thus the impact on preoperative care is to find unsuspected N2 disease. Unsuspected N2 disease is most common in posterior mediastinal lymph nodes inaccessible by mediastinoscopy. Thus one should consider endoscopic ultrasound fine-needle aspiration, especially for patients clinically staged as I and II, even if the nodes are negative on positron emission tomographic scanning and computed tomographic scanning.**

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Lung cancer is responsible for more cancer deaths than the next three most common cancers combined. In particular, nonsmall cell lung cancer (NSCLC) accounts for approximately 75% to 85% of all newly diagnosed lung cancers [1]. Treatment of NSCLC depends on stage. The best tests for assessing the clinical stage are the computed tomographic (CT) scan and dedicated positron emission tomographic (PET) scan using 2-dexoy-2-18F–flouro-D-glucose (FDG-PET). These tests often detect suspicious areas of metastases that should be further investigated with other tests such as a bone scan, ultrasound, and magnetic resonance imaging. Procedures that biopsy these sites, such as mediastinoscopy, endoscopic ultrasound fine-needle aspiration (EUS-FNA) and ultrasound-guided biopsy of the liver are mandatory. However, despite all these sophisticated tests and even the use of integrated FDG-PET/CT scanning, which we have shown to be superior to dedicated FDG-PET scanning in the staging of patients with NSCLC [2], the pathologic stage often differs from the predicted clinical stage [2–5].

We decided to prospectively assess the accuracy of the predicted clinical stage and compare it with the actual pathologic stage; we also wanted to see at which stage it most commonly fails. We specifically addressed each separate lymph node station and assessed how many patients could have their care improved by having more accurate clinically staging. Until the ongoing studies that examine the use of neoadjuvant therapy for the early stages of NSCLC (ie, stages Ib and II) are completed, the current standard of care is to use surgical resection followed by adjuvant chemotherapy. Thus, for now it is only the discovery of unsuspected N2 or M1 disease that alters preoperative treatment. The EUS-FNA is a noninvasive procedure that affords biopsies of posterior mediastinal (N2) lymph nodes at locations 5, 7, 8, and 9 [6]. It is highly accurate in these nodal stations [7, 8]. We also evaluated the potential impact that the EUS-FNA would have if it had been performed on all patients prior to pulmonary resection.

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Address reprint requests to Dr Cerfolio, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, 1900 University Blvd, THT 712, Birmingham, AL 35294; e-mail: robert.cerfolio@ccc.uab.edu.


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## Patients and Methods

### *Patient Selection*

Patients who presented to one surgeon (RJC) between September 2002 and August 1, 2004 with an indeterminate pulmonary nodule or a biopsy proven NSCLC and underwent integrated FDG-PET/CT scanning at our institution and CT scanning were eligible to participate in this study. Patients were excluded if they were less than 19 years of age, had a history of type I diabetes, or received preoperative chemotherapy or radiation. All patients were clinically staged using the T, N, and M classification system [9]. A stage was given for each patient based on the FDG-PET/CT scan, which was read by a nuclear radiologist, and based on the CT scan, which as read by a chest radiologist.

### *Radiologic Imaging*

The FDG-PET/CT scans were performed on an integrated PET/CT scanner (GE Discovery LS PET/CT Scanner, Milwaukee, WI). Patients were asked to fast for 4 hours and then subsequently received 555 MBq (15mCi) of FDG intravenously followed by PET scanning after 1 hour. The scans were performed from the skull base to mid-thigh level. The computed tomography examination was used for attenuation correction of PET images. The scanning time for positron emission tomography was 5 minutes per bed position. Iterative reconstruction with CT attenuation correction was performed. The most recent CT scan of the chest was also available for visual correlation. Maximum standard uptake value (maxSUV) of the primary lymph node and of each suspicious lymph node station was determined by drawing regions of interest on the attenuation corrected FDG-PET/CT images around it. It was then calculated by the software contained within the PET or PET/CT scanner by the formula [10]:

$$\text{maxSUV} = \frac{\text{C}(\mu\text{Ci/mL})}{\frac{\text{ID}(\mu\text{Ci})}{\text{w(kg)}}}$$

in which C = activity at a pixel within the tissue defined by the regions of interest, and ID = injected dose per kg of patients body weight (w). The maximum standard uptake value (maxSUV) within the selected regions of interest was used exclusively throughout this study.

### *Procedures, Staging, and Surgery*

Patients were meticulously staged. All suspicious N2, N3, or M1 areas (maxSUV $>$ 2.5) were biopsied prior to pulmonary resection. Mediastinoscopy was used to biopsy suspicious lymph nodes in the paratracheal area (stations 2R, 4R, 2L, and 4L), and endoscopic transesophageal ultrasound was used to biopsy suspicious posterior aorta-pulmonary window nodes (5), subcarinal (7), periesophageal (8) and inferior pulmonary ligament nodes (9). Endoscopic ultrasound (EUS) was performed under conscious sedation as previously described [7], and these were all performed by a single experienced endosonographer (MAE) ($>$ 2,500 EUS procedures). A radial echoendoscope (GF-UM130 [Olympus America, Melville, NY]) was first used to evaluate the presence or absence of a lymphadenopathy. Once a suspicious lymph node was identified (the endosonographic criteria for malignant lymph node involvement was previously described [11]), the radial echoendoscope was removed and a curvilinear echoendoscope (Olympus UC-30P or UCT 140, Melville, NY) was inserted. The EUS-FNA of the target lesions by the PET/CT scans and the CT scans was performed as previously described [12]. EUS-FNAs were preformed using a 22-gauge adjustable length Echotip needle (Wilson-Cook Inc, Winston Salem, NC). Cytological diagnosis of the aspirated lesion was reported as either positive for metastatic cancer or negative. The endosonographer (MAE) was blinded to the CT scan report and to the FDG-PET/CT scan report. In general, nodes targeted as abnormal by these modalities were biopsied, but if they could not be located by EUS, then they were not biopsied.

Patients with suspected M1 disease in the liver, adrenal, or contralateral lung underwent definitive biopsy to prove or disprove M1 cancer. If the bone or brain was suspected to harbor metastases, magnetic resonance imaging was considered the standard reference. If patients had biopsy proven N3 or M1 disease the stage was recorded but they were not resected. If there was no evidence of N2 or higher disease, patients underwent thoracotomy, pulmonary resection, and complete thoracic lymphadenectomy. Pathologic review was performed by standard techniques and immunohistochemical staining was used when appropriate. The pathologic stage was assessed using the international staging system [9].

A patient was defined as having unsuspected N2 disease if neither the FDG-PET/CT scan nor the CT scan suggested any cancer in any of the N2 nodes (clinically called N2 negative) but the patient had pathologic proof of metastatic NSCLC cancer in at least one N2 node. The University of Alabama at Birmingham's institutional review board approved both this prospective trial and the electronic prospective database used for this study.

### *Statistical Methods*

Data was stored using an Access database (Microsoft, Seattle, WA) and analyzed using EpiInfo (Centers for Disease Control, Atlanta, GA) and the SAS program, version 9.0 (SAS, Cary, NC). Efficacy (ie, sensitivity, specificity, positive predicted value, negative predicted value and accuracy) was determined for CT scanning and FDG-PET/CT scanning using the pathology or biopsy results as the gold standard. Standard definitions were used to calculate these parameters [13]. Table 1 depicts how the true positives, true negatives, false positives, and false negatives for the clinical stage were defined for calculation of the efficacy. It also shows how the percentage for unsuspected N2 disease was calculated. The binomial approximation test was used to compare efficacy.