Prospective Comparative Study of Integrated Positron Emission Tomography-Computed Tomography Scan Compared With Remediastinoscopy in the Assessment of Residual Mediastinal Lymph Node Disease After Induction Chemotherapy for Mediastinoscopy-Proven Stage IIIA-N2 Non–Small-Cell Lung Cancer: A Leuven Lung Cancer Group Study

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ABSTRACT
Purpose
Mediastinal restaging after induction therapy for non–small-cell lung cancer remains a difficult and controversial issue. The goal of this prospective study was to compare the performance of integrated positron emission tomography (PET)–computed tomography (CT) and remediastinoscopy in the evaluation of mediastinal lymph node metastasis after induction chemotherapy.

Patients and Methods
Thirty consecutive stage IIIA-N2 non–small-cell lung cancer patients surgically treated at our institution were entered onto this prospective study. N2 disease was proven by cervical mediastinoscopy, at which a mean number of 3.8 lymph node levels were biopsied. After completion of induction chemotherapy, the mediastinum was reassessed by integrated PET-CT and remediastinoscopy. All patients underwent thoracotomy with attempted complete resection and systematic nodal dissection.

Results
PET-CT showed no evidence of nodal disease (N0) in 13 patients, Hilar nodal disease (N1) disease in three patients, and residual mediastinal disease (N2) in 14 patients. Remediastinoscopy was positive in only five patients. The preinduction involved lymph node level could be accurately re-evaluated in 18 patients. This was not the case in the other 12 because of extensive fibrosis and adhesions. In 17 patients, persistent N2 disease was found at thoracotomy. The sensitivity, specificity, and accuracy of PET-CT were 77%, 92%, and 83%, respectively. These parameters for remediastinoscopy were 29%, 100%, and 60%, respectively. Sensitivity (P < .0001) and accuracy (P = .012) were significantly better for PET-CT.

Conclusion
After a thorough staging mediastinoscopy, postinduction remediastinoscopy had a disappointing sensitivity because of adhesions and fibrosis. Integrated PET-CT yielded a better result than that obtained in previous studies with side-by-side PET and CT images.

INTRODUCTION
Although the optimal treatment of patients with stage IIIA-N2 non–small-cell lung cancer (NSCLC) is still under investigation, there may be a role for surgery following induction treatment in patients with downstaging of mediastinal lymph nodes (LNs) and complete resection.1–4 Mediastinal restaging after induction chemotherapy or chemoradiotherapy for NSCLC remains a difficult and controversial issue. Positron emission tomography (PET) scanning is accurate in primary LN staging,5 but the available results after induction treatment are less convincing. In a prospective multicenter study, the sensitivity of PET in the detection of residual mediastinal LN disease after induction chemotherapy was only 50%.6 Remediastinoscopy offers the advantage of providing histologic evidence of
the mediastinal LN status, but it is technically challenging because of the mediastinal LN status, but it is technically challenging because of fibrosis and adhesions after prior mediastinoscopy and induction treatment. Only a few centers have reported their experience with mediastinoscopy. A sensitivity of 70% to 73% was obtained.7,8

The aim of this prospective study was to compare the performance of mediastinoscopy and integrated PET–computed tomography (CT) in the evaluation of mediastinal LN metastasis after induction chemotherapy.

PATIENTS AND METHODS

Cohort Assembly

From April 2002 to April 2005, all consecutive stage IIIA-N2 NSCLC patients with surgical treatment at our institution who fulfilled the inclusion criteria entered in this prospective study with informed consent. Stage IIIA-N2 was certified by mediastinoscopy, including inspection and sampling of the left and right upper paratracheal nodes (levels 2L and 2R on the Mountain-Dressler map), left and right lower paratracheal nodes (levels 4L and 4R), and subcarinal nodes (level 7). Patients received three to four courses of cisplatin-based induction chemotherapy (mostly cisplatin + gemcitabine). No patients received induction radiotherapy. Patients with response or stable disease on CT scan were considered for thoracotomy.

PET-CT Acquisition

The integrated PET-CT scan was performed 3 to 4 weeks after the last chemotherapy course. All patients were examined on a dual-modality PET-CT tomograph (biograph LSO Duo; Siemens Medical Solutions Inc, Hoffman Estates, IL), which consists of a two-row spiral CT (Siemens Medical Solutions Inc) and a full-ring lutetium oxy-orthosilicate (LSO)-PET (Siemens Medical Solutions Inc). Patients fasted for at least 4 hours before the examination. Serum glucose levels were measured, and scans for patients with glucose levels greater than 180 mg/dL were rescheduled.

PET-CT images were acquired 75 minutes after the intravenous administration of fluorodeoxyglucose (FDG) 4.5 MBq/kg. Patients were scanned from the groin to the head in the arms-up position. Single-section, whole-body, spiral CT (85 mAs, 130 kV, slice thickness 5 mm, table feed 12 mm/rotation) was performed after 120 mL of a contrast agent that contained 300 mg iodine/mL (Ketrax 300; Guerbet, Sulzbach, Germany) was intravenously injected using an automated injector (1.6 mL/sec, scan delay 100 seconds). A limited breath-hold technique was used to avoid motion-induced artifacts in the area of the diaphragm. On completion of the CT portion, the PET data (5 minutes/bed position) were acquired in 3-D mode.

CT images were reconstructed using conventional-filtered back-projection at 3.4-mm axial intervals to match the slice separation of the PET data. Both attenuation-corrected PET images (using the CT data) and nonattenuation-corrected images were reconstructed using an ordered subsets expectation-maximization algorithm.

PET-CT Image Analysis

PET images were interpreted by a nuclear medicine physician (S.S.) and were blinded for the CT portion and any clinical information other than site of the primary tumor. Any focally increased FDG uptake greater than the normal background activity in the hilum or mediastinum was considered residual mediastinal LN involvement. CT images were interpreted by a chest radiologist (W.D.). When the shortest diameter of the LN on CT was ≥1 cm, the LN was considered positive.

The nuclear medicine physician (S.S.) and chest radiologist (W.D.) interpreted the integrated and software-fused PET-CT. For this purpose, only focal uptake that projected onto an LN was considered positive for residual tumor was present at the end of the surgical procedure.

Thoracotomy

In the absence of N3 disease at mediastinoscopy, a postero-lateral thoracotomy with the aim of complete resection was done. At thoracotomy, a systematic hilar and mediastinal LN dissection was performed.14 LN downstaging was defined as the absence of viable tumor cells in the resected mediastinal LN specimen. Resection was defined as complete (R0) in case of the removal of all of the tumor, microscopic tumor-free margins at the primary site, and removal of all affected LNs, with the resected margins and the most proximally resected LN level free of tumor at microscopy of the resected specimen. Resection was defined as incomplete when microscopic (R1) or macroscopic (R2) residual tumor was present at the end of the surgical procedure.

Statistics

The study hypothesis was that mediastinoscopy would have a superior sensitivity of 80% compared with a sensitivity of 57% for PET-CT with FDG. The latter sensitivity was based on the interim analysis of our multicenter prospective study15 and the former on available literature data, in which the sensitivity of mediastinoscopy is reported to be 70% to 73%.7,8 Thirty patients were needed to study this hypothesis with a power of 80% and a significance level of <.05.

The sensitivity, specificity, accuracy, and predictive values of CT and PET were calculated using the standard definitions. The relative accuracy of PET-CT versus mediastinoscopy was compared by a McNemar test for correlated proportions.

RESULTS

Thirty patients were included in a 3-year period between April 2002 and April 2005 (Table 1). The mean age was 64 years (range, 45 to 75 years). Most tumors (73%) were located in the upper lobes. Two-thirds of tumors were right-sided. Pathology revealed squamous cell carcinoma in 17 patients and adenocarcinoma in 13. In all patients, N2 disease was confirmed by mediastinoscopy. The mean number of LN levels biopsied was 3.8 (range, 3 to 5). Subcarinal LNs were biopsied in all 30 patients. One-third of patients had multilevel N2 disease; subcarinal LNs were positive in 50% of patients.

Accuracy of CT Alone, PET Alone, and PET-CT in Restaging

The accuracy of CT alone in restaging mediastinal LN disease was 60%, the accuracy of PET alone was 70%, and that of PET-CT was 83% (Table 2). PET-CT fusion images mainly resulted in improved specificity. In three patients with N2-3 disease on PET scan, fusion images showed that FDG uptake was in a thickened pleura after previous talc usage for a contralateral pneumothorax, in normal vascular structure (Fig 1), or in brown fatty tissue. In one patient, PET-CT images detected N2 disease by demonstrating that a moderate uptake of FDG was in a necrotic LN (Fig 2).

Remediastinoscopy

Remediastinoscopy was scheduled 4 weeks after completion of induction chemotherapy. The mean time interval between the first
mediastinoscopy and remediastinoscopy was 106 days (range, 83 to 129 days). The mean operative time for remediastinoscopy was 53 minutes (range, 40 to 70 minutes). No intraoperative complications occurred during remediastinoscopy. The mean number of levels biopsied at remediastinoscopy was 3.6 (range, 0 to 5). The preinduction involved LN levels could be evaluated by mediastinoscopy in 18 patients; this was not the case in the other 12 because of extensive fibrosis and adhesions (Table 3). Thoracotomy revealed that the subcarinal level concerned was not adequately biopsied, because it was encapsulated in a firm fibrotic capsule. In the other seven patients with false-negative remediastinoscopy, tumor deposits were found at pathologic examination, whereas, in two others, thoracotomy revealed that the LN level concerned was not previously involved LN level.

**Thoracotomy**

Because no N3 disease was found at remediastinoscopy, thoracotomy with attempted complete resection and LN dissection was performed in all patients (Table 3). No resection was performed in one patient with adenocarcinoma of the right middle lobe. His remediastinoscopy was negative, but persistent, multilevel N2 disease was found at thoracotomy, and the planned pneumonectomy for central trans fissural disease was aborted. A complete resection (R0) could be achieved in 22 patients (73%), but resection was incomplete in seven patients (four R1 and three R2). PET-CT showed persistent residual mediastinal disease in six of seven patients with incomplete resection (Table 4). The four R1 resections had positive mediastinal LNs, which were shown by PET-CT scan.

No mortality occurred in the hospital. The mean hospital stay was 11.6 days (standard deviation, 6.9 days). Ten patients developed postoperative complications. The most frequent postoperative complication, occurring in six patients, was respiratory infection; prolonged ventilation and intensive care (> 48 hours) were required in two. Other complications were atrial fibrillation (n = 4) and pulmonary embolus (n = 1).

### Comparative Accuracy: Persistent N2 Disease After Induction Chemotherapy

N2 disease was present in 17 patients (57%, Table 5). PET-CT was positive in 14 patients; one was a false positive resulting from silicosis and inflammation in a patient who had deposits of squamous cell carcinoma in the subcarinal nodes at initial mediastinoscopy. PET-CT was negative in 16 patients. In four of these patients, metastatic mediastinal LNs were present—three with small microscopic tumor deposits detected at definitive pathological examination only and one with an enlarged LN that contained tumor within a firm fibrotic capsule at thoracotomy.

Remediastinoscopy was positive in only five patients. At thoracotomy, all positive mediastinal LNs were within the normal reach of classical mediastinoscopy. In 12 patients, remediastinoscopy was false-negative (Table 5). In three patients, only small microscopic tumor deposits were found at pathologic examination, whereas, in two others, thoracotomy revealed that the LN level concerned was not adequately biopsied, because it was encapsulated in a firm fibrotic capsule. In the other seven patients with false-negative remediastinoscopy findings, severe fibrosis and adhesions impeded biopsy of the previously involved LN level.

Consequently, the sensitivity of PET-CT for the detection of residual mediastinal LN disease after induction chemotherapy was 77%, the specificity was 92%, and the accuracy was 83%; negative and positive predictive values were 75% and 93%, respectively. The figures for remediastinoscopy were 29%, 100%, 60%, respectively, and negative and positive predictive values were 52% and 100%, respectively. Sensitivity (P < .0001) and accuracy (P = .012) were significantly better for PET-CT.

Comparison of PET-CT and resectability results was useful. In 16 patients with a PET-CT negative for residual mediastinal LN disease, complete resection was achieved in 15. One resection was incomplete because of positive peribronchial tissue at the bronchial margin. However, of the 14 patients with positive nodes at PET-CT, only eight had complete resection (P = .018).

### Discussion

Primary surgery for mediastinoscopy-proven N2 NSCLC is unrewarding—the 5-year survival rate is less than 10%. Small
randomized studies have suggested that the prognosis can be improved by adding cisplatin-based induction chemotherapy.\textsuperscript{17,18} A favorable outcome can be expected, particularly in patients with downstaging of the mediastinal nodes and complete resection.\textsuperscript{1-4} Because our experience with FDG-PET in the assessment of mediastinal LN metastasis after induction chemotherapy\textsuperscript{15} was inferior to the one achieved in baseline staging,\textsuperscript{19} we hypothesized that tissue sampling by means of remediastinoscopy would improve sensitivity. To our

\begin{figure}
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\includegraphics[width=\textwidth]{image1.png}
\caption{A moderate but focally increased fluorodeoxyglucose (FDG) uptake above normal background activity is seen in the mediastinum. On the basis of sensitive reading of positron emission tomography (PET) scan, this patient was assigned PET stage N2. However, integrated PET-computed tomography demonstrated that FDG uptake was localized in vascular structures (N0), which proved correct at thoracotomy (pN0).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{In this patient, the positron emission tomography scan shows moderate uptake of fluorodeoxyglucose in the mediastinum after induction chemotherapy. Fusion images clearly show that this uptake is localized in a necrotic mediastinal lymph node (N2), which proved correct at thoracotomy (pN2).}
\end{figure}
After induction therapy, PET still performs better than CT, but its accuracy is not as good as that for initial staging. The studies that have evaluated this question are quite heterogeneous, both in methods and in results (Table 6). First, some studies were prospective, and others were retrospective. Second, in most studies, only a subgroup of patients had mediastinoscopy-proven N2 disease before induction treatment. Third, some studies reported on patients with chemotherapy induction, others on a mixed population with chemotherapy or chemoradiotherapy induction, and some on patients with only chemoradiotherapy. Radiotherapy has been associated with false-positive findings because of postinduction inflammatory reactions. Overall, the sensitivity in the detection of residual mediastinal LN disease was between 50% and 67% (with an outlier of 20%), and the specificity was between 61% and 100%. This rather low sensitivity may result from small residual tumor nests that are surrounded by fibrosis and are more difficult to detect. On the basis of these results, we could not recommend PET after induction therapy as a reliable indicator of surgical resection in patients with mediastinal clearance nor as a means of avoiding thoracotomy in those with persistent mediastinal LN disease.

The current study results are clearly better than in previous reports. In 1997, we identified the lack of anatomic information about PET and the improved interpretation when PET images and CT images are viewed side by side. Current fusion scanners now acquire superimposed PET and CT images. This new tool has been evaluated recently in the primary staging of NSCLC, and integrated PET–CT yielded additional information compared with visual correlation of images. In this postinduction study, we analyzed mediastinal PET findings more sensitive compared with chemotherapy-naive patients and with previous studies. Even a slight increase of uptake above mediastinal bloodpool activity was considered positive. Therefore, PET alone sensitivity was 71%. However, because of physiologic uptake of FDG in mediastinal structures, specificity could only be maintained by fusion imaging.

Remediastinoscopy offers the advantage of providing histological evidence of mediastinal LN status after induction therapy. Only a few small series have been reported. Mateu-Navarro et al reported on 24 patients in a 5-year period, 12 of whom had a positive remediastinoscopy. In the 12 patients with negative remediastinoscopy, thora-
cotomy with nodal dissection identified five false-negative cases (sensitivity, 70%). In the series of Van Schil et al, on a total of 27 patients in a 7-year period, the results were comparable (sensitivity, 73%). Pitz et al reported on 15 patients who had remediastinoscopies after induction chemotherapy for stage IIIB NSCLC. Because of fibrosis and adhesions, incomplete or no biopsies were obtained in six
patients (40%). The other nine patients had adequate remediastinoscopy, which was positive in two and negative in seven patients. In the latter seven patients, remediastinoscopy was false negative at subsequent thoracotomy in two patients. The authors concluded that remediastinoscopy was disappointing because of incompleteness or false-negative findings.

In our series, remediastinoscopy was positive in only five patients and false-negative in 12 cases; this yielded a sensitivity of 29% and an accuracy of 60%. The reasons for the differences among studies are speculative. First, previous studies were retrospective and covered longer treatment intervals, but our trial had a prospective design open for all consecutive cases. Second, the performance of mediastinoscopy for initial staging of NSCLC is largely variable. In our study, all mediastinoscopies consisted of a thorough exploration with LN biopsies of all mediastinal nodal levels reachable by cervical mediastinoscopy, which led to an average of 3.8 LN levels biopsied. In the series that report a higher sensitivity for remediastinoscopy, no data exist on the thoroughness (eg, the number of LN levels biopsied) of the first mediastinoscopy. We believe that a more extensive initial mediastinoscopy will result in more adhesions and fibrosis, causing remediastinoscopy to be more difficult and inaccurate. Finally, in our series, one-third of patients had multilevel LN disease, which was present in only three of 26 patients in the series of Mateu-Navarro et al and was not reported in the series of Van Schil et al. Accurate evaluation of multilevel LN disease may be more demanding at remediastinoscopy.

A limitation of the present study is that correlative studies on pretreatment or post-treatment PET scans are not possible, because only two-thirds of patients had their pretreatment scan in our hospital. Future studies should determine the possible correlation between decrease of standardized uptake value in the primary tumor and downstaging on PET-CT and finally pathology.

In conclusion, our study shows the difficulty of performing thorough remediastinoscopy and the disappointing sensitivity of postinduction remediastinoscopy that results from adhesions and fibrosis, which impede the reach to concerned LN stations, especially in the subcarinal space. Because the results of remediastinoscopy were disappointing in our study, we consider the role of remediastinoscopy in restaging after induction chemotherapy investigational. Other techniques that provide histological confirmation (endoscopic ultrasound-fine needle aspiration or transbronchial needle aspiration) should be investigated in baseline or post-treatment staging.

Integrated PET-CT yields better results than those obtained in previous studies with separate PET and CT images. As a result, sensitivity and accuracy in assessing LN downstaging were significantly better for PET-CT than for remediastinoscopy. Moreover, the positive predictive value of PET-CT for persistent mediastinal LN metastasis and for the risk of an incomplete resection was high. Our study indicates that PET-CT may be useful in determining the operability after induction chemotherapy for N2 disease. Our results should be confirmed by other studies; mature survival analyses are required.

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Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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