Screening-Detected Lung Cancers
Is Systematic Nodal Dissection Always Essential?

Giulia Veronesi, MD, Patrick Maisonneuve, ING,† Giuseppe Pelosi, MD,‡ Monica Casiraghi, MD,* Bernardo G. Agoglia, MD,* Alessandro Borri, MD,* Laura L. Travaini, MD,§ Massimo Bellomi, MD,‖¶ Cristiano Rampinelli, MD,‖ Daniela Brambilla, MSc,* Raffaella Bertolotti, MSc,* and Lorenzo Spaggiari, MD*¶*

Background: To address whether systematic lymph node dissection is always necessary in early lung cancer, we identified factors predicting nodal involvement in a screening series and applied them to nonscreening-detected cancers.

Methods: In the 97 patients with clinical T1–2N0M0 lung cancer (<3 cm), enrolled in the Continuous Observation of Smoking Subjects computed tomography (CT) screening study, who underwent curative resection with radical mediastinal lymph node dissection, we examined factors associated with hilar extrapulmonary and mediastinal nodal involvement. Nodule size plus positive/negative positron emission tomography (PET)-CT (usually as maximum standard uptake value [maxSUV]) were subsequently evaluated retrospectively for their ability to predict nodal involvement in 193 consecutive patients with nonscreening-detected clinical stage I lung cancer.

Results: Among Continuous Observation of Smoking Subjects patients, 91 (94%) were pN0, and six (6.2%) were pN+. All patients with maxSUV <2.0 ($p = 0.08$) or pathological nodule ≤10 mm ($p = 0.027$) were pN0 (62 cases). Nodal metastases occurred in 6 cases among the 29 (17%) patients with lung nodule >10 mm and maxSUV ≥2.0 ($p = 0.002$ versus the other 62 cases). In the nonscreening series, 42 of 43 cases with negative PET-CT (usually maxSUV <2.0) or nodule ≤10 mm were pN0; 33 of 149 (22%) cases with positive PET-CT (usually maxSUV ≥ 2.0) and nodule >10 mm were pN+ ($p = 0.001$ versus the 43 cases).

Conclusions: This limited experience suggests that in early-stage clinically N0 lung cancers with maxSUV <2.0 or pathological nodule size ≤10 mm, systematic nodal dissection can be avoided as the risk of nodal involvement is very low.

Divisions of *Thoracic Surgery, †Epidemiology and Biostatistics, ‡Pathology, §Nuclear Medicine, ‖Radiology, European Institute of Oncology; and ¶School of Medicine, University of Milan, Milan, Italy.

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Address for correspondence: Dr. Giulia Veronesi, Division of Thoracic Surgery, European Institute of Oncology, Via Ripamonti 435, Milan 20141, Italy.

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With advances in imaging technology and the introduction of lung cancer screening, many more early-stage lung cancers are being diagnosed than in the past.[1–3] In our Continuous Observation of Smoking Subjects (COSMOS) screening study,[2] more than 80% of the lung cancers diagnosed were stage I or II, and most were less than 1 cm in diameter. Very early-stage lung cancers may be less aggressive than those conventionally diagnosed,[4] suggesting that a less aggressive surgical approach that reduces morbidity and improves quality of life might be appropriate, provided cure rate can be maintained. A less aggressive surgical approach might also enhance the effectiveness of computed tomography (CT) screening,[5] reducing the duration and complications of surgery,[6] and overall cost of screening.

The current standard surgical treatment for localized non-small cell lung cancer (NSCLC) is lobectomy or pneumonectomy,[7–9] irrespective of the size of the tumor or its metabolic features on positron emission tomography (PET). Nevertheless, this approach may be overtreatment for very small cancers.[10,11] Similarly, systematic nodal dissection, considered essential for accurate intrathoracic staging of NSCLC,[12–16] may be unnecessary in selected clinical stage I cases, as most are N0.[17] If N0 cases could be reliably identified before nodal dissection, systematic nodal dissection could be avoided. A reliable preoperative predictor of N0 disease would also have implications for future studies analyzing the role of limited resection in very early peripheral lung cancers.

To address the issue of systematic lymph node dissection in early lung cancer, we analyzed a consecutive series of patients with clinically N0 screening-detected lung cancer (including cases other than NSCLC) who underwent preoperative staging with ^{18}F-fluorodeoxyglucose (FDG) PET/CT, with anatomical resection of the primary tumor and systematic lymph node dissection. Our immediate aim was to identify variables predicting patients with N0 disease and subsequently to refine indications for systematic nodal resection.

Subsequently, we investigated the utility of the predictive factors identified in a retrospective series of nonscreening-detected lung cancers.

PATIENTS AND METHODS

We recruited 5201 asymptomatic volunteers to our single-center prospective COSMOS screening study in 2004 and 2005[2] and followed up them annually for 5 years. Those eligible were aged 50 years or older, heavy (≥20 pack-years) smokers or former heavy smokers who stopped not more than 10 years previously. All gave written informed consent to receive annual low-dose CT for 5 consecutive years. The CT machine was a High Speed Advantage multidetector (General Electric, Milwaukee, WI); contrast was not used for screening scans, which were taken in a single breath with the machine set at 140 kVp and 30 mA, with 2.5 mm slice thickness. Patients with suspicious lung nodules underwent FDG-PET-CT using an in-line system (Discovery LS, GE Medical Systems Waukesha, WI) consisting of an Advance NXi PET scanner and an eight-slice Light Speed Plus CT scanner. Nodules that were PET-CT positive or growing at repeat scans underwent surgical biopsy and additional interventions.

PET findings were recorded either as maximum standard uptake value (maxSUV) of FDG or positive or negative by visual assessment. CT-PET was considered positive if the maxSUV was more than 2.0 in the region of interest calculated automatically on lesions identified by CT. We used this low threshold because the consequence (treatment delay) of a false negative was more undesirable than that of a false positive (unnecessary biopsy or surgery).[2]

Patient data were recorded prospectively. In this study, we were interested in patients with clinical stage T1-2N0M0 disease (single lung nodule <3 cm maximum diameter, with no abnormal FDG uptake at hilar or mediastinal nodal stations) who underwent curative anatomical resection plus systematic node dissection between 2004 and 2009. Those with history of lung malignancy, requiring extended lung resection (such as sleeve resection, pneumonectomy, and chest wall resection) or who received PET-CT more than 2 months before surgery, were excluded.

Patients were fasted 6 hours, and after checking that blood glucose was less than 150 mg/dl, they were administered 5 MBq/kg FDG intravenously; they then waited in calm conditions (minimum movement and no speaking) for 50 to 60 minutes. Images were acquired with a combined CT-PET in-line system (Discovery LS, GE Medical Systems) consisting of an Advance NXi PET scanner and an eight-slice Light Speed Plus CT scanner. Patients were first positioned head-first supine and moved to the CT scanning position. A scout scan was acquired to define the axial imaging range, which for whole-body CT-PET typically extended from the lower jaw to the upper thighs. CT settings were 140 kV and 80 mA. Patients were instructed to breathe normally.

Results for FDG-PET (as maxSUV), nodule size on preoperative CT, position of the lesion (central or peripheral), and nodule size at intropeative pathological evaluation (using the fixed cutoff values ≤10 mm, more than 10 ≤20 mm, and more than 20 mm) were investigated together with patient and tumor characteristics (age, sex, type of surgery, side, site, and histology) to assess their role in predicting lymph node status. Similar findings were then examined in an independent series of consecutive patients with nonscreening-detected cancers and comparable clinical characteristics who underwent surgical resection at our institute during the same period. In this group, PET findings were recorded either as maxSUV (157 cases) or positive or negative by visual assessment (36 cases); negative cases were assumed to have maxSUV less than 2. All cases underwent systematic lymph node dissection, defined as removal of hilar extrapulmonary nodes and mediastinal nodes from stations 2, 4, 7, 8, 9, and 10 on the right side, and stations 5 to 10 on the left, in accordance with international guidelines.[13,15] Confirmation of systematic lymph node dissection was obtained by review of the number of explored stations and number of lymph nodes removed from the surgical and pathological reports. The nodule was considered as peripheral if the center of the tumor was located in the outer third of the lung in the transverse, coronal, or sagittal plan.

Statistical Analysis

We used the Mantel-Haenszel χ^2 test for trend and Fisher's exact test to assess associations between lymph node status (ordinal variables pN0, pN1, and pN2) and clinical and pathological characteristics. We then combined the discriminatory variables for lymph node status at univariate analysis in the screening group (tumor size and positive/negative PET) to assess their joint predictive value. Survival was represented by Kaplan-Meier curves and the log-rank test used to assess the significance of differences in survival experience. All tests were two sided. The analyses were performed with SAS, version 8.2 (Cary, NC).

RESULTS

During the study period, a lung cancer was detected by screening in 162 COSMOS patients; of these, 97 satisfied the inclusion criteria of the present analysis. We also analyzed 193 consecutive patients with clinical stage I lung cancer not detected by screening and treated in our Division during the same period. Table 1 lists the clinical and pathological characteristics of both groups.

In the screening group, 91 (94%) patients were N0 at pathological examination, and six (6.2%) were N+. Three variables were associated with nodal status in the screening group: pathological nodule size, maxSUV, and nodule location (central versus peripheral). It is noteworthy that all patients with maxSUV less than 2.0 ($p = 0.08$ versus maxSUV ≥2.0) or lung nodule ≤10 mm ($p = 0.027$ versus nodule >10 mm) or both—a total of 62 cases (Table 2)—were N0 at pathological examination, whereas one patient with peripheral nodule more than 10 mm and maxSUV less than 2 had pN2 disease (Table 2). All other nodal metastases occurred among the 29 patients with both nodule more than 10 mm and maxSUV ≥2.0. The rate of nodal involvement in the latter group was 17.1% (six patients) ($p = 0.002$ versus those with maxSUV less than 2.0 or nodule ≤10 mm). Radiological module size on preoperative CT was a less reliable indicator than pathological size: two cases in the