Modern Outcome and Risk Analysis of Surgically Resected Occult N2 Non-Small Cell Lung Cancer

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Background. This study was performed to assess the incidence, survival, and risk factors associated with unsuspected pathologic N2 disease in patients with resectable clinical N0-1 non-small cell lung cancer.

Methods. Between January 2002 and December 2010, 1,821 patients with clinical N0-1 non-small cell lung cancer underwent pulmonary resection and mediastinal lymph node dissection. Clinical outcomes and risk factors for pathologic N2 disease were retrospectively analyzed for this cohort.

Results. Unsuspected pathologic N2 disease was identified in 196 patients (10.8%). The most common type of resection was lobectomy (81.6%). Adjuvant therapy was administered in 177 patients (90.3%). The median follow-up time was 28 months (range, 1 to 101 months). N2 involvement was single-station in 121 (66.8%) and multiple-station in 65 (33.2%). The 5-year overall and disease-free survival rates were 56.1% and 35.0%, respectively. The 5-year survival rates of single-station and multiple-station N2 were 66.6% and 36.4%, respectively (p < 0.001). Adenocarcinoma, clinical N1, tumor size (>3 cm), and a right middle lobe tumor were identified as independent risk factors for unsuspected multiple-station N2 disease by multivariate analysis. Incidence of unsuspected multiple-station N2 disease in low-risk classes (aggregate score, 0 to ≤2) was only 5.5%.

Conclusions. The incidence of unsuspected N2 disease in our cohort was similar to that of previous reports. Survival outcomes were favorable for unsuspected single-station N2 disease but were poor for unsuspected multiple-station N2 disease. Clinical N0-1 non-small cell lung cancer patients with risk class of low score for unsuspected multiple-station N2 disease can be exempted from aggressive mediastinal staging.

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unsuspected N2 disease and to identify the risk factors associated with unsuspected N2 disease from resectable cN0-1 NSCLCs.

Patients and Methods

The Asan Medical Center Institutional Review Board approved this study.

Patients

This study was a retrospective review of patients prospectively entered into a database of the Seoul Asan Medical Center from January 2002 to December 2010. All patients with clinical N0 or N1 stage NSCLC were enrolled. Patients with clinically suspicious N2 or N3 disease on PET-CT or CT, regardless of mediastinoscopy or EBUS-TBNA results, were excluded. Of the 1,821 patients who underwent anatomical pulmonary resection and systematic mediastinal lymph node dissection, 196 were diagnosed with unsuspected N2 disease.

We routinely dissected mediastinal lymph nodes, including ipsilateral upper and lower paratracheal, subcarinal, and inferior pulmonary ligament lymph nodes in all patients. Dissections of paraaortic and subaortic lymph nodes were added in patients with left-sided lung cancer. Clinical and pathologic stagings were based on the seventh edition of the TNM classification for lung cancer.

Staging

All patients underwent chest CT and PET-CT to evaluate clinical staging and pulmonary function tests to evaluate operability. Brain magnetic resonance imaging was recommended for patients above stage IB according to NCCN guidelines. Patients with any bone symptoms underwent a bone scan. Clinical stages were determined after chest CT and PET-CT. If needed, bronchoscopy or lung perfusion scans were also performed. Mediastinoscopies were not routinely performed.

If N3 disease was suspected after a PET-CT or CT scan, a mediastinoscopic lymph node biopsy was done to rule out N3 disease. A chest CT finding of lymph nodes with a short axis size exceeding 1 cm, growth in size, or a positive PET-CT finding (as determined by the radiologist) was considered indicative of metastasis. Unsuspected N2 disease was defined as an intraoperative or postoperative pathologic N2 disease in clinical N0-1 patients.

Statistical Analysis

All statistical analyses were performed using SPSS 15.0 (SPSS, Chicago, IL) and SAS 9.3 (SAS Institute, Cary, NC) software. Categoric variables are presented as frequencies and percentages. The overall survival and disease-free survival rates were estimated using the Kaplan-Meier method, and the difference in survival between groups was compared using a log-rank test. Multivariate analysis for risk factors was assessed using the logistic regression method. Results are expressed as odds ratios with 95% confidence intervals.

For each sample, a stepwise logistic regression was performed. If the final stepwise model variables occurred in more than 50% of the bootstrap models, the original final stepwise regression model was judged to be stable. Only reliable predictors (bootstrap frequency >50% in 1,000 simulated samples) were used to conduct the final aggregate score. The scoring system was developed by proportional weighing of the significant predictors estimates assigned a value of 1 to the smallest coefficient. A p value of less than 0.05 was considered statistically significant.

Results

The study included 196 patients (119 men), and their characteristics are listed in Table 1. The median follow-up time was 28 months (range, 1 to 101 months). Lobectomy was the most common type of pulmonary resection. We routinely recommended chemoradiotherapy for patients with postoperative N2 disease. Notably, neither chemotherapy nor radiotherapy alone was possible in some patients with a poor performance status or treatment toxicities. Adjuvant therapy was completed in 177 patients (90%), and 19 did not receive adjuvant therapy due to intolerance or treatment refusal. Of the 58 patients diagnosed with unsuspected N2 disease from clinical N1 NSCLC, 53 (91.4%) received adjuvant therapy, most commonly chemoradiation.

In the total cohort of clinical N0-1 NSCLC patients, the incidence of unsuspected N2 disease was 10.8% (196 of 1,821), and an incidence of single-station and multiple-station N2 involvement was 131 patients (7.2%) and 65 patients (3.6%), respectively. The mean number of metastatic N2 stations was 1.51 ± 0.84.

Of our full cohort of 1,821 patients who underwent operations for NSCLC, 1,525 (83.7%) were clinical N0 and 296 (16.3%) were N1 patients. Metastasis to the mediastinal lymph nodes was postoperatively detected in 9.0% (138 of 1,525) of patients with clinical N0 disease and in 19.6% (58 of 296) of patients with clinical N1 disease (p < 0.001). The incidence of unsuspected N2 disease in the clinical T1 N0 stage was 7.7% (53 of 690). The incidence of unsuspected N2 disease in clinical T2 N0, T3 N0, and T4 N0 patients was 10.9%, 4.7%, and 8.3%, respectively (Table 2).

Early death (<30 days) occurred in 3 patients due to pneumonia (2 patients) and aggravation of idiopathic pulmonary fibrosis (1 patient). Seventy deaths occurred during follow-up, and the time-related mortality rate after 5 years was 43.9%. Of these 70 deaths, 50 were cancer-related. There were 88 recurrences and a 5-year recurrence rate of 59.8%. Local, distant, and locodistant recurrences numbered 13, 72, and 3, respectively. The 5-year overall survival rate with unsuspected N2 disease was 56.1%. The median survival time was 76 months. The 5-year disease-free survival rate for patients with unsuspected N2 disease was 35.0% ± 4.1%. The median disease-free survival time was 19.4 months. The 5-year survival rate of patients with unsuspected single-station N2 disease was significantly higher than that of patients...
with unsuspected multiple-station N2 disease (66.6% vs 36.4%, \( p < 0.001 \); Fig 1).

Table 3 summarizes our logistic regression analysis of the risk factors for unsuspected N2 disease. Multivariate analysis showed age younger than 70
years, adenocarcinoma histology, clinical N1 disease, and a tumor size exceeding 3 cm were independent risk factors for unsuspected N2 disease (Table 3A). Risk factors for unsuspected multiple-station N2 disease included adenocarcinoma histology, clinical N1 disease, a tumor size exceeding 3 cm, and a right middle lobe (RML) location of primary tumor (Table 3B).

From the multivariate analysis of risk factors for unsuspected multiple-station N2 disease, we developed a scoring system to predict the risk of unsuspected multiple-station N2 disease. RML location (coefficient, 0.879; standard error, 0.373; bootstrap frequency, 64.9%; \( p = 0.018 \)), clinical N1 disease (coefficient, 1.184; standard error, 0.326; bootstrap frequency, 90.3%; \( p < 0.001 \)), and adenocarcinoma (coefficient, 1.674; standard error, 0.440; bootstrap frequency, 99.9%; \( p < 0.001 \)) were identified as significant and reliable predictors of unsuspected multiple-station N2 disease by stepwise logistic regression. A tumor size exceeding 3 cm, which was a risk factor by multivariate analysis, was not included due to bootstrap frequency of less than 50%.

The individual factor scores were assigned based on their coefficients (Table 4A). The formula for an aggregate score was \([1 \times \text{RML}) + (1 \times \text{clinical N1 disease}) + (1.5 \times \text{adenocarcinoma}),\] and the area under curve (AUC) for this aggregate score was 0.705. To obtain an aggregate score, the individual scores were summed in each patient to calculate a range from 0 to 3.5. Patients were then grouped into four risk classes according to their aggregate scores, which were significantly associated with incremental risk of unsuspected multiple-station N2 disease (\( p < 0.0001 \); Table 4B).

**Comment**

Despite the recommendation of the NCCN guidelines that pathologic mediastinal staging should be undertaken at all stages of NSCLC, there is currently no suitable modality to detect N2 disease from cases of clinical N0 or N1 disease. The sensitivity of mediastinoscopy or EBUS-TBNA for N2 detection in unsuspected N2 cases is lower than that in the overall N2 population [8, 11]. A prospective study by Cerfolio and colleagues [11] reported a detection rate of N2 disease by mediastinoscopy from clinical N0 disease of 2.9% and that mediastinoscopy could not detect 73% of pathologic N2 disease cases. The false-negative rate of mediastinoscopy is therefore relatively high, whereas that of integrated PET-CT is low. EBUS-TBNA combined with mediastinoscopy decreases this false-negative rate, but conducting EBUS-TBNA is difficult when the mediastinal lymph node is not enlarged. The efficiency of mediastinoscopy or EBUS-TBNA for diagnosis is uncertain for clinical N0 disease detected on integrated PET-CT. At this point, we have to consider cost-effectiveness.

| Table 3. Multivariate Analysis of Risk Factors for (A) Unsuspected N2 disease and (B) Unsuspected Multiple-Station N2 Disease |
| Variables | Odds Ratio | 95% Confidence Interval | \( p \) Value |
| (A) | | | |
| Age (<70) | 1.78 | 1.09–2.89 | 0.020 |
| Clinical N1 disease | 2.86 | 1.96–4.17 | <0.001 |
| Right middle lobe | 1.89 | 1.15–3.09 | 0.012 |
| Adenocarcinoma | 2.01 | 1.35–3.01 | <0.001 |
| Tumor size (>3 cm) | 1.59 | 1.14–2.22 | 0.006 |
| (B) | | | |
| Clinical N1 disease | 3.27 | 1.73–6.19 | <0.001 |
| Adenocarcinoma | 5.34 | 2.25–12.64 | <0.001 |
| Tumor size (>3 cm) | 1.84 | 1.05–3.20 | 0.032 |
| Right middle lobe | 2.41 | 1.16–5.01 | 0.018 |

**Table 4. (A) Points Assigned at Individual Variables and (B) Distribution of Patients and Incidence of Unsuspected Multiple-Station N2 Disease by Class of Risk**

| Variables | Points Assigned at Individual Variable |
| (A) | | |
| Right middle lobe | 1 |
| Clinical N1 disease | 1 |
| Adenocarcinoma | 1.5 |

| Risk Class | Patients (No. (%)) | Incidence of Unsuspected Multiple-Station N2 Disease (n = 65) No. (%) |
| (B) | | |
| Class A (score 0 to ≤1) | 834 (45.8) | 12 (1.4) |
| Class B (score 1 to ≤2) | 804 (44.1) | 33 (4.1) |
| Class C (score 2 to ≤3) | 170 (9.3) | 17 (10.0) |
| Class D (score 3 to ≤4) | 13 (0.7) | 3 (23.1) |
| \( \chi^2 \) p value | <0.0001 | |
| C index | 0.705 (95% confidence limits, 0.64 and 0.77) | |

\( \text{C index} = \text{area under the receiver operating characteristic curve.} \)
The 10.8% incidence of unsuspected N2 in this patient cohort was slightly lower than that reported previously [12, 13]. An overall 5-year survival rate of 56.1% for unsuspected N2 disease in our present study cohort was higher than the overall N2 disease rate reported previously [14, 15]. This discrepancy is likely because our cohort comprised patients with highly specialized N2 disease, whereas overall, N2 disease is very heterogeneous, ranging from clinically unsuspected microscopic N2 disease that is initially resected to clinically bulky N2 disease that cannot be resected.

Moreover, the completion rate for adjuvant therapy in our current study population was quite high because our center routinely provides these treatments for patients with postoperative pathologic N2 disease. Yanagawa and colleagues [6] reported that adjuvant cisplatin-based chemotherapy confers an overall survival benefit for N2 nodal involvement discovered postoperatively. Cerfolio and colleagues [14] reported better survival rates in patients with single-station, rather than multiple-station, N2 disease when resection was followed by adjuvant therapy.

The unsuspected N2 population in our present study was heterogeneous. On one side of the spectrum were patients with negative preoperative mediastinal lymph nodes with a single-station metastasis of the mediastinal lymph node at the time of operation. The other group had multiple-station metastases of the mediastinal lymph node. The incidence of unsuspected multiple-station N2 was 33% of unsuspected N2 cases and 3.6% of our total cohort.

Our current data also indicate that unsuspected single-station N2 disease has a better survival outcome than unsuspected multiple-station N2 disease. The survival rates for the patients with unsuspected multiple-station N2 disease in our present study were as poor as those reported for clinical N2 disease in various studies [15]. This indicates that other treatment plans in accordance with preoperative pathologic N staging for the cases of unsuspected multiple-station N2 disease may be necessary than resection followed by adjuvant therapy. However, it is unknown whether neoadjuvant therapy, followed by resection for unsuspected multiple-station N2 disease identified by mediastinoscopy or EBUS-TBNA, increases survival rates to a greater extent than an operation followed by adjuvant therapy. If neoadjuvant therapy does not have survival benefits, preoperative pathologic documentation of N2 disease in clinical N0 or N1 cases, as determined on integrated PET-CT, would not be mandatory. A prospective trial will be needed to fully address this issue.

Gomez-Caro and colleagues [8] reported previously that female sex, adenocarcinoma, and pathologic N1 are risk factors of occult N2 lymph nodes, and Sakao and colleagues [16] have reported that occult intrapulmonary metastasis and clinical N2 are independent risk factors for multilevel N2 NSCLC. Cerfolio and colleagues [11] have recommended mediastinoscopy in patients who are clinically staged as N0 after integrated PET-CT and CT, or in those with adenocarcinoma, upper-lobe tumors, or tumors with a maximum standard uptake value of 10 or higher.

In our present study, multivariate analysis revealed adenocarcinoma histology, clinical N1 disease on PET-CT or CT, a tumor size exceeding 3 cm, and RML location of the primary tumor as risk factors for unsuspected multiple-station N2 disease. These risk factors could not be applied to the clinical decision, however, because the range they provided was too broad to investigate N2 disease. Thus, we chose to develop an aggregate score to stratify the risk of unsuspected multiple-station N2 disease. Four risk classes were defined, and it easily appears that a risk of unsuspected multiple-station N2 disease increases according to risk class A to D. Although a risk of unsuspected multiple-station N2 disease in class D, which is the highest risk group, was 23.1%, the risk in class D was 16 times higher than a risk in class A (1.4%). Conversely, patients in class A and B had a minimal risk of unsuspected multiple-station N2 disease (5.5%), and these are patients who have cost-effectiveness by exemption from aggressive mediastinal staging with mediastinoscopy or EBUS-TBNA or both.

Our current study has some limitations. Our analyses were retrospective in nature, with inherent selection biases. In addition, the use of adjuvant therapy in a large proportion of the patients in our study cohort prompts further analysis to verify the influence of adjuvant therapy on unsuspected N2 disease. We also realized that the number of RML tumors in our study cohort was too small (only 11 patients) to have statistical power, although a RML location of the primary tumors was a significant risk factor for unsuspected multiple-station N2 disease.

This current study could not answer whether adenocarcinomas with a lepidic growth pattern that have a lower probability of mediastinal lymph node involvement can be exempted from pathologic mediastinal staging because we did not analyze the risk according to histologic subtypes of adenocarcinoma.

In conclusion, the observed incidence of unsuspected N2 disease in patients with clinical N0 or N1 NSCLC in this study was similar to previous reports. Survival outcomes for unsuspected single-station N2 disease were favorable, but those for unsuspected multiple-station N2 disease were poor. Clinical N0-1 NSCLC patients with lower aggregate score of risk factors for unsuspected multiple-station N2 disease can be exempted from aggressive mediastinal staging.

References
INVITED COMMENTARY

Is this article by Cho and colleagues [1] just another paper on unsuspected or occult N2? In fact, the authors found occult N2 in about 1 in 10 patients with clinical N0. Occult N2 disease found at thoracotomy has been a source for an everlasting dispute between surgeons looking at locally advanced disease from different perspectives. In fact, arguments have been raised supporting the need for systematic frozen section analysis of mediastinal nodes during thoracotomy. Some have suggested that, should a positive N2 node station be identified, the resection is aborted and the patient sent for chemotherapy or for chemoradiation and only in the presence of complete response retracted back to the operative room. According to this interpretation, occult N2 would then be expression of a staging failure and the patient should be brought back to the venue of conventional multimodality treatments in order to warrant the best disease-free survival rate. Indeed, what would be an acceptable surgical treatment for “resectable” N2 disease? The study by Cho and colleagues serves the purpose to support the opposite view; the finding of occult N2 should not contraindicate pulmonary resection. The reasons lie in the remarkable survival data emerging from the authors’ analysis; 67% and 36% 5-year survival rates for single and multiple station N2 disease, respectively. How do we interpret the outcome of multivariate analysis which identified the adenocarcinoma histotype, cN1, T size larger than 3 cm, and, middle lobe tumor as predictors of multistation nodal involvement, thus identifying subsets to be aggressively staged? Most probably, larger numbered series are needed to substantiate these findings (and the suggested classes of risk) but these results seem at least intuitive to the experienced thoracic surgeon.

In the arena of locally advanced non-small cell lung cancer, this manuscript suggests that occult N2 represents a league of its own, potentially yielding very significant survival figures after parenchymal resection and complete mediastinal nodal dissection, irrespective of single or even multiple station involvement. Without claiming victory, the merit of this paper is to take occult N2 out of the guideline quagmire for managing locally advanced non-small cell lung cancer and to place it squarely in the surgical domain.

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