A Clinical Prediction Rule to Estimate the Probability of Mediastinal Metastasis in Patients with Non-small Cell Lung Cancer

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Introduction: Estimating the clinical probability of mediastinal metastasis in patients with non-small cell lung cancer (NSCLC) can facilitate the selection and interpretation of staging tests.

Purpose: We sought to identify independent clinical predictors of mediastinal metastasis and to develop a prediction rule to estimate the pretest probability of nodal metastasis in patients with NSCLC.

Methods: We used data from a randomized controlled trial of selective versus routine mediastinoscopy to develop a clinical prediction model.

Results: Five hundred sixty-six patients were included, with a mean age of 65 ± 9 years; 31% had positive lymph nodes. Independent predictors of positive nodes included adenocarcinoma or large cell histology (OR 2.6, 95% confidence interval [CI] = 1.8–3.9), apparent metastatic disease on chest radiography (OR 2.4, 95% CI = 1.2–4.7), central location of the primary tumor (OR 2.1, 95% CI = 1.4–3.3), symptoms from the primary tumor (OR 1.6, 95% CI = 1.1–2.4), tumor diameter ≥3.6 cm (OR 1.5, 95% CI = 1.0–2.3), and age less than 65 years (OR 1.5, 95% CI = 1.0–2.2). Model accuracy and calibration were good, with an area under the receiver operating characteristic curve of 0.70 (95% CI = 0.66–0.75) and good agreement between observed and predicted probabilities of mediastinal metastasis.

Conclusions: Our prediction rule can be used to estimate the pretest probability of mediastinal metastasis in patients with NSCLC. Such estimates can facilitate clinical decision making when selecting and interpreting the results of noninvasive and invasive staging tests.

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In patients with non-small cell lung cancer (NSCLC), accurate staging is crucial to guide treatment decisions and to reliably estimate prognosis. The optimal treatment and the best chance at cure for eligible patients with NSCLC is surgical resection. Unfortunately, patients with mediastinal lymph node (N2) involvement are for the most part considered unresectable and are unlikely to survive for 5 years.[1–4]

Reliable and accurate detection of N2 disease is important to avoid the morbidity, mortality, and costs associated with performing unnecessary surgery in patients who will not benefit. More importantly, accurate staging will reduce the number of missed thoracotomies in patients with diseases that are incorrectly classified as being unresectable. There continues to be some debate as to the most cost-effective strategy for preoperative staging in patients with NSCLC. Some thoracic surgeons perform mediastinoscopy routinely, whereas others use it selectively or not at all.[5–7] Minimally invasive biopsy procedures continue to be underused.[8] Anecdotally, positron emission tomography (PET) with F-18 fluorodeoxyglucose tends to be used routinely where available, despite its high cost. Identifying patients at high or low risk for N2 metastases may help stratify candidates for noninvasive and/or invasive diagnostic procedures before offering potentially curative surgery.[9]

In prior research, we demonstrated that the effectiveness and cost-effectiveness of different strategies for lung cancer diagnosis and staging depend critically on the pretest probability of disease.[10,11] More fundamentally, it is difficult to select and interpret diagnostic test results correctly without making an estimate of the patient's pretest probability. In this study, we sought to identify independent clinical predictors of N2 metastasis and to develop and internally validate a clinically useful prediction rule to estimate the pretest probability of N2 metastases in patients with NSCLC. It is important to note that this model is not intended for use as a stand-alone diagnostic test but, rather, to estimate the pretest probability and to guide subsequent diagnostic test selection.

METHODS

We analyzed data from a randomized controlled trial of selective versus routine mediastinoscopy that was performed by the Canadian Lung Oncology Group. The study enrolled 685 patients with potentially resectable lung cancer from six centers in Canada between November 1987 and September

1990.[12] Institutional review board approval and written patient consent were obtained by each participating center before enrollment. Deidentified data were used for the purposes of our study.

We identified several potential clinical predictors of N2 metastasis in the trial database that would be available to clinicians after performing a routine clinical evaluation. Included were patient demographic characteristics; presence of symptoms from primary tumor and N2 spread; tumor characteristics such as size, location, and histology; chest radiograph (CXR) appearance of the mediastinum; and selected laboratory values. Mediastinoscopy and thoracotomy results were used to determine the presence of N2 involvement. We included patients who had N2 metastasis confirmed by either mediastinoscopy or thoracotomy and those in whom lymph node metastasis was excluded by thoracotomy.

Data Analysis

We report means and standard deviations to describe continuous variables that were normally distributed. We report frequencies to describe categorical data. We performed unpaired *t* tests to compare differences in continuous variables, and we performed the chi-square test statistic or Fisher's exact test to compare categorical variables. We accepted a two-tailed p value <0.05 as statistically significant for all analyses.

We entered all potential predictors of N2 metastasis into a multiple logistic regression model without using backward or forward selection methods. We arrived at a parsimonious clinical prediction rule by removing all predictor variables that had a p value >0.05.[13] All variables that were not included in the final model had odds ratios (OR) that were close to 1 and p values >0.3. We dichotomized continuous variables by using the median value as the cutoff point. All clinically plausible interactions were tested, but none were statistically significant, so they were not included in the final model. We report OR and 95% confidence intervals (CI) for statistically significant predictors. We generated predicted probabilities of N2 metastasis and their 95% CI for patients, using all possible combinations of predictor variables in the final model.

We used the Hosmer–Lemeshow goodness-of-fit statistic ($p > 0.05$) to evaluate model fit.[14,15] We evaluated the accuracy of the final prediction equation by calculating the area under the receiver operating characteristic (ROC) curve.[16] To assess model calibration, we divided the study cohort into quintiles according to the predicted probability of N2 metastasis and then plotted observed probability as a function of predicted probability.[17]

We internally validated the model by using a cross-validation procedure (modified jackknife), which enabled us to use the full data set for model development.[18] To do this, we divided the study population into 10 equal groups by sampling randomly without replacement. Subsequently, we generated predicted probabilities of metastasis for individual patients in each of the 10 groups by using data from the other nine groups to fit models that included all variables from the final prediction equation. We calculated the area under the ROC curve that described the tradeoff between sensitivity and specificity of the resulting predicted probabilities at multiple thresholds for a positive diagnosis. All predicted probabilities from patients in all 10 groups were used to construct this ROC curve.

We analyzed data by using SPSS for Windows version 12.0 (SPSS, Chicago, IL) and SAS version 9.1. (SAS Institute, Cary, NC).

RESULTS

From the study cohort of 685 patients, we excluded 74 patients with a primary diagnosis other than NSCLC and 45 patients in whom N2 status was not definitively established; 566 patients met our inclusion criteria (Table 1). Positive N2 were identified in 175 (31%) patients. The mean age of patients was 65 ± 9 years, and 28% were women. At the time of enrollment in the study, symptoms from the primary tumor

TABLE 1. Patient Characteristics

Characteristic	All (n = 566)	Node Positive (n = 175)	Node Negative (n = 391)	p
Age (yr)	65 ± 9	63 ± 9	66 ± 9	0.007
Gender (% female)	28	30	27	0.57
Hemoglobin (g/liter)	137 ± 15	136 ± 14	137 ± 15	0.49
Symptoms from primary tumor (%)	56	66	51	0.001
Weight loss (%)	7	10	6	0.10
Symptoms from mediastinal spread (%)	5	6	5	0.48
Tumor size (cm)	3.8 ± 1.8	4.1 ± 1.8	3.6 ± 1.8	0.006
Tumor location (%)				
Upper lobes	71	72	70	0.64
Central location	26	38	21	0.0
Histology (%)				
Squamous/mixed	50	43	53	0.03
Adenocarcinoma or large cell	42	55	36	0.0
Other	8	2	11	0.0
Mediastinal metastasis suspected on chest radiology (%)	8	14	5	0.0

(e.g., cough, dyspnea, and hemoptysis) were reported by 56% of patients, 5% had symptoms from N2 spread, and 7% noted weight loss (defined as weight loss of >10% in the preceding 6 months). The mean tumor size was 3.8 ± 1.8 cm, with the majority of the tumors located peripherally (74%) and in the upper lobes (71%). Fifty percent of tumors had histology compatible with mixed (3%) or squamous cell carcinoma (47%), and 42% were adenocarcinomas (31%) or large cell tumors (11%). Bronchoalveolar cell carcinoma was found in 5% of patients. Study surgeons suspected N2 metastasis on CXR in 8% of patients.

Patients who had positive N2 were younger than node-negative patients (mean age 63 versus 66, $p = 0.007$) and were more likely to report symptoms from their primary tumor (66 versus 51%, $p = 0.001$). There was no statistically significant difference between the two groups in the frequency of weight loss or symptoms from N2 spread. Patients with positive N2 had larger mean tumor size (4.1 versus 3.6 cm, $p = 0.006$) and were more likely to have centrally located (defined as no air between the mediastinum and the lesion) tumors (38 versus 21%, $p = 0.0$). Fifty-five percent of the tumors in the node-positive group were adenocarcinoma or large cell carcinomas, compared with 36% in the node-negative group. Patients who were node negative were more likely than the node-positive group to have squamous cell or mixed cell histology (53 versus 43%, $p = 0.03$). On initial CXR, surgeons were more likely to suspect N2 metastasis in patients in the node-positive group (14 versus 5%, $p < 0.001$).

Using multiple logistic regression, we identified six independent predictors of N2 disease (Table 2). In the final model, adenocarcinoma or large cell histology, apparent N2 metastatic on CXR, central location of the primary tumor, symptoms from the primary tumor, tumor diameter ≥3.6 cm, and age <65 years were all independently associated with the presence of N2 metastasis. Five other potential predictors (hemoglobin, gender, symptoms from N2 spread, weight loss, and upper-lobe location of the primary tumor) were not associated with N2 metastasis and were therefore not included in the final model.

Patients with adenocarcinoma or large cell carcinoma were approximately 2.5 times more likely than patients with squamous cell carcinoma or mixed histology to have N2 disease at presentation, as were patients who had an abnormal-looking mediastinum on CXR compared with those who did not. Patients with centrally located lesions were approximately two times more likely to have N2 metastases than patients with peripheral tumors. Finally, patients with symptoms related to the primary tumor, patients with tumors >3.6 cm in diameter, and patients under 65 years of age were 1.5 times more likely than patients without these characteristics to have positive N2.

The clinical prediction model is given by the equations:

$$\text{probability of metastatis} = e^x/(1 + e^x) \quad (1)$$

$$x = -1.806 + (0.955*\text{adeno}) + (0.876*\text{abnormal Cxr}) + (0.749*\text{central}) + (0.485*\text{primary symptom}) + (0.435*\text{size}) - (0.408*\text{age} > 65) \quad (2)$$

where e is the base of the natural logarithm, adeno = 1 if histology is adenocarcinoma or large cell carcinoma (otherwise 0), abnormal CXR = 1 if the mediastinum appears abnormal on CXR, central = 1 if the primary tumor is located in the central third of the lung, primary symptom=1 if the patient has symptoms attributable to the primary tumor, size = 1 if the tumor is ≥3.6 cm in diameter, and age >65 = 1 if the patient is at least 65 years old.

Goodness-of-fit testing revealed that the model accounted for the outcome better than chance alone ($p < 0.001$) and that the predicted likelihood of the outcome was similar to the observed likelihood ($p = 0.61$). A correlation matrix of parameter estimates revealed no evidence of multicollinearity. The accuracy of the model was good, with an area under the ROC curve of 0.70, 95% CI = 0.66 to 0.75. The predicted probabilities that we generated with the cross-validation procedure had a similar area under the ROC curve of 0.69, 95% CI = 0.64 to 0.73.

Model calibration was excellent for patients in the first, second, third, and fifth quintiles of predicted probability, although the model slightly overestimated the probability of metastasis for patients in the fourth quartile. Otherwise, predicted probabilities closely matched the observed frequency of N2 metastasis.

We used the model to generate predicted probabilities of N2 metastasis for patients with 64 different combinations of clinical characteristics (see Table 3 for selected combinations and the Appendix for all combinations). For example, in an asymptomatic, 70-year-old patient with a peripherally located adenocarcinoma measuring <3.6 cm in diameter and with no evidence of N2 metastasis on CXR, the predicted probability of N2 disease was 22% (95% CI = 16–30%). By comparison, in a symptomatic 60-year-old patient with a centrally located squamous cell carcinoma measuring >3.6 cm in size and an abnormal-looking mediastinum on CXR, the predicted probability of N2 disease was 68% (95% CI = 50–81%).

TABLE 2. Predictors of Mediastinal Nodal Involvement

Predictor	Odds Ratio	95% CI
Adenocarcinoma or large cell	2.6	1.8–3.9
Mediastinal metastasis suspected on chest radiology	2.4	1.2–4.7
Central location	2.1	1.4–3.3
Symptoms from primary tumor	1.6	1.1–2.4
Tumor size >3.6 cm	1.5	1.0–2.3
Age <65 yr	1.5	1.0–2.2

CI, confidence interval.

DISCUSSION

Reliable and accurate detection of N2 disease is crucial in the staging of NSCLC and is essential in preventing unnecessary surgery in patients who will not benefit. In this study, we identified six independent clinical predictors of N2

TABLE 3. Probability of Mediastinal Nodal Involvement for Patients with a Selected Combination of Clinical Predictors

Symptoms from Primary	Central Location	Mediastinal Metastasis Suspected on CXR	Adeno/Large	Size >3.6	Age >65	Probability %	95% CI (%)
0	0	0	0	0	1	9.9	6.4–14.8
0	1	0	0	0	1	18.8	11.6–29.0
0	0	0	1	0	1	22.1	15.6–30.4
0	1	0	0	1	0	34.9	22.9–49.2
0	0	1	1	0	1	40.6	24.5–58.9
1	0	1	0	1	0	49.7	31.4–68.1
1	1	1	0	0	0	57.6	39.5–73.8
0	0	1	1	1	0	61.3	42.0–77.6
1	1	1	0	1	0	67.7	50.3–81.2
1	1	1	1	1	0	84.5	71.7–92.1

CXR, chest radiograph; adeno/large, adenocarcinoma or large cell; CI, confidence interval; 0 indicates that the finding is absent; 1 indicates that the finding is present.

metastasis. Importantly, we developed a novel, parsimonious clinical prediction equation that estimates patient-specific probabilities of N2 metastasis with good accuracy and calibration. To our knowledge, this is the first quantitative model of pretest probability for staging in NSCLC to be developed.

Other groups have identified individual predictors of N2 disease. In a retrospective analysis of 387 patients with NSCLC, Takamochi et al.[19] found that a maximum tumor dimension of ≥2 cm and carcinoembryonic antigen level of ≥5.0 ng/mL were statistically significant predictors of N2 involvement. Similarly, in a study of 440 patients (102 with N2 disease), Suzuki et al.[7] confirmed that tumor size (>2.0 cm), an elevated carcinoembryonic antigen level, and adenocarcinoma histology were significant predictors of pathologic N2 disease. Serological tumor markers were not available in our database and, thus, were not included in our clinical model. However, there is growing evidence that the presence of multiple tumor markers is correlated with more advanced disease and worse prognosis.[20,21]

In agreement with the studies mentioned above, we did not find an increased frequency of N2 metastasis based on lobar location. Other investigators have noted that lower-lobe tumors are associated with a higher frequency of N2 disease and upstaging after surgery.[22] In our series of patients, centrally located tumors were noted, for the first time, to be significantly associated with N2 disease.

The most novel aspect of our model is that it can be used to generate predicted pretest probabilities of N2 metastasis in patients with NSCLC; such estimates can facilitate interpretation of the results of invasive and noninvasive staging tests. For example, we previously showed that PET imaging with F-18 fluorodeoxyglucose has a sensitivity of 80% and a specificity of 90% for identifying N2 metastasis; the corresponding positive and negative likelihood ratios are 8.1 and 0.2.[9] Using these estimates and the likelihood ratio form of Bayes' theorem,[23] the calculated posttest probability of N2 involvement is approximately 70% when pretest probability is relatively low (22%) and when PET results are positive. Thus, patients with low to moderate pretest probability clearly should not be denied potentially curative surgery on the basis of positive PET results alone.

For a similar patient with a relatively low pretest probability of 22% who has a negative PET result, the calculated posttest probability of N2 metastasis is 6%. When pretest probability is 68%, the posttest probability of N2 metastasis in the setting of a negative PET is 32%. In the former case, it may be argued that a 6% probability of N2 metastasis is low enough to forgo confirmatory mediastinoscopy and to proceed to potentially curative thoracotomy. However, in the patient with a high pretest probability of N2 metastasis, a negative PET result clearly does not exclude N2 involvement.

Our model can also be incorporated into a formal cost-effectiveness analysis, as has been done with a similar equation that predicts the pretest probability of malignancy in patients with solitary pulmonary nodules.[11,24]

Our prediction model has several limitations. We developed the model using data that had been collected previously. Although it would be preferable to collect data prospectively, this would require substantial time, effort, and additional funding. Instead, we chose to take advantage of the available data from a well-designed RCT to develop the best model possible at this time. The dataset included information about a large number of clinical variables, but no information about tumor markers was available.

Although computed tomography (CT) is neither highly sensitive nor specific for mediastinal staging,[9] inclusion of CT findings may have improved the model's predictive ability. Unfortunately, CT results were available for only half of the patients in our sample. Despite this, clinicians can incorporate CT results into probability calculations by using estimates of pretest probability from a slightly modified version of our model and the likelihood ratio form of Bayes' theorem.[23] The modification is required because the variable, N2 metastases suspected on CXR, is likely to be positively correlated with the presence of enlarged lymph nodes on CT and, therefore, not independent of the CT results. Because our sample included relatively few patients with suspected N2 metastasis on CXR, the coefficients of all other predictor variables were similar whether or not this variable was included in the model. Thus, we suggest using a five-variable model (excluding the term for suspected N2 metastasis) when

calculating posttest probabilities after CT. For example, we previously demonstrated that the presence of lymph node enlargement on CT (≥1 cm in short-axis diameter) has a likelihood ratio of 2.8 for N2 metastasis. When we assume that the estimated pretest probability of N2 metastasis is 67%, and CT reveals enlarged lymph nodes, the pretest odds are 2 to 1, the posttest odds are 5.6 to 1 (2.8*2), and the updated probability of metastasis is 85%. Parenthetically, the calculated posttest probability of metastasis in this patient is 96% when the enlarged lymph nodes are hypermetabolic by PET.

Although some might argue that the accuracy of the model was only fair to good, the area under the ROC curve compares favorably with the accuracy of CT reported in previous studies.[9,25] Furthermore, our prediction model is not intended to be used as a stand-alone diagnostic test but, rather, as a tool to help guide the selection and interpretation of subsequent diagnostic tests. Although cross-validation of the model yielded a similar area under the curve, our results still require external validation in an independent cohort of patients with NSCLC.

In conclusion, we identified six independent predictors of N2 metastasis in patients with NSCLC. N2 metastasis is most likely in younger patients with large, symptomatic, centrally located tumors; adenocarcinoma or large cell histology; and/or suspected N2 metastasis on chest x-ray. The pretest probability of N2 metastasis can be quantified using a parsimonious clinical prediction equation that has the potential to facilitate clinical decision making in the staging of patients with NSCLC.

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TABLE A1. Probability of Mediastinal Nodal Involvement for Patients with All Possible Combinations of Clinical Predictors

Symptoms from Primary	Central Location	Mediastinal Metastasis Suspected on CXR	Adeno/Large	Size >3.6	Age >65	Probability (%)	95% CI (%)
0	0	0	0	0	1	9.9	6.4–14.8
0	0	0	0	0	0	14.1	9.4–20.6
0	0	0	0	1	1	14.4	9.2–21.9
1	0	0	0	0	1	15.1	10.1–22.0
0	1	0	0	0	1	18.8	11.6–29.0
0	0	0	0	1	0	20.2	13.0–30.1
0	0	1	0	0	1	20.8	10.9–36.0
1	0	0	0	0	0	21.1	14.7–29.2
1	0	0	0	1	1	21.5	14.8–30.3
0	0	0	1	0	1	22.1	15.6–30.4
0	1	0	0	0	0	25.8	16.9–37.3
0	1	0	0	1	1	26.3	16.4–39.3
1	1	0	0	0	1	27.3	18.6–38.2
0	0	1	0	0	0	28.3	15.2–46.5
0	0	1	0	1	1	28.8	15.7–46.9
1	0	0	0	1	0	29.2	20.6–39.5
1	0	1	0	0	1	29.9	16.7–47.6
0	0	0	1	0	0	29.9	22.1–39.1
0	0	0	1	1	1	30.5	21.6–41.2
1	0	0	1	0	1	31.6	22.4–42.5
0	1	0	0	1	0	34.9	22.9–49.2
0	1	1	0	0	1	35.7	20.1–5.1
1	1	0	0	0	0	36.1	26.6–46.8
1	1	0	0	1	1	36.7	26.3–48.5
0	1	0	1	0	1	37.5	24.7–52.4
0	0	1	0	1	0	37.9	21.2–58.0
1	0	1	0	0	0	39.1	22.9–58.0
1	0	1	0	1	1	39.7	23.9–58.0
0	0	0	1	1	0	39.7	29.0–51.5
0	0	1	1	0	1	40.6	24.5–58.9
1	0	0	1	0	0	41.0	31.1–51.6
1	0	0	1	1	1	41.6	31.1–53.0
0	1	1	0	0	0	45.5	27.3–65.0
0	1	1	0	1	1	46.2	27.8–65.7
1	1	0	0	1	0	46.6	35.6–57.9
1	1	1	0	0	1	47.4	30.1–65.4
0	1	0	1	0	0	47.5	34.0–61.3
0	1	0	1	1	1	48.1	33.2–63.4
1	1	0	1	0	1	49.4	35.4–63.5
1	0	1	0	1	0	49.7	31.4–68.1
0	0	1	1	0	0	50.6	32.5–68.6
0	0	1	1	1	1	51.3	33.2–69.0
1	0	0	1	1	0	51.7	40.7–62.6
1	0	1	1	0	1	52.6	34.2–70.3
0	1	1	0	1	0	56.3	36.1–74.6
1	1	1	0	0	0	57.6	39.5–73.8
1	1	1	0	1	1	58.2	40.5–74.0
0	1	0	1	1	0	58.2	43.2–71.9
0	1	1	1	0	1	59.1	38.9–76.6
1	1	0	1	0	0	59.5	46.7–71.1
1	1	0	1	1	1	60.1	46.4–72.5
0	0	1	1	1	0	61.3	42.0–77.6
1	0	1	1	0	0	62.5	43.8–78.1
1	0	1	1	1	1	63.1	45.0–78.2

TABLE A1. (*Continued*)

Symptoms from Primary	Central Location	Mediastinal Metastasis Suspected on CXR	Adeno/Large	Size >3.6	Age >65	Probability (%)	95% CI (%)
1	1	1	0	1	0	67.7	50.3–81.2
0	1	1	1	0	0	68.4	49.0–83.1
0	1	1	1	1	1	69.0	49.5–83.5
1	1	0	1	1	0	69.4	57.4–79.2
1	1	1	1	0	1	70.1	51.5–83.8
1	0	1	1	1	0	72.0	54.7–84.6
0	1	1	1	1	0	77.0	59.3–88.5
1	1	1	1	0	0	77.9	61.9–88.4
1	1	1	1	1	1	78.4	62.8–88.6
1	1	1	1	1	0	84.5	71.7–92.1

CXR, chest radiograph; adeno/large, adenocarcinoma or large cell; CI, confidence interval.