View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

GTS

A prediction model for N2 disease in T1 non–small cell lung cancer

Yang Zhang, MD,[a,b] Yihua Sun, MD,[a,b] Jiaqing Xiang, MD,[a,b] Yawei Zhang, MD,[a,b] Hong Hu, MD,[a,b] and Haiquan Chen, MD[a,b]

Objective: Controversy remains over the routine use of mediastinoscopy or positron emission tomography in T1 non–small cell lung cancer without lymph node enlargement on computed tomography because the risk of N2 involvement is comparatively low. We aimed to develop a prediction model for N2 disease in cT1N0 non–small cell lung cancer to aid in the decision-making process.

Methods: We reviewed the records of 530 patients with computed tomography–defined T1N0 non–small cell lung cancer who underwent surgical resection with systematic lymph node dissection. Correlations between N2 involvement and clinicopathologic parameters were assessed using univariate analysis and binary logistic regression analysis. A prediction model was built on the basis of logistic regression analysis and was internally validated using bootstrapping.

Results: The incidence of N2 disease was 16.8%. Four independent predictors were identified in multivariate logistic regression analysis and included in the prediction model: younger age at diagnosis (odds ratio, 0.974; 95% confidence interval, 0.952-0.997), larger tumor size (odds ratio, 2.769; 95% confidence interval, 1.818-4.217), central tumor location (odds ratio, 3.204; 95% confidence interval, 1.512-6.790), and invasive adenocarcinoma histology (odds ratio, 3.537; 95% confidence interval, 1.740-7.191). This model shows good calibration (Hosmer–Lemeshow test: $P = .784$), reasonable discrimination (area under the receiver operating characteristic curve, 0.726; 95% confidence interval, 0.669-0.784), and minimal overfitting demonstrated by bootstrapping.

Conclusions: We developed a 4-predictor model that can estimate the probability of N2 disease in computed tomography–defined T1N0 non–small cell lung cancer. This prediction model can help to determine the cost-effective use of mediastinal staging procedures. (J Thorac Cardiovasc Surg 2012;144:1360-4)

The wide application of computed tomography (CT) has increased the detection of T1 (≤3 cm)[1] lung cancers. Surgical resection is considered the optimal treatment for T1 non–small cell lung cancer (NSCLC) without mediastinal lymph node (N2) involvement or distant metastasis. However, patients with T1 lung cancer with N2 involvement should take definitive concurrent chemoradiation or induction chemotherapy.[2-4] Accurate mediastinal staging is a key factor for the successful management of NSCLC.

Mediastinoscopy is deemed the gold standard for mediastinal lymph node staging.[5,6] However, the risk of morbidity and mortality (2% and 0.08%, respectively)[7] cannot be overlooked because of the invasive nature of mediastinoscopy. Controversy remains as to whether routine mediastinoscopy should be performed in patients with T1 lung cancer who have no nodal enlargement on CT scans (CT-defined N0) because the risk of N2 disease is low in such patients.[8,9] Although positron emission tomography (PET) showed superiority over CT in the mediastinal staging of NSCLC[10,11] and a promise to reduce the need for invasive staging tools, its high expense is an obstacle to the routine application in many countries.[12] Moreover, the benefit of PET for CT-defined clinical stage IA in patients also remains controversial.[13]

Some studies sought to determine the cost-effective strategies of applying invasive or expensive diagnostic procedures.[14,15] To obtain pretest probability of N2 disease is essential for the cost-effectiveness measurement of subsequent diagnostic tests. Therefore, this study aimed to develop a risk prediction model of N2 disease in CT-defined T1N0 NSCLC.

PATIENTS AND METHODS

Patients

From June 2007 to August 2011, we retrospectively reviewed our database of all patients who underwent resection with curative intention at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Hospital, Shanghai, China. We routinely performed contrast-enhanced chest CT scans at the Fudan University Shanghai Cancer Hospital before surgery, even for the patients who had received CT scans in other hospitals. Other routine preoperative examinations included cardiopulmonary tests, brain magnetic resonance imaging or CT, bone scanning, and abdominal CT or ultrasonography. Lymph nodes were considered to be positive if the short axis exceeded 1 cm on chest CT images. Peripheral nodules were defined

From the Department of Thoracic Surgery,[a] Fudan University Shanghai Cancer Center, Shanghai, China; and Department of Oncology,[b] Shanghai Medical College, Fudan University, Shanghai, China.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Feb 16, 2012; revisions received May 14, 2012; accepted for publication June 18, 2012; available ahead of print July 23, 2012.

Address for reprints: Haiquan Chen, MD, Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, 270 Dong-An Rd, Shanghai 200032, China (E-mail: hqchen1@yahoo.com).

0022-5223/$36.00
Copyright © 2012 by The American Association for Thoracic Surgery
http://dx.doi.org/10.1016/j.jtcvs.2012.06.050

Abbreviations and Acronyms

CT = computed tomography
NSCLC = non–small cell lung cancer
PET = positron emission tomography
ROC = receiver operating characteristic

as tumors with the center located within the outer one third of the lung on CT scans. Inclusion criteria included (1) NSCLC 3 cm or less in diameter measured on CT scans without evidence of positive lymph nodes or distant metastasis (cT1N0M0) and (2) systematic lymph node dissection. Patients who had adenocarcinoma in situ or minimally invasive adenocarcinoma histology according to the new lung adenocarcinoma classification[16] were excluded (only invasive adenocarcinomas were included). Patients who received neoadjuvant chemotherapy or radiotherapy were excluded. Patients with a history of malignant tumors were excluded.

Clinicopathologic data on age, gender, smoking history, family history of lung cancer, symptoms at presentation, tumor site, tumor size measured on CT, type of surgery, histology, and lymph nodal status according to pathologic reports were collected.

This study was conducted in accordance with the Helsinki Declaration and approved by the institutional review board of the Fudan University Shanghai Cancer Center, Shanghai, China. Informed consent was waived because this was a retrospective analysis.

Statistical Analyses

In univariate analyses, we used Pearson's chi-square test or the Fisher exact test to evaluate the correlation between a mediastinal lymph node metastasis and a categoric variable, and an independent sample *t* test to assess the association between N2 involvement and a continuous variable. Variables with a *P* value less than .2 were entered into a binary logistic regression analysis that formed the basis of a prediction model. We used forward stepwise selection procedures with the likelihood-ratio test. Factors statistically significant at the .05 level remained in the final model.

Calibration (concordance between predicted and observed probabilities) of the final model was determined with the Hosmer–Lemeshow statistic and the calibration plot using 10 equal contiguous risk ranges showing observed versus predicted probabilities. The discriminative ability of the model was assessed with the area under the receiver operating characteristic (ROC) curve, which ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination).

A problem with a predictive model is that the performance is overestimated when assessed on the sample used to build the model.[17] We internally validated this model by bootstrapping, which is reported to be more efficient than other alternatives, such as cross-validation or split-sample analyses.[17] We applied Harrell and colleagues'[18] method of using bootstrapping to estimate the bias-corrected area under the ROC curve and the extent of "overfitting." One thousand bootstrap samples were drawn, each with a sample size equal to the original (530 in our study), by randomly sampling 530 subjects with replacement from the original sample.

We used SPSS for Windows (v. 16.0; Chicago, Ill), Stata (v. SE/11.1; StataCorp, College Station, Tex), and R (version 2.10.0; R Foundation for Statistical Computing, Vienna, Austria) for statistical analysis. All tests were 2-tailed.

RESULTS

Patient characteristics are listed in Table 1. A total of 530 patients (251 female and 279 male) were reviewed. The median age at diagnosis was 59 years (interquartile range, 13). Tumor size ranged from 0.4 to 3.0 cm (median, 2.0; interquartile range, 1.0). The most common lobar location was the left upper lobe (30.4%), followed by the right upper lobe (28.7%). The majority (91.5%) of patients underwent lobectomy.

The incidence of mediastinal lymph node metastasis was 16.8% (89/530). In univariate analysis (Table 1), N2-positive patients were significantly younger than N2-negative patients ($P = .028$). The mean tumor diameter of patients with mediastinal nodal involvement was significantly larger than those without mediastinal nodal involvement ($P < .001$). The incidence of N2 disease in patients with invasive adenocarcinoma was 19.5% compared with 9.6% in patients with other histology ($P = .006$). Patients with positive N2 nodes were more likely to be never-smokers (69.7% vs 58.0%; $P = .041$) and to have centrally located tumors (18.0% vs 10.2%; $P = .036$).

Finally, 4 independent predictors were included in the prediction model after multivariate logistic regression. Odds ratios, 95% confidence intervals, and *P* values of significant predictors are listed in Table 2. Larger tumor size ($P < .001$), central tumor location ($P = .002$), invasive adenocarcinoma histology ($P < .001$), and younger age at diagnosis ($P = .025$) were independent predictors of mediastinal lymph node metastasis.

A formula was developed to estimate the probability of having mediastinal lymph node metastasis on the basis of the results of the binary logistic regression analysis. A score is calculated using tumor diameter, tumor location, histology, and age at diagnosis: score $= -3.449 + (1.018 \cdot \text{diameter}) + (1.164 \cdot \text{location}) + (1.263 \cdot \text{histology}) - (0.026 \cdot \text{age})$. The units for diameter and age are centimeter and year, respectively. If the tumor is centrally located, location = 1 (location = 0 if the tumor is peripherally located). If the tumor is adenocarcinoma in histology, histology = 1 (histology = 0 for other histology). The likelihood of N2 nodal involvement is then calculated: likelihood of positive N2 nodes $= e^{\text{Score}}/(1 + e^{\text{Score}})$. A nomogram to predict the probability of N2 involvement was also developed on the basis of the multivariate analysis (Figure 1). For example, for a 65-year-old patient who had a peripherally located tumor that is adenocarcinoma in histology and 2.0 cm in diameter, score $= -3.449 + (1.018 \cdot 2) + (1.164 \cdot 0) + (1.263 \cdot 1) - (0.026 \cdot 65) = -1.84$, likelihood of positive N2 nodes $= e^{-1.84}/(1 + e^{-1.84}) = 0.137$. We can also refer to the nomogram and find that the probability is between 0.1 and 0.2.

Hosmer–Lemeshow test of goodness-of-fit was not significant ($P = .784$), suggesting a high concordance between predicted and observed probabilities. The calibration plot (Figure 2) showed that predicted probabilities closely

TABLE 1. Patient characteristics and univariate analyses of clinicopathologic factors associated with mediastinal nodal metastasis

Variable	All (n = 530)	N2 positive (n = 89)	N2 negative (n = 441)	*P*
Age (y)				
Median	59	57	60	
IQR	13	11	13	.028
Female	251	44	207	.667
Symptomatic	289	54	235	.202
Never-smoker	318	62	256	.041
Family history	43	3	40	.072
Tumor size (cm)				
Median	2.0	2.5	2.0	
IQR	1.0	0.9	1.0	<.001
Tumor location				
Central location	61	16	45	.036
Upper lobes	313	46	267	.121
Invasive adenocarcinoma	384	75	309	.006

IQR, Interquartile range.

matched observed probabilities in each of the 10 risk ranges. The area under the ROC curve (Figure 3), which measures the model's accuracy, was reasonable (odds ratio, 0.726; 95% confidence interval, 0.669-0.784). Internal validation by bootstrapping showed the bias-corrected area under the ROC curve was 0.717, and the extent of "over-optimism" was minimal (0.009, 1.2%), indicating that this prediction model holds for future patients.

DISCUSSION

Accurate mediastinal staging is critical for the appropriate management of NSCLC. Although CT achieved only a moderate diagnostic efficacy,[19] there remains controversy over the routine use of invasive (eg, mediastinoscopy) or expensive (eg, PET) diagnostic tools in T1 NSCLC without lymph node enlargement on CT because of the low incidence of N2 involvement. To select the cost-effective strategies of staging, we have to obtain pretest probability of nodal metastasis. Our center has surgically treated (with systematic lymph node dissection) a large number of patients with CT-defined T1N0 NSCLC in the past 5 years. The current study took this advantage and generated a risk prediction model including 4 independent predictors of N2 disease: younger age at diagnosis, larger tumor size, central location, and invasive adenocarcinoma histology. The prediction model displays good calibration, reasonable discriminative performance, and minimal optimism demonstrated by internal validation using bootstrapping. Our prediction model should help to select candidates for different staging strategies.

TABLE 2. Independent predictors of mediastinal lymph node metastasis in binary logistic regression analysis

Variable	OR	95% CI	*P*
Age (y)	0.974	0.952-0.997	.025
Tumor size (cm)	2.769	1.818-4.217	<.001
Central location	3.204	1.512-6.790	.002
Invasive adenocarcinoma	3.537	1.740-7.191	<.001

OR, Odds ratio; *CI,* confidence interval.

Shafazand and Gould[20] developed a clinical prediction rule to calculate the probability of mediastinal lymph node metastasis. However, their prediction model was not suitable to estimate the risk of nodal involvement in CT-defined T1N0 NSCLC in several ways. First, CT findings were not included in the model because only half of the patients in their sample received CT scans. Because suspected mediastinal metastasis on chest x-ray, which was 1 of the 6 predictors in that model, possibly correlated with enlarged lymph nodes on CT, we could expect the presence of clinical N2 cases if CT was applied to those patients. Second, the enrolled patients were not limited to stage T1 only, and tumor size greater than 3.6 cm was used as a risk predictor in their model. This cutoff value could not stratify patients with T1 ($\leq$3 cm in diameter) into high- and low-risk categories, which is contradictory to our findings that larger tumor size is an independent risk predictor of N2 involvement in patients with clinical T1N0.

The 4 predictors of N2 disease in our prediction model were also identified in other studies. De Leyn and colleagues[21] reported that T1N0 (defined by CT) adenocarcinoma was more likely to have a positive mediastinoscopy than T1N0 squamous cell carcinoma. Defranchi and colleagues[9] retrospectively reviewed 59 cases of N2 disease in T1 NSCLC and found central tumor location in 41 cases (69%). A study on 503 patients with completely resected invasive T1 NSCLC revealed that tumor size independently affected nodal metastasis.[22] Shafazand and Gould[20] showed that age less than 65 years was an independent predictor of mediastinal lymph node metastasis. Younger patients with NSCLC were more likely to present with more aggressive disease and have a lower degree of suspicion of lung cancer, which might lead to delayed diagnosis.[23] Suzuki and colleagues[24] also revealed that adenocarcinoma histology and large tumor dimension were predictive factors for pathologic N2 in patients with NSCLC with a negative mediastinum on CT scans.

However, our prediction model can calculate the probability of N2 disease, which has direct implications for the selection of diagnostic tools for patients with CT-defined T1N0 NSCLC. For example, for a 69-year-old patient who has a peripherally located tumor that is squamous cell carcinoma in histology and 1.3 cm in diameter, we calculate a score of –3.916, and therefore the predicted probability of N2 disease is 2.0%, which is low enough for the patient to go directly to surgery.

If a patient has a moderate risk of nodal involvement (eg, 12%), doctors might advise the patient to receive mediastinoscopy because a cost-effectiveness study conducted by Meyers and colleagues[15] suggested that if the risk of N2

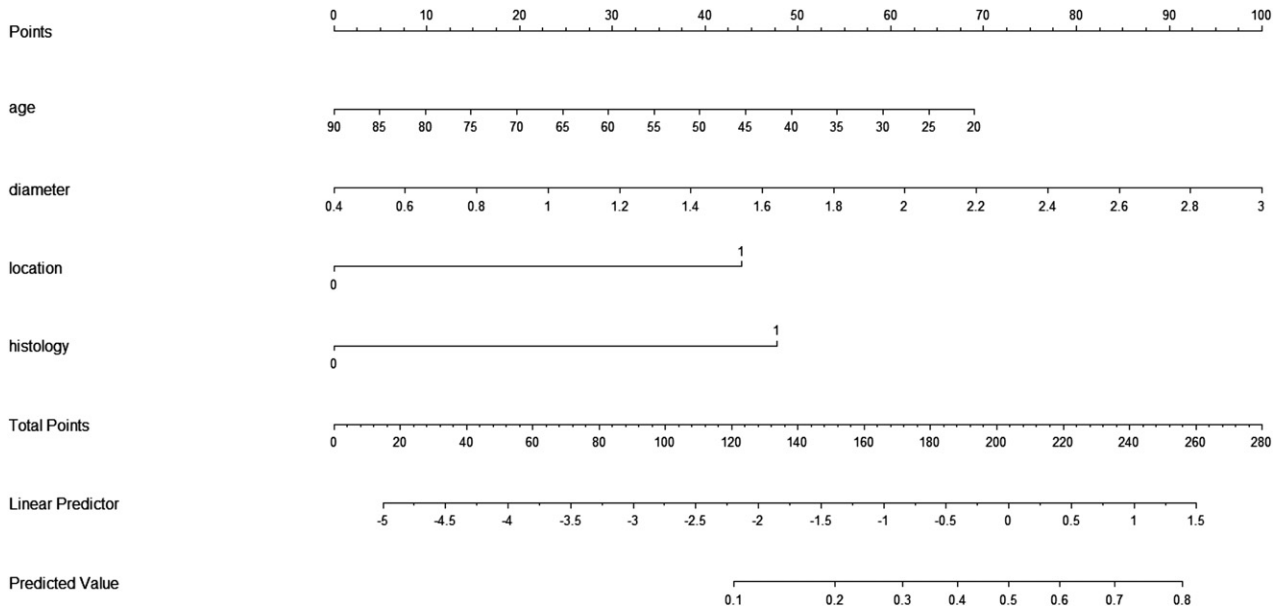

FIGURE 1. Nomogram for predicting the probability of N2 disease in T1 NSCLC. The units for diameter and age are center and year, respectively. If the tumor is centrally located, location = 1 (location = 0 if the tumor is peripherally located). If the tumor is adenocarcinoma in histology, histology = 1 (histology = 0 for other histology). Locate patient's age on "age" axis, and draw a perpendicular line to the "points" axis to determine associated points. Repeat for all the remaining predictors. Locate sum on the "total points" axis, and draw a perpendicular line to get the predicted probability. *NSCLC*, Non–small cell lung cancer.

disease is more than 10%, mediastinoscopy would have good yields (<100,000 dollars per life-year gained). However, the doctors may deem this risk not high enough to justify an invasive diagnostic procedure and would rather prescribe a PET scan first. A meta-analysis estimated that the pooled sensitivity and specificity of fluorodeoxyglucose PET for detecting mediastinal lymph node involvement were 83% and 92%, respectively.[10] According to Bayes' theorem, the post-test probability after a positive PET scan will be 58.6%; the post-test probability after a negative PET scan will be 2.5%. A decision can be made at this point (mediastinoscopy after a positive PET scan and surgery after a negative PET scan). However, if the estimated pretest likelihood of N2 disease for a patient is as high as 50%, the post-test likelihood even after a negative PET scan will be

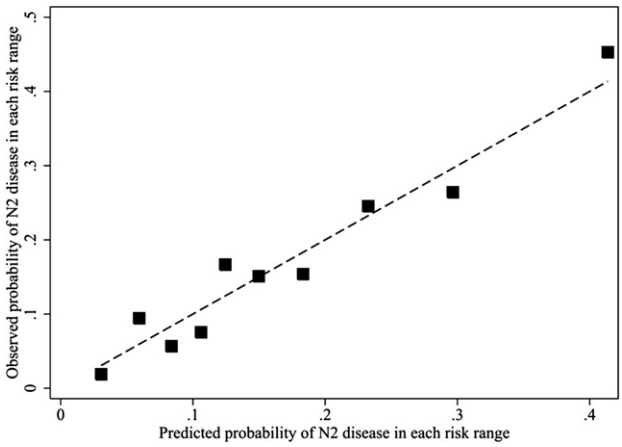

FIGURE 2. Calibration plot. The *dashed line* indicates prefect concordance between observed and predicted probabilities.

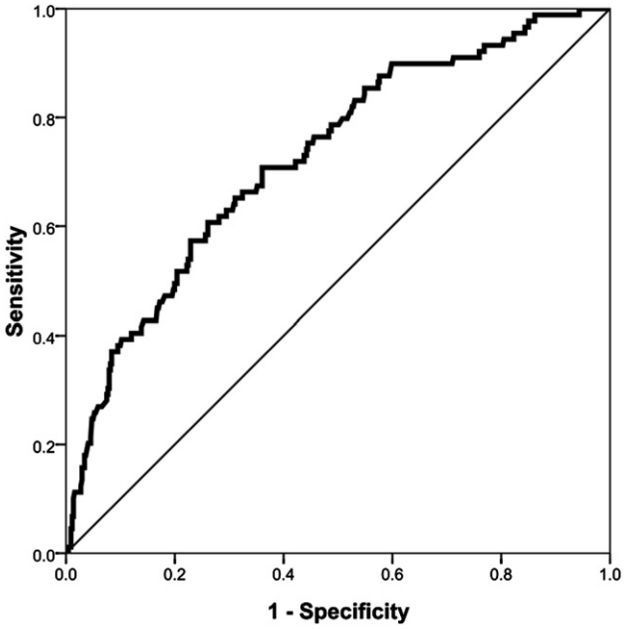

FIGURE 3. ROC curve for the 4-predictor model. The area under the ROC curve was 0.726 (95% confidence interval, 0.669-0.784). *ROC*, Receiver operating characteristic.

15.6%, which could not rule out the use of mediastinoscopy. Therefore, PET scans should not be performed in patients with high pretest likelihoods of N2 nodal involvement.

Study Limitations

Our study has several limitations. It should be noted that action thresholds may vary among doctors. For example, some doctors deem that a patient with a probability less than 10% of N2 involvement can go directly to surgery, whereas others might argue a risk of 8% is still too high to exclude mediastinoscopy. This discrepancy could not be resolved through our prediction model. However, this model provides quantified predicted probability, which can be incorporated in the decision-making process and help the cost-effective selection of diagnostic strategies.

Another factor worthy of note is that PET scan is now routinely used in some developed countries, such as the United States, which may thus limit the generalizability of this model. However, as we described earlier, this prediction model could provide a pretest probability that can be used to calculate a posttest probability after a PET scan according to Bayes' theorem. In other words, it can facilitate the interpretation of PET results and subsequently guide the selection of invasive diagnostic procedures.

Some may criticize that the c statistic (0.726) of our model is only fair. Although the discriminative ability of our model may not be good enough if it is used as a stand-alone diagnostic test, this simple clinical prediction model can estimate pretest probabilities of N2 disease, which would help the selection of subsequent diagnostic tools. However, our prediction model is built retrospectively and only on Chinese patients with NSCLC. Despite the minimal optimism revealed by bootstrapping, further external validation is still warranted to investigate the generalizability of this prediction model.

CONCLUSIONS

We developed a 4-predictor model for N2 disease in patients with T1 NSCLC without lymph node enlargement on CT scans. The predicted likelihood of N2 nodal involvement has implications for the cost-effective use of diagnostic procedures, such as mediastinoscopy and PET, in staging mediastinal lymph nodes in CT-defined T1N0 NSCLC.

References

1. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest*. 2009;136:260-71.
2. Ettinger DS, Akerley W, Bepler G, Blum MG, Chang A, Cheney RT, et al. Non-small cell lung cancer. *J Natl Compr Canc Netw.* 2010;8:740-801.
3. Kirn DH, Lynch TJ, Mentzer SJ, Lee TH, Strauss GM, Elias AD, et al. Multimodality therapy of patients with stage IIIA, N2 non-small-cell lung cancer. Impact of preoperative chemotherapy on resectability and downstaging. *J Thorac Cardiovasc Surg*. 1993;106:696-702.
4. Uy KL, Darling G, Xu W, Yi QL, De Perrot M, Pierre AF, et al. Improved results of induction chemoradiation before surgical intervention for selected patients with stage IIIA-N2 non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2007;134:188-93.
5. Gonzalez-Stawinski GV, Lemaire A, Merchant F, O'Halloran E, Coleman RE, Harpole DH, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2003;126:1900-5.
6. Kramer H, Groen HJ. Current concepts in the mediastinal lymph node staging of nonsmall cell lung cancer. *Ann Surg*. 2003;238:180-8.
7. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):202S-20S.
8. Choi YS, Shim YM, Kim J, Kim K. Mediastinoscopy in patients with clinical stage I non-small cell lung cancer. *Ann Thorac Surg*. 2003;75:364-6.
9. Defranchi SA, Cassivi SD, Nichols FC, Allen MS, Shen KR, Deschamps C, et al. N2 disease in T1 non-small cell lung cancer. *Ann Thorac Surg*. 2009;88:924-8.
10. Birim O, Kappetein AP, Stijnen T, Bogers AJ. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg*. 2005;79:375-82.
11. Reed CE, Harpole DH, Posther KE, Woolson SL, Downey RJ, Meyers BF, et al. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2003;126:1943-51.
12. Whitson BA, Groth SS, Maddaus MA. Recommendations for optimal use of imaging studies to clinically stage mediastinal lymph nodes in non-small-cell lung cancer patients. *Lung Cancer.* 2008;61:177-85.
13. Kozower BD, Meyers BF, Reed CE, Jones DR, Decker PA, Putnam JB Jr. Does positron emission tomography prevent nontherapeutic pulmonary resections for clinical stage IA lung cancer? *Ann Thorac Surg*. 2008;85:1166-70.
14. Kelly RF, Tran T, Holmstrom A, Murar J, Segurola RJ Jr. Accuracy and cost-effectiveness of [18F]-2-fluoro-deoxy-D-glucose-positron emission tomography scan in potentially resectable non-small cell lung cancer. *Chest*. 2004;125:1413-23.
15. Meyers BF, Haddad F, Siegel BA, Zoole JB, Battafarano RJ, Veeramachaneni N, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. *J Thorac Cardiovasc Surg*. 2006;131:822-9.
16. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. *J Thorac Oncol*. 2011;6:244-85.
17. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol*. 2001;54:774-81.
18. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361-87.
19. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s–meta-analytic comparison of PET and CT. *Radiology.* 1999;213:530-6.
20. Shafazand S, Gould MK. A clinical prediction rule to estimate the probability of mediastinal metastasis in patients with non-small cell lung cancer. *J Thorac Oncol*. 2006;1:953-9.
21. De Leyn P, Vansteenkiste J, Cuypers P, Deneffe G, Van Raemdonck D, Coosemans W, et al. Role of cervical mediastinoscopy in staging of non-small cell lung cancer without enlarged mediastinal lymph nodes on CT scan. *Eur J Cardiothorac Surg*. 1997;12:706-12.
22. Flieder DB, Port JL, Korst RJ, Christos PJ, Levin MA, Becker DE, et al. Tumor size is a determinant of stage distribution in t1 non-small cell lung cancer. *Chest*. 2005;128:2304-8.
23. DeCaro L, Benfield JR. Lung cancer in young persons. *J Thorac Cardiovasc Surg*. 1982;83:372-6.
24. Suzuki K, Nagai K, Yoshida J, Nishimura M, Takahashi K, Nishiwaki Y. Clinical predictors of N2 disease in the setting of a negative computed tomographic scan in patients with lung cancer. *J Thorac Cardiovasc Surg*. 1999;117:593-8.