Ten-year follow-up of a province-wide cohort of surgical lung cancer patients in Nova Scotia

Daniel R. Wong, MD, MPH;* Harry J. Henteleff, MD, MSc†

Background: After a diagnosis of lung carcinoma, survival is poor for all patients. We sought to assess 10-year survival and predictors of outcome after surgery for lung cancer in Nova Scotia. **Methods:** We identified all patients (n = 130) undergoing resection for lung cancer in Nova Scotia in 1994 from the Nova Scotia Cancer Registry and hospital charts and followed them prospectively for 10 years. We used Cox proportional hazards modelling to identify predictors of survival. **Results:** The patients' mean age at operation was 67.7 (standard deviation [SD] 8.2) years, and 70% of the patients were men. Most of the operations (n = 80, 61.5%) were performed in Halifax, and adenocarcinoma (n = 55, 42.3%) was the most common histologic type. At the time of surgery, 66.9% of the cases were stage 1, 20.0% were stage 2 and 13.1% were stage 3. Survival at 5 and 10 years was 34% and 13%, respectively. Age of 70 years or older (hazard ratio [HR] 1.79, 95% confidence interval [CI] 1.20–2.68), large cell carcinoma (HR 2.27, 95% CI 1.31–3.94) and stage 3 cancer (HR 2.21, 95% CI 1.25–3.90) were significant independent predictors of survival. Hospital site was not associated with any difference in survival (p = 0.66), although there was a trend toward differential rates of lymph node sampling across sites (p = 0.06). The presence of node sampling was associated with improved survival in a separate multivariate model (HR 0.51, 95% CI 0.29–0.89). **Conclusion:** Actuarial survival after resection of lung carcinoma in Nova Scotia in 1994 was 34% at 5 years and 13% after 10 years. Age, stage and histology are independent predictors of survival; lymph node sampling was associated with greater survival.

Contexte : Après un diagnostic de cancer du poumon, la survie est médiocre chez tous les patients. Nous avons cherché à évaluer la survie à 10 ans et les prédicteurs des résultats après une intervention chirurgicale contre un cancer du poumon en Nouvelle-Écosse. **Méthodes :** Nous avons trouvé, dans le Registre du cancer de la Nouvelle-Écosse et les dossiers d'hôpital, tous les patients (n = 130) ayant subi une résection pour un cancer du poumon en Nouvelle-Écosse en 1994 et nous les avons suivis de façon prospective pendant 10 ans. Nous avons utilisé le modèle des risques proportionnels de Cox pour identifier les prédicteurs de survie. **Résultats :** Au moment de l'intervention, les patients avaient en moyenne 67,7 ans (écart-type [ET] 8,2 ans) et 70 % étaient des hommes. La plupart des interventions (n = 80, 61,5 %) ont été pratiquées à Halifax et l'adénocarcinome (n = 55, 42,3 %) était le type histologique le plus répandu. Au moment de l'intervention chirurgicale, 66,9 % des cas en étaient au stade 1, 20,0 %, au stade 2, et 13,1 %, au stade 3. La survie à 5 et à 10 ans s'est établie à 34 % et 13 % respectivement. L'âge de 70 ans ou plus (taux de risque [TR] 1,79, intervalle de confiance [IC] à 95 %, 1,20–2,68), le carcinome à grandes cellules (TR 2,27, IC à 95 %, 1,31–3,94) et le cancer de stade 3 (TR 2,21, IC à 95 %, 1,25–3,90) étaient des prédicteurs indépendants importants de la survie. Le centre hospitalier n'était associé à aucune différence au niveau de la survie (p = 0,66), même si on a constaté une tendance à des taux différentiels de prélèvement d'échantillons des ganglions lymphatiques entre les sites (p = 0,06). On a établi un lien entre le prélèvement d'échantillons des ganglions et une amélioration de la survie dans un modèle distinct à variables multiples (TR 0,51, IC à 95 %, 0,29–0,89). **Conclusion :** La survie actuarielle après une résection d'un cancer du poumon pratiquée en Nouvelle-Écosse en 1994 s'établissait à 34 % à 5 ans et à 13 % après 10 ans. L'âge, le stade et l'histologie sont des prédicteurs indépendants de la survie. On a établi un lien entre le prélèvement d'échantillons des ganglions lymphatiques et une survie plus longue.

*From the Divisions of *Cardiac Surgery and †Thoracic Surgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS*

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Correspondence to: *Dr. H.J. Henteleff, Department of Surgery, Room 7-011, Queen Elizabeth II Health Sciences Centre–Victoria General site, Halifax NS B3H 2Y9; fax 902 473-5851; harry.henteleff@dal.ca*

Lung cancer is the leading cause of cancer death in Canada and is largely preventable with a risk attributable to smoking of 85%. An estimated 1 in 12 men and 1 in 22 women will die from lung cancer across the nation. In Nova Scotia, the 5-year age-standardized survival for patients diagnosed with lung cancer is 13% for men and 16% for women.[1] Stage at the time of presentation and treatment have been known to affect mortality; survival among patients undergoing surgical resection is expected to be better than survival among the overall group of patients, owing to selection and treatment biases. Reported cause-specific survival from large study centres for stage I non–small cell lung cancer (NSCLC) is in the range of 60%–80% at 5 years.[2,3] Nevertheless, current long-term outcomes of surgical treatment are less well characterized, particularly in Canadian practice paradigms and in the real world for all-comer surgical patients. Nova Scotia represents a stable population of patients suitable for such analysis. The purpose of this study was to analyze the 10-year overall survival for the defined cohort of all patients undergoing surgery for lung cancer in the province during 1 year and to assess the impact of various parameters, including institutional differences and lymph node dissection on survival.

Methods

Data collection

In Nova Scotia, a single tertiary university teaching institute in Halifax and several peripheral hospitals provide surgical treatment for patients with lung cancer. Distribution of patients is at the discretion of referring physicians. We identified all patients (n = 130) undergoing surgery for lung cancer in Nova Scotia in 1994 from the Nova Scotia Cancer Registry (NSCR) and from hospital records and abstracted baseline characteristics. Operative and pathological data included the hospital site, stage, histology, procedure and whether lymph node sampling (generally including formal lymph node dissection) was performed. Operative management and technique were at the discretion of the attending surgeon and included a majority of complete, anatomical resections (largely pneumonectomy and lobectomy, although lesser resections were performed for selected patients). At the time, routine adjuvant chemo- or radiotherapy was reserved for stage III disease. The study group was followed prospectively through the NSCR and analyzed retrospectively in an analysis linked to vital statistics for the province. Death clearances were performed on a quarterly basis, and we obtained the date of death or last contact from the NSCR or surgeons' office records at the end of 2004.

Statistical analysis

All statistical tests were performed with SAS software (SAS version 8, SAS Institute). Univariate tests included Student's t test for categorical variables and the χ^2 test for discrete variables. Survival was calculated according to Kaplan–Meier estimates, with the log-rank test for comparison between groups. We used multivariable Cox proportional hazards modelling to identify independent predictors of late mortality, with a stepwise selection with entry and stay criteria of 0.10 and 0.05, respectively. Stage (I, II and III, with no patients having stage IV cancer) and histology (squamous cell carcinoma [SCC], adenocarcinoma, large cell carcinoma [LCC], small cell carcinoma [SmCC] and other) were modelled as categorical variables, and age was dichotomized at 70 years. An analysis was performed to determine whether the lack of lymph node sampling affected stage and survival. Stage was reassessed with the assumption that all unsampled N1 nodes were actually positive. We considered $p < 0.05$ to be significant with no adjustment for multiple testing.

Results

Study population

In 1994, 130 patients underwent surgical resection for lung cancer. Their mean age was 67.7 (standard deviation [SD] 8.2) years, and 70.0% of the patients were men. With regard to hospital site, 61.5% of the patients had their surgery performed in Halifax, 19.2% in Sydney, 8.5% in Kentville and 10.8% at other sites. Complete resections included pneumonectomy (n = 36, 27.7%), lobectomy (n = 67, 51.5%) and bilobectomy (n = 10, 7.7%). Four patients (3.1%) underwent segmentectomy, and 13 patients (10.0%) had wedge resection. The tumour was located in the left upper lobe in 30.0%, left lower lobe in 17.7%, right upper lobe in 22.3%, right middle lobe in 6.2% and right lower lobe in 20.0% (3.8% were not specified). Most patients (n = 112, 86.2%) underwent N1 lymph node sampling. Adenocarcinoma was the most frequent histology (42.3%) followed by SCC (33.1%), LCC (13.1%) and SmCC (3.1%). Other histologic diagnoses included adenosquamous carcinoma (2.3%) and carcinoma (3.8%); they were not otherwise specified in 2.3% of the cases.

Survival

At 10-year follow-up, there had been 100 deaths among the 130 patients. Median survival was 3.1 years (25th and 75th percentiles, 0.9 and 6.9, respectively). Actuarial crude survival was 34% at 5 years and 13% at 10 years. There were significant differences between the baseline characteristics of patients who survived and those who did not (Table 1). Hospital site (Halifax v. other) was not associated with any difference in survival (p = 0.66), nor was the site (sidedness or lobe) of the lesion (p = 0.15). There was a reduction in crude survival associated with lesser resection (p = 0.02).

Effect of lymph node sampling

If we did not have information to the contrary, we assumed in all analyses that unsampled lymph nodes were negative; this included the 18 patients who did not undergo any sampling of nodes. Lack of lymph node sampling was associated on a univariate basis with lesser resections (2/13 sampled, $p < 0.001$) and LCC ($p = 0.02$). Nodes were sampled more often in SCC ($p = 0.03$), lobectomy ($p = 0.04$) and pneumonectomy ($p = 0.02$). A trend to greater sampling was associated with the Halifax site ($p = 0.06$). With multivariate analysis, the presence of N1 node sampling was an independent predictor of improved survival, in addition to age, LCC and advanced stage (Table 2).

To determine the effect of lymph node sampling on staging and survival, we performed an analysis in which we assumed that patients who did not have lymph nodes sampled actually had positive N1 lymph nodes. Had this been the case, it would have resulted in a redistribution of patients into higher stages (Fig. 1), with a shift in survival estimates for each stage (Fig. 2). Survival at 5 years would have increased for stage 1 (42% v. 37%), while survival for stages 2 and 3 would have decreased (27% v. 34%, and 17% v. 18%, respectively). However, owing to the small number of patients affected by this analysis, the resulting changes in stratified, stage-specific survival did not attain statistical significance ($p = 0.42$, 0.52 and 0.90, respectively).

Table 1

Selected baseline characteristics of the cohort, stratified by survival

Characteristics	Survival; no. (and %)*		*p* (logrank)
	Alive (*n* = 30)	Dead (*n* = 100)	
Age, y			
Mean (SD)	66.9 (6.7)	70.0 (8.6)	0.01
≥ 70	10 (33.3)	48 (48.0)	
Sex			0.16
Male	20 (66.7)	71 (71.0)	
Female	10 (33.3)	29 (29.0)	
Histology			0.01
Adenocarcinoma	9 (30.0)	46 (46.0)	
Large cell carcinoma	1 (3.3)	16 (16.0)	
Small cell carcinoma	1 (3.3)	3 (3.0)	
Squamous cell carcinoma	15 (50.0)	28 (28.0)	
Other	4 (13.3)	7 (7.0)	
Adenosquamous	0	3 (3.0)	
Carcinoma	3 (10.0)	2 (2.0)	
Not specified	1 (3.3)	2 (2.0)	
Stage			0.05
1	21 (70.0)	66 (66.0)	
1A	6 (20.0)	26 (26.0)	
1B	15 (50.0)	40 (40.0)	
2	7 (23.3)	19 (19.0)	
2A	1 (3.3)	1 (1.0)	
2B	6 (20.0)	18 (18.0)	
3 (3A)	2 (6.7)	15 (15.0)	
Procedure			
Pneumonectomy	9 (30.0)	27 (27.0)	0.66
Lobectomy	18 (60.0)	49 (49.0)	0.38
Bilobectomy	1 (3.3)	9 (9.0)	
Other	2 (6.7)	15 (15.0)	0.02
Segmentectomy	1 (3.3)	3 (3.0)	
Wedge	1 (3.3)	12 (12.0)	

*Unless otherwise indicated.

Discussion

Survival for Nova Scotians after lung cancer surgery has not been well documented. We therefore examined the results for the 1994 cohort of such patients. At that time, surgery alone was standard care for stage I and II cancer, with adjuvant therapy being reserved for stage III disease. In Nova Scotia, actuarial crude survival after resection of lung carcinoma remains fairly low at 34% at 5 years and 13% after 10 years and represents the real-world survival after treatment in the province.

Unlike other large benchmark series, which report cancer-specific mortality from such venerable institutions as the M. D. Anderson Cancer Center,[2] our survival data include the effect of competing deaths from other comorbidities and, as such, represent the overall impact on these patients, the health system and this province. With a mean age of nearly 68 years and 10-year follow up, the likely impact of other causes of death is not insignificant. Unfortunately, disease-specific mortality was not available for this study, and we do not believe that obtaining this information retrospectively from death certificates would be reliable.

Table 2

Independent predictors of long-term mortality

Predictors	Hazard ratio	95% confidence interval
Age ≥ 70 y	1.70	1.13–2.56
Large cell carcinoma	2.42	1.36–4.30
Stage 3	1.98	1.12–3.50
N1 nodes sampled	0.51	0.29–0.89

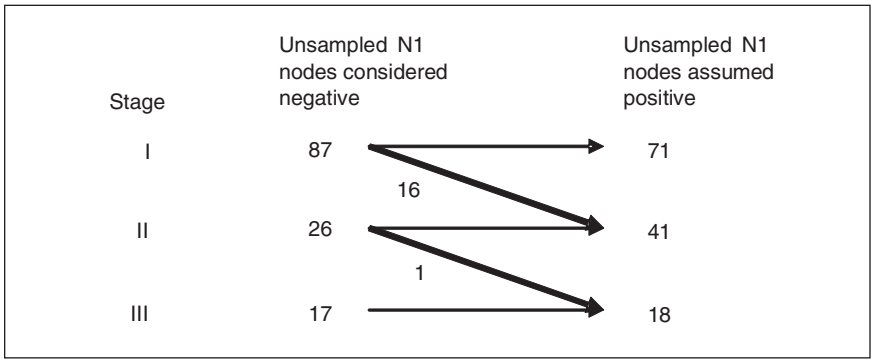

FIG. 1. Number of patients by stage based on assumed status of unsampled N1 lymph nodes.

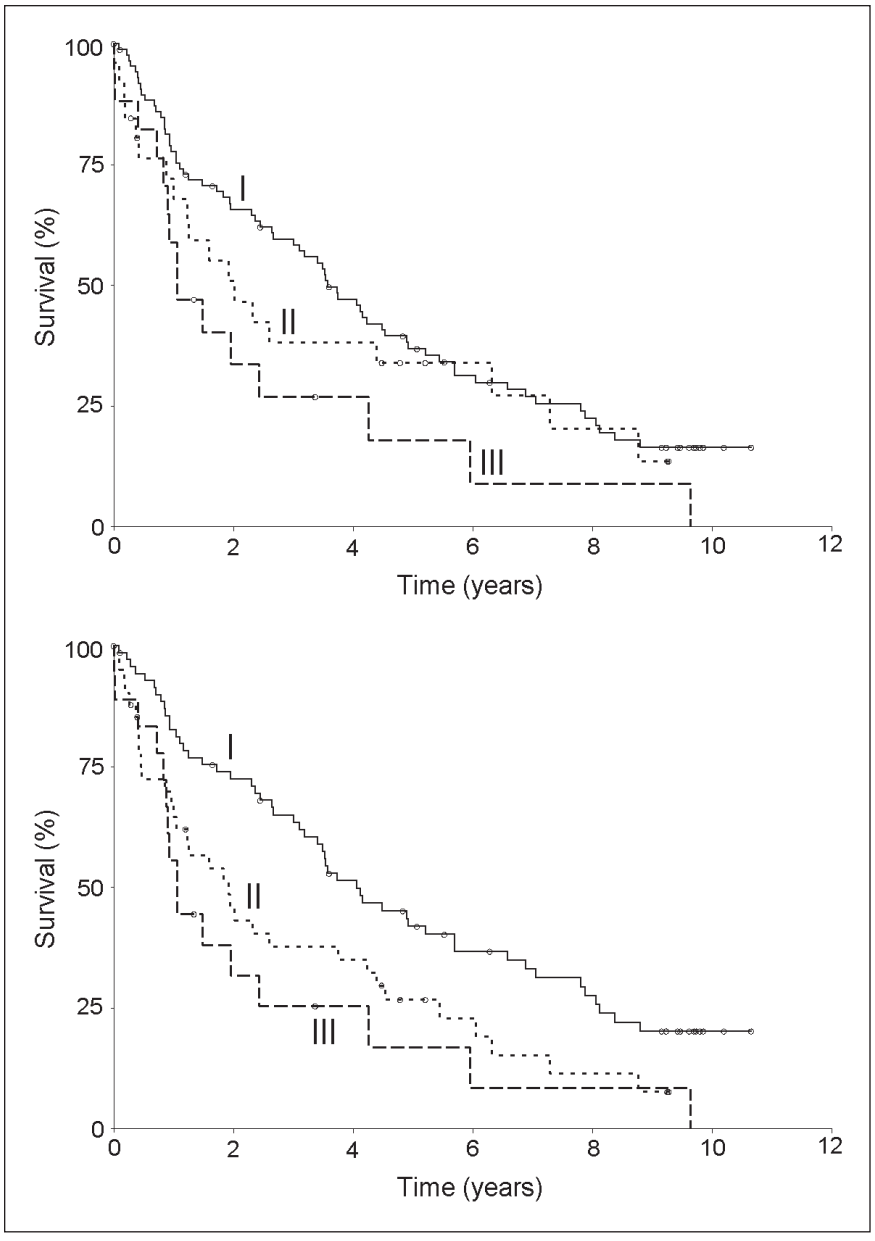

FIG. 2. Survival stratified by stage of lung cancer (upper) assuming unsampled lymph nodes are negative and (lower) assuming they are positive.

Thus, outside the confines of clinical trials in which patients are prospectively followed and clearly defined causes of death assessed, determining cancer-specific mortality is fraught with problems. While all the patients studied were fit enough to undergo surgery, the fact that 13% underwent lesser resections suggests their comorbid status prohibited more aggressive surgery, although we did not have more detailed information on comorbidities. In our analysis, age, stage, histology and the presence of lymph node sampling were independent predictors of survival.

From a health services perspective, hospital site was not associated with risk of long-term mortality. This is important when one is considering the merits and outcomes of different health systems paradigms, especially in light of potentially large variations in institutional practice. For instance, we found differences across the province in such process variables as lymph node sampling, with a trend to more frequent lymph node sampling in the tertiary care referral institution.

In our cohort, lymph node sampling, and the lack thereof, had important potential implications for staging and stage-specific survival estimates. Stage migration is a phenomenon that occurs when incomplete diagnostic and pathological information lead to systematic misclassification in staging that results in seemingly worse outcomes for the lower-risk groups. While the change in stage-specific survival in our relatively small, single-year, provincial cohort did not reach statistical significance, the magnitude of this effect would be considerably greater over several years or on a national level. This is consistent with the findings of Schulze and colleagues,[4] who did not report mediastinal nodal status and reported lower 5-year survival among patients with stage 1 NSCLC (63% and 50% for T1 and T2 primary tumours, respectively) compared with others (for instance about 80% and 62% reported by the Mayo group[3]).

Moreover, it is well recognized that, even within the literature, there is a significant difference in survival based on pathological versus clinical stage, reflecting understaging.[2] For these reasons, it is often difficult to compare real-world stage-specific survival with survival in other large series in which standardized protocols were used to ensure complete lymph node sampling. In addition, our results cannot be compared with large trial data in which strict eligibility criteria are often enforced and in which referral patterns may be quite different from ours.

The association of lymph node sampling with improved survival is a complex one because the occurrence of node sampling is not uniform and is confounded by comorbidities and other clinical factors that influence both operative decision-making and survival. For instance, a frail, elderly, medically unwell patient may be more likely to have a wedge resection performed without lymph node sampling because anatomical resections may not afford much benefit to such a patient.[5]

The association of lack of lymph node sampling with lesser resection deserves emphasis because there is evidence in the literature that lesser resection is associated with worse outcomes, even after controlling for patient medical status. In one observational study of 598 patients with stage I NSCLC, complete excision by wedge resection or segmentectomy in 62 patients (11%) was associated with a 50% recurrence rate and significantly reduced survival at 5 and 10 years (59% and 35%, respectively); similar 5- and 10-year survival (59% and 32%, respectively) was reported for the 38 patients who did not undergo lymph node dissection.[6] A trial of lesser resection versus complete anatomical resection demonstrated increased locoregional recurrence, but no difference in 5-year survival, in the group with a lesser resection, although the lack of a midterm survival benefit may have been affected by reresection for local recurrence.[7,8] Nevertheless, attaining disease-free survival at 5 years appears to be a beneficial goal because these patients do well in terms of late recurrence and 10-year survival, regardless of their initial stage and histology.[9]

Given the increasing evidence for and use of adjuvant therapy for stage I and II disease,[10–13] a strategy of lesser resection and/or foregoing lymph node sampling may have important implications for patient care: it may preclude proper staging, which in turn leads to stage migration, and it may confound subsequent decisions about disease management, which may potentially result in the withholding of life-saving treatment. It has been demonstrated that the degree of mediastinal node dissection is correlated with the number of N2 nodes discovered.[14,15] Other groups have confirmed that the number of N1 nodes sampled is an important factor that affects postoperative care.[16] Thus, despite ongoing debate about the optimal management of high-risk patients in the real world, where comorbidities have important effects on decision-making, we posit that the routine use of lesser resection cannot be justified in view of our findings.[17] Nevertheless, there is ongoing interest in further studying this matter, particularly in regard to small cancers (< 1–1.5 cm) identified through computed tomography (CT) screening, where no trial data exist favouring lesser resections, and where some evidence supporting routine screening has emerged.[18]

Our results should be considered in the light of several important limitations. There was a relatively small cohort, and few patients had higher-stage cancer; such patients are often not candidates for surgery. We were not able to assess patients who were scheduled for surgery but did not survive to the time of their operation, thus this analysis comprises patients who actually had surgery; it does not assess the strategy of surgery, although the differences may be small. Follow-up was limited to contact with the NSCR, including follow-up of patients who left the province after the time of their surgery. Given a lack of uniform provincial protocols, significant heterogeneity in surgical decision-making was likely. We did not undertake further risk stratification and adjustment by other clinical characteristics of patients or by their comorbidities, which might have explained some of the differences in the N1 lymph node sampling strategies as well as the reduced survival in this cohort. Finally, these cases do not reflect recent changes in the management of lung cancer, including the current more aggressive use of adjuvant therapy; however, our analysis of treatment during a single year reduced the likelihood of longitudinal changes over time.

In summary, this analysis of late survival after surgical resection of lung cancer documents real-world outcomes in a stable population of all comers in Nova Scotia. The health care delivery model in this province may differ significantly from that reported by many large study centres, but it may be similar to practices in other Canadian centres. Apart from the previously known risk factors of age, stage and histology, we demonstrated a relation between reduced survival and lack of N1 lymph node sampling, which may be a marker for other comorbidities and a strategy of lesser resection. Incomplete lymph node sampling was associated with lesser resection and had important implications for staging as well as survival. Although limited by patient factors in real practice, improved lymph node sampling might permit more accurate staging, which may influence decision-making, especially in light of emerging evidence to support adjuvant chemotherapy for earlier-stage disease. Collecting, analyzing and documenting long-term outcomes data are important first steps in improving the quality of care for lung cancer patients. They must be developed and promoted in Nova Scotia and in the rest of Canada.

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Contributors: Dr. Henteleff designed the study. Both Drs. Henteleff and Wong acquired and analyzed data, wrote and reviewed the article and gave final approval for publication.

References

1. Ellison LF, Gibbons L; Canadian Cancer Survival Analysis Group. Five-year relative survival from prostate, breast, colorectal and lung cancer. *Health Rep* 2001;13:23-34.

2. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1710-7.

3. Williams DE, Pairolero PC, Davis CS, et al. Survival of patients surgically treated for stage I lung cancer. *J Thorac Cardiovasc Surg* 1981;82:70-6.

4. Schulze S, Holm-Bentzen M, Høier-Madsen K, et al. Results of surgical treatment for lung cancer. *Scand J Thorac Cardiovasc Surg* 1983;17:61-4.

5. Mery CM, Pappas AN, Bueno R, et al. Similar long-term survival of elderly patients with non-small cell lung cancer treated with lobectomy or wedge resection within the surveillance, epidemiology, and end results database. *Chest* 2005;128: 237-45.

6. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg* 1995;109:120-9.

7. Ginsberg RJ, Rubinstein LU; Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1N0M0 non-small-cell lung cancer. *Ann Thorac Surg* 1995;60:615-23.

8. Warren WH, Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. *J Thorac Cardiovasc Surg* 1994;107:1087-93.

9. Martini N, Rusch VW, Bains MS, et al. Factors influencing ten-year survival in resected stages I to IIIa non-small cell lung cancer. *J Thorac Cardiovasc Surg* 1999; 117:32-6.

10. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non–small-cell lung cancer. *N Engl J Med* 2005;352:2589-97.

11. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-60.

12. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): report of Cancer and Leukemia Group B (CALGB) protocol 9633 [abstract 7019]. *J Clin Oncol* 2004;22:621s.

13. Douillard J, Rosell R, Delena M, et al. (OBS) in completely resected (stage I-III) non-small-cell lung cancer (NSCLC) patients (PTS): final results after 70-month median follow-up [abstract 7013]. *J Clin Oncol* 2005;23:624s.

14. Bollen EC, van Duin CJ, Theunissen PH, et al. Mediastinal lymph node dissection in resected lung cancer: morbidity and accuracy of staging. *Ann Thorac Surg* 1993; 55:961-6.

15. Izbicki JR, Passlick B, Karg O, et al. Impact of radical systematic mediastinal lymphadenectomy on tumor staging in lung cancer. *Ann Thorac Surg* 1995;59:209-14.

16. Sawyer TE, Bonner JA, Gould PM, et al. Factors predicting patterns of recurrence after resection of N1 non-small cell lung cancer. *Ann Thorac Surg* 1999;68:1171-6.

17. Sugarbaker DJ. Lung cancer: the case for limited surgical resection in non-small cell lung cancer. *Thorax* 2003;58:639-41.

18. International Early Lung Cancer Action Program Investigators; Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763-71.