Survival after Surgery in Stage IA and IB Non–Small Cell Lung Cancer

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***Rationale*: Whether histologic subtype of non–small cell lung cancer (NSCLC) has an important effect on prognosis after surgery is unknown.**

***Objectives*: We hypothesized that we could predict mortality more effectively by integrating precise tumor size and histology rather than relying on conventional staging.**

***Methods*: We used the SEER (Surveillance, Epidemiology, and End Results) registry. Inclusion criteria were as follows: (*1*) primary squamous cell or adenocarcinoma; (*2*) potentially curative surgery, defined as a lobectomy or bilobectomy; (*3*) lymph node dissection performed; and (*4*) pathologic stage IA or IB.**

***Measurements and Main Results*: From 1988 to 2000, 7,965 patients were included. For both all-cause and lung cancer–associated mortality, tumor size demonstrated the strongest association (log-rank $P < 0.0001$ for each). When tumors were small ($\leq$2 cm), lung cancer–associated mortality was similar for adenocarcinoma when compared with squamous cell carcinoma. When tumors were 3 cm or larger in size, lung cancer–associated mortality was higher for adenocarcinoma. The increased risk of lung cancer–associated mortality with adenocarcinoma was more pronounced in those younger than 65 years. Survival prediction using precise size and histology had much better discriminatory power than conventional TNM (tumor-node-metastasis) staging ($P = 0.005$).**

***Conclusions*: Staging that takes into account size, histology, late recurrence risk, and patient age is more accurate than the current TNM system and is clinically relevant because improved prediction can facilitate better decisions on the use of adjuvant chemotherapy.**

Keywords: lung cancer; lung cancer staging; adenocarcinoma; lung cancer epidemiology

For those with early-stage lung cancer, surgery remains the key. Most older trials failed to demonstrate any benefit of adjuvant chemotherapy over surgery alone in the treatment of stage I and II disease (1, 2). However, with more effective chemotherapeutic regimens, particularly those using cisplatinum, the outlook for adjuvant chemotherapy after lung cancer surgery has improved (3, 4). Several recently published randomized trials have suggested that adjuvant chemotherapy improves survival after lung cancer surgery (3–6). These advances in therapeutics require us to reevaluate our approach to risk stratification. However, it is still controversial whether patients with stage IA or IB non–small cell lung cancer (NSCLC) should receive chemotherapy and whether or not histology should play a role in decision making. In addition, given the significant toxicity profile associated with chemotherapy, better quantification of risk for patients with different histologic types of NSCLC may improve clinical decision making and facilitate the design of future trials (5, 7).

The goal of this study was to assess survival for patients undergoing surgery for stage IA or IB NSCLC using the SEER (Surveillance, Epidemiology, and End Results) database. Our specific hypothesis was that precisely specifying tumor size and histology would allow improved mortality prediction as compared with the current TNM (tumor-node-metastasis) staging system, which does not distinguish between histologic subtypes and dichotomizes patients into two classes based solely on tumor size ($\leq$3 and $>$3 cm). The main focus of this study pertains to lung cancer–associated mortality. Some of the results of this study have been previously reported in the form of an abstract (8).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The current staging system for non–small cell lung cancer (NSCLC) arbitrarily categorizes stage I tumors based on a size cutoff of 3 cm and ignores differences between adenocarcinoma and squamous cell carcinoma.

What This Study Added to the Field

After surgery for stage I NSCLC, larger adenocarcinomas are associated with a higher rate of late lung cancer recurrence and mortality. Using precise tumor size and histology results in improved ability to predict lung cancer survival.

METHODS

All patients with squamous cell or adenocarcinoma (no prior cancers and no second primaries) who had undergone potentially curative primary surgery, defined as lobectomy or bilobectomy, had lymph node dissections performed, and had pathologic stage IA or IB disease between 1988 and 2000 in the SEER registry were selected (9). Only those with a lymph node dissection were included because patients without a nodal dissection may be understaged, and hence have worse outcomes due to occult nodal involvement. SEER defines regional lymph nodes as including the aortic (including aorticopulmonary window), periesophageal, peritracheal (including those that may be designated tracheobronchial such as the lower peritracheal), subcarinal, pre- and retrotracheal (including precarinal), and pulmonary ligament lymph nodes. For each patient, year of diagnosis, tumor size, stage, histologic type (adenocarcinoma or squamous cell carcinoma), age, race, and sex were recorded. We examined all-cause mortality and lung cancer mortality from 1 month postdiagnosis to limit the impact of perioperative mortality on the analysis. Death due to lung cancer is recorded in the SEER database as a separate field.

Statistical Methods

Characteristics of patients with adenocarcinomas were compared with those of patients with squamous cell carcinomas using χ^2 statistics for

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categorical variables and *t* tests for continuous variables to identify potential differences between patients with these two types of carcinomas.

Kaplan-Meier survival curves were used to visually compare the survival experience of subjects stratified by tumor size, tumor histology, and TNM classification. For the lung cancer mortality analysis, patients who died of other causes were also considered right censored. Mantel-Cox log-rank tests were used to compare survival among the strata.

Cox proportional hazards multivariable models were used to identify additional predictor variables of lung cancer mortality. For all predictor variables, the proportional hazards assumption was assessed using time-dependent covariates to represent the interactions of the original covariates and time and by graphical analysis of the log–log survivor plot (10). Both tumor histology and tumor size exhibited a lack of proportionality in the hazard ratios. For this reason, the models were stratified by tumor size and histology (i.e., 12 strata, 6 tumor sizes by 2 histology types). From the stratified model, we derived estimates of the adjusted hazard ratios by pooling information across the strata. Variables were entered into a backward stepwise analysis using *P* values of 0.20 for entry and 0.05 for removal. Adjusted hazard ratios with 95% confidence intervals (CIs) were calculated for each significant variable from the final stepwise model. For comparison, unadjusted hazard ratios with 95% CIs were calculated for each candidate variable using univariate Cox analyses to assess the impact of the adjustment.

Mantel-Cox log-rank statistics were used to determine which alternative classification scheme provided the best survival assessment. The methods of classification compared were the conventional TNM staging system, staging using precise tumor size (6 strata), or staging using precise tumor size and histology (12 strata).

The associations between the covariates used in the Cox model and the Kaplan-Meier stratification variables were evaluated using a correlation matrix that contained Pearson product moment correlation coefficients for continuous data and phi coefficients (interpreted as correlation coefficients) for categorical data to identify highly associated variables.

Statistical analyses were performed at a significance level of 0.05. No adjustments were made for multiple comparisons. SAS version 9.1 (SAS Institute, Cary, NC) was used for all of the statistical analyses. An SAS macro, SMOOTH (10), was used to plot hazard functions based on a kernel smoothing method described by Ramlau-Hansen and colleagues (11).

RESULTS

There were 7,965 patients in the SEER registry from 1988 to 2000 with stage IA or IB non–small cell carcinomas who underwent lobectomy or bilobectomy, had lymph node dissections, and survived for greater than 1 month postsurgery. No information on adjuvant chemotherapy was available. Radiation therapy was given in 434 (5.4%) patients. The distributions of characteristics at diagnosis are given in Table 1. Compared with patients with squamous cell carcinoma, those with adenocarcinoma were significantly more likely to be younger, female, and to have smaller tumors.

Overall Survival

To evaluate the effect of tumor size on overall survival, Kaplan-Meier product-limit estimates of survival functions for patients with each tumor size were compared using the Mantel-Cox log-rank statistic. There was a strong monotonic effect of tumor size on overall survival that continued for years after diagnosis (log-rank χ^2 $P < 0.0001$); the larger the tumor, the worse the cumulative survival at every time point.

A second set of Kaplan-Meier estimates of survival functions for patients with adenocarcinoma and for patients with squamous cell carcinoma were compared. Patients with adenocarcinomas had a small but consistently higher unadjusted cumulative survival rate than patients with squamous cell carcinomas ($P = 0.0007$). For many years, the difference in cumulative survival between the two groups remained small. For example, at 6 years, patients with adenocarcinoma had a cumulative survival of 53.3% (SE = 0.90%), whereas patients with squamous cell carcinoma had a cumulative survival that was 2.3% lower (51.1%, SE = 1.1%). The statistical significance was a reflection of the large sample size rather than a large difference in cumulative survival between the two groups. These results are unadjusted for differences in age, sex, or tumor size.

Lung Cancer–associated Mortality

The effect of tumor size on lung cancer–associated mortality is shown in the Kaplan-Meier survival curves in Figure 1A. As tumor size increases, survival decreases ($P < 0.0001$). The Kaplan-Meier survival curves in Figure 1B show the effect of tumor histology on lung cancer mortality. Although there is no overall difference in cumulative survival between the adenocarcinoma and squamous cell carcinoma groups, we note that patients with adenocarcinoma have a lower early cumulative

TABLE 1. POPULATION DEMOGRAPHICS AND DISEASE CHARACTERISTICS OF SEER PATIENTS UNDERGOING SURGERY WITH STAGE IA OR IB NON–SMALL CELL LUNG CANCER FROM 1988 TO 2000 (n = 7,965)

Characteristics	Squamous Cell Carcinoma (*n = 2,951*)	Adenocarcinoma (*n = 5,014*)	*P* Value
Mean age at diagnosis, yr (SD)	67.6 (9.0)	64.7 (10.1)	<0.0001
Sex			
Male	1,928 (65.3%)	2,475 (49.4%)	<0.0001
Female	1,023 (34.7%)	2,539 (50.6%)	
Race			
White	2,526 (85.6%)	4,276 (85.3%)	0.69
Nonwhite	425 (14.4%)	738 (14.7%)	
Stage IA	1,432 (48.5%)	3,153 (62.9%)	<0.0001
Stage IB	1,519 (51.5%)	1,861 (37.1%)	
Size, cm			
⩽1 cm	96 (3.3%)	235 (4.7%)	<0.0001
>1 and ⩽2	572 (19.4%)	1,477 (29.5%)	
>2 and ⩽3	764 (25.9%)	1,441 (28.7%)	
>3 and ⩽4	598 (20.3%)	865 (17.3%)	
>4 and ⩽5	386 (13.1%)	477 (9.5%)	
>5	535 (18.1%)	519 (10.4%)	
Radiation therapy			
None	2,751 (93.2%)	4,773 (95.2%)	0.003
Before surgery	12 (0.4%)	19 (0.4%)	
After surgery	167 (5.7%)	205 (4.1%)	
Before and after surgery	3 (0.1%)	3 (0.1%)	
Given but sequence unknown	18 (0.6%)	14 (0.3%)	

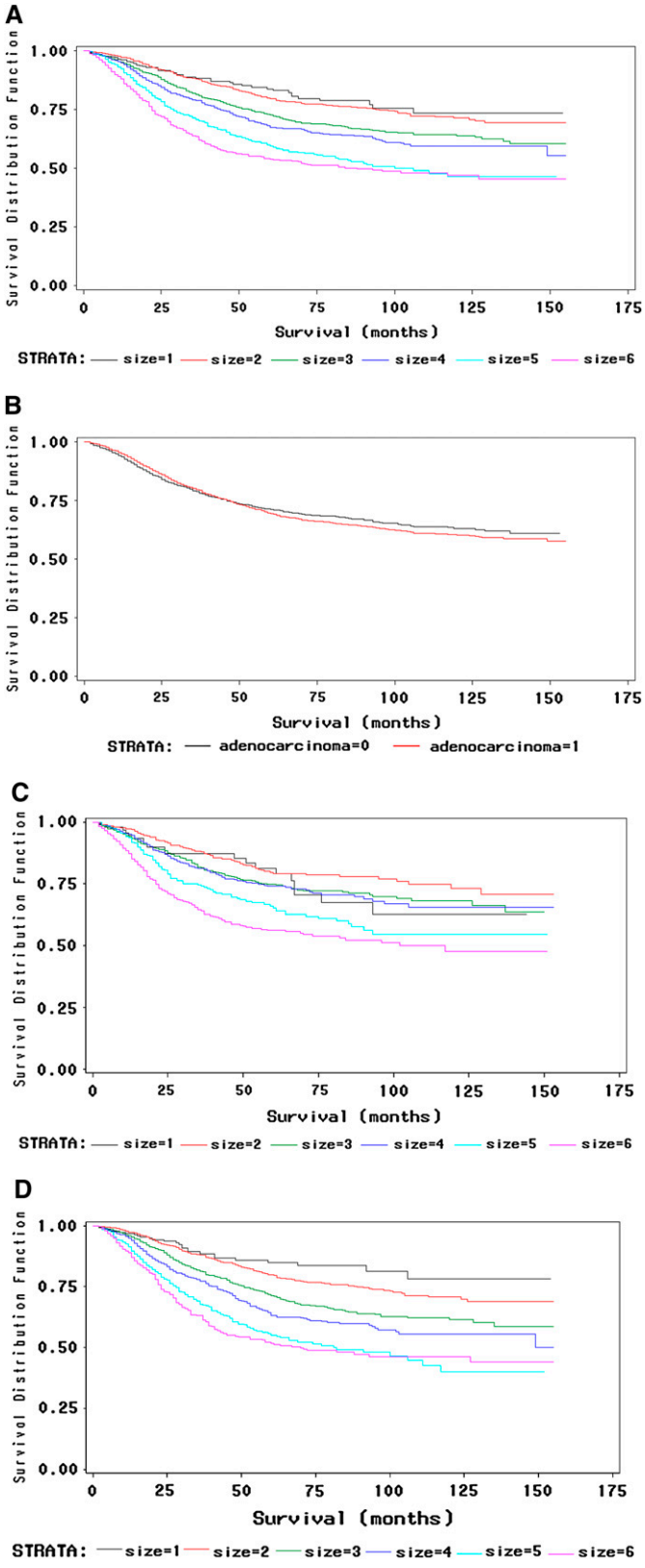

Figure 1. Kaplan-Meier curves for mortality due to lung cancer in patients postlobectomy (*A*) according to size (log-rank $p < 0.0001$) and (*B*) according to histology, either adenocarcinoma (*red*) or squamous cell carcinoma (*black*). (*C*) Classified according to size for squamous cell carcinoma (log-rank $P < 0.0001$). (*D*) Classified according to size for adenocarcinomas (log-rank $P < 0.0001$).

mortality from lung cancer than patients with squamous cell carcinoma. After 2 years, this trend reverses. That is, among patients who survived for 2 years or more, those with adenocarcinoma had a higher lung cancer mortality compared with those with squamous cell carcinoma (unadjusted hazard ratio, 1.42; 95% CI, 1.17–1.71; $P = 0.0003$; hazard ratio adjusted for age and sex, 1.42; 95% CI, 1.18–1.72; $P = 0.0003$).

The joint effect of tumor size and tumor histology on lung cancer mortality is shown in Figures 1C and 1D, which display separate survival curves for adenocarcinoma by tumor size and for squamous cell carcinoma by tumor size. For both histologic types, the survival curves for the six size strata are noticeably different (log-rank χ^2 $P < 0.0001$). For each of the histologic types, an increase in tumor size is associated with an increase in mortality, with one exception: squamous cell carcinoma mortality is higher for patients with the smallest tumors than for patient groups with larger tumor sizes. Note that this group is the smallest subgroup and consists of only 96 patients, with 17 deaths.

To more clearly demonstrate the benefits of including tumor histology in the assessment of cancer survival for various tumor sizes, Kaplan-Meier curves for lung cancer–associated mortality, classified by tumor histology, are presented separately for tumor sizes ⩽2 cm, >2 cm to ⩽3 cm, >3cm to ⩽4cm, and >4 cm (Figure 2). For smaller tumors (⩽3cm), the effect of tumor histology is minimal; and lung cancer–associated mortality is similar for adenocarcinoma and squamous cell carcinoma. However, for tumors larger than 3 cm, adenocarcinoma is associated with significantly higher lung cancer–associated mortality, with the curves beginning to separate at 24 months (for tumors >3 cm and ⩽4 cm: log-rank $P = 0.017$; for tumors >4 cm: log-rank $P = 0.016$).

Examination of hazard rates (Figure E1 of the online supplement) illustrates that, for larger tumors, adenocarcinoma has a higher hazard rate than squamous cell carcinoma and that, after 24 months, the risk difference between the two is fairly constant. In contrast, although larger tumor size is associated with increased risk, the risk difference between sizes decreases with time (Figure E2). For squamous cell carcinomas, the difference in mortality rates of lung cancer death between larger tumors and those less than 2 cm in size is negligible after about 4 years. For adenocarcinomas, the risk difference between larger tumors and those less than 2 cm in size decreases but persists out beyond 7 years.

In Figure 3, each set of Kaplan-Meier curves shown in Figure 2 is stratified by age. Patients younger than 65 who have adenocarcinomas greater than 2 cm in size demonstrate considerably higher hazards of late cancer–related death than patients with squamous cell carcinoma (log-rank $P < 0.05$ for each size category). This pattern is not seen in patients older than 65, except for tumors greater than 4 cm in size (log-rank $P = 0.05$).

Comparison with the Current TNM Classification

The primary aim of this study was to examine whether the precise specification of tumor size (using six categories) and tumor histology would improve the prediction of overall mortality and lung cancer mortality, as compared with the current TNM system, which does not distinguish between histologic subtypes and dichotomizes patients into two classes based solely on tumor size (⩽3 cm and >3 cm). To address this issue, the survival patterns for lung cancer–free survival in the subgroups defined by tumor size and/or tumor histology, as described above, were compared with the survival patterns for the subgroups defined by the standard TNM classification.

To compare the alternative classifications of lung cancer pathology (TNM vs. size and histology), we examined three sets

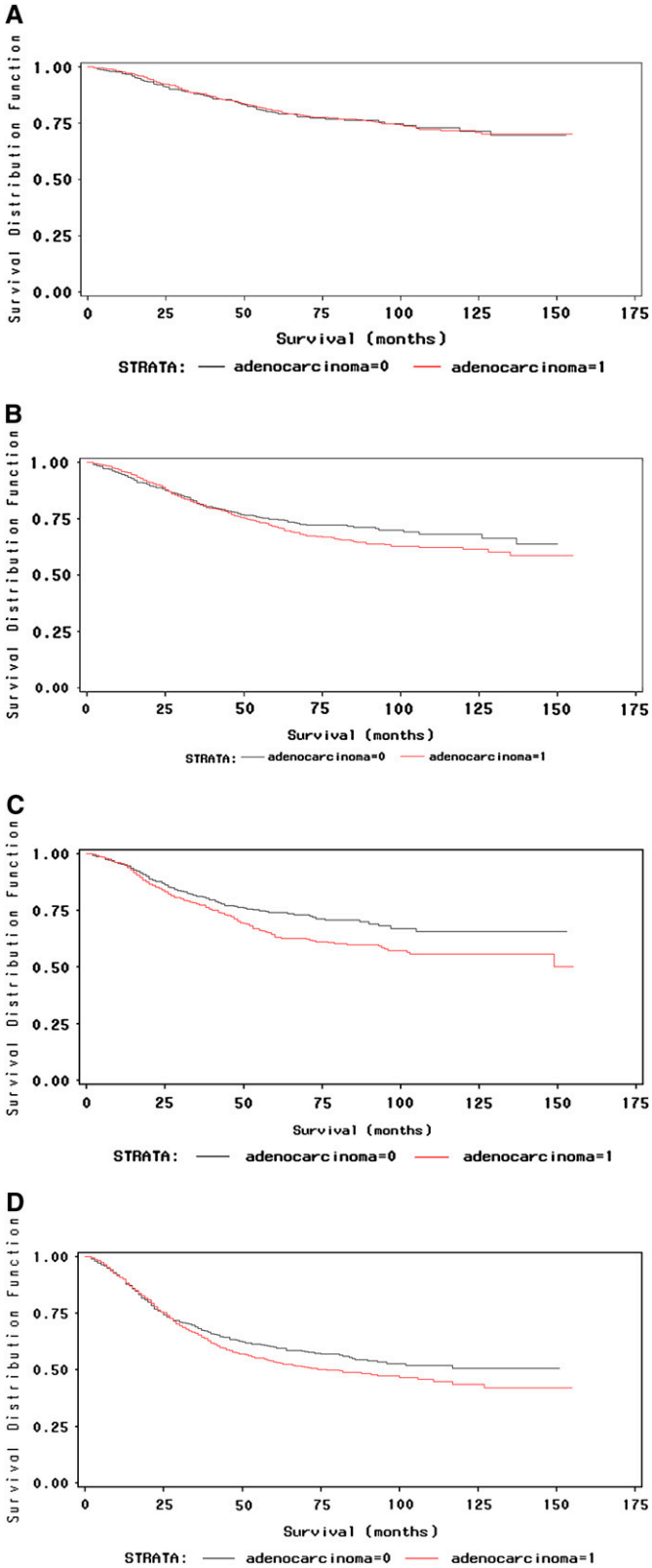

Figure 2. Kaplan-Meier curves for mortality due to lung cancer in patients postlobectomy stratified according to size. *Red* represents adenocarcinoma, *black* indicates squamous cell carcinoma. (*A*) Tumors ⩽2 cm in size (log-rank $P = 0.76$); (*B*) tumors >2cm but ⩽3cm in size (log-rank $P = 0.23$); (*C*) tumors >3 cm but ⩽4 cm in size (log-rank $P = 0.007$); (*D*) tumors >4 cm in size (log-rank $P = 0.10$).

of lung cancer–free survival functions (Table 2), categorized by (*1*) TNM alone (2 classes), (*2*) precise size alone (6 classes), and (*3*) precise size and histology (12 classes). The log-rank statistics for TNM compared with precise size alone differed significantly ($P < 0.0001$), indicating that the six size categories provided significantly better discrimination than the two TNM categories. Similarly, the log-rank statistics for TNM compared with precise size and histology differed significantly ($P < 0.0001$). To test whether the 12 size-by-histology categories produced significantly more separation between survival functions than the six size categories alone, these two χ^2 statistics were compared and results were significant ($P = 0.005$), indicating that the 12-category system, which used histology, provided significantly better discrimination than the six size categories.

These conclusions about the superiority of classification by size and histology over TNM classification can be visually observed by examining Kaplan-Meier curves. Figure 4 presents Kaplan-Meier curves for lung cancer–associated mortality, classified by TNM. The distance between the curves for the two TNM subgroups is considerably less than the distance between the stratum when using both size and histology (Figures 1C and 1D). The 5-year cumulative survival is 77% (SE = 0.8%) for the lower risk TNM group and 61% (SE = 1%) for the higher risk TNM group. The difference between the two cumulative survivals at 5 years is 16% (SE = 1%). In contrast, the 5-year cumulative survival for patients with adenocarcinomas 1 cm or less is 85% (SE = 3%); for patients with adenocarcinomas larger than 5 cm, it is 52% (SE = 3%). The difference between the two cumulative survivals at 5 years is 33% (SE = 4%). This is about twice the difference using the TNM classification. The TNM classification did not produce nearly as fine a discrimination between survival patterns as did tumor size and histology.

The case for using tumor size and histology to replace the TNM classification is further supported by the Kaplan-Meier curves in Figures 2 and 3, which were discussed previously. Adenocarcinoma presents an increasingly high risk of lung cancer mortality for larger tumors. This risk is more pronounced for patients younger than 65 years with tumors greater than 2 cm in size. The TNM classification, which ignores histology, leads to an underestimation of the risk of lung cancer death from adenocarcinoma while overestimating the risk from squamous cell carcinoma (Figure 2). Furthermore, the magnitude of the underestimation is more pronounced in patients who are younger and therefore less likely to die of competing diseases (Figure 3).

Cox Proportional Hazards Survival Analyses

Table 3 presents the results obtained from univariate and multivariable Cox models that were used to identify variables other than tumor size or adenocarcinoma that were significantly related to lung cancer mortality. Additional univariate analysis with time-dependent covariates can be found in Tables E1 and E2. There is a marked similarity between the unadjusted and adjusted hazard ratios for all of these variables, indicating that the variables exert relatively independent effects on survival. Correlations among variables were very weak, with absolute values ranging from 0.004 to 0.15.

Because there were significant differences between patients with adenocarcinoma and squamous cell carcinoma in terms of size, age, and sex, we used stratified Cox analysis to evaluate the association between adenocarcinoma and lung cancer–associated mortality (Table 4) for each tumor size. There was no difference between adenocarcinoma and squamous cell carcinoma for smaller tumors (⩽3 cm), but for larger tumors, adenocarcinoma was associated with a significantly increased mortality risk.

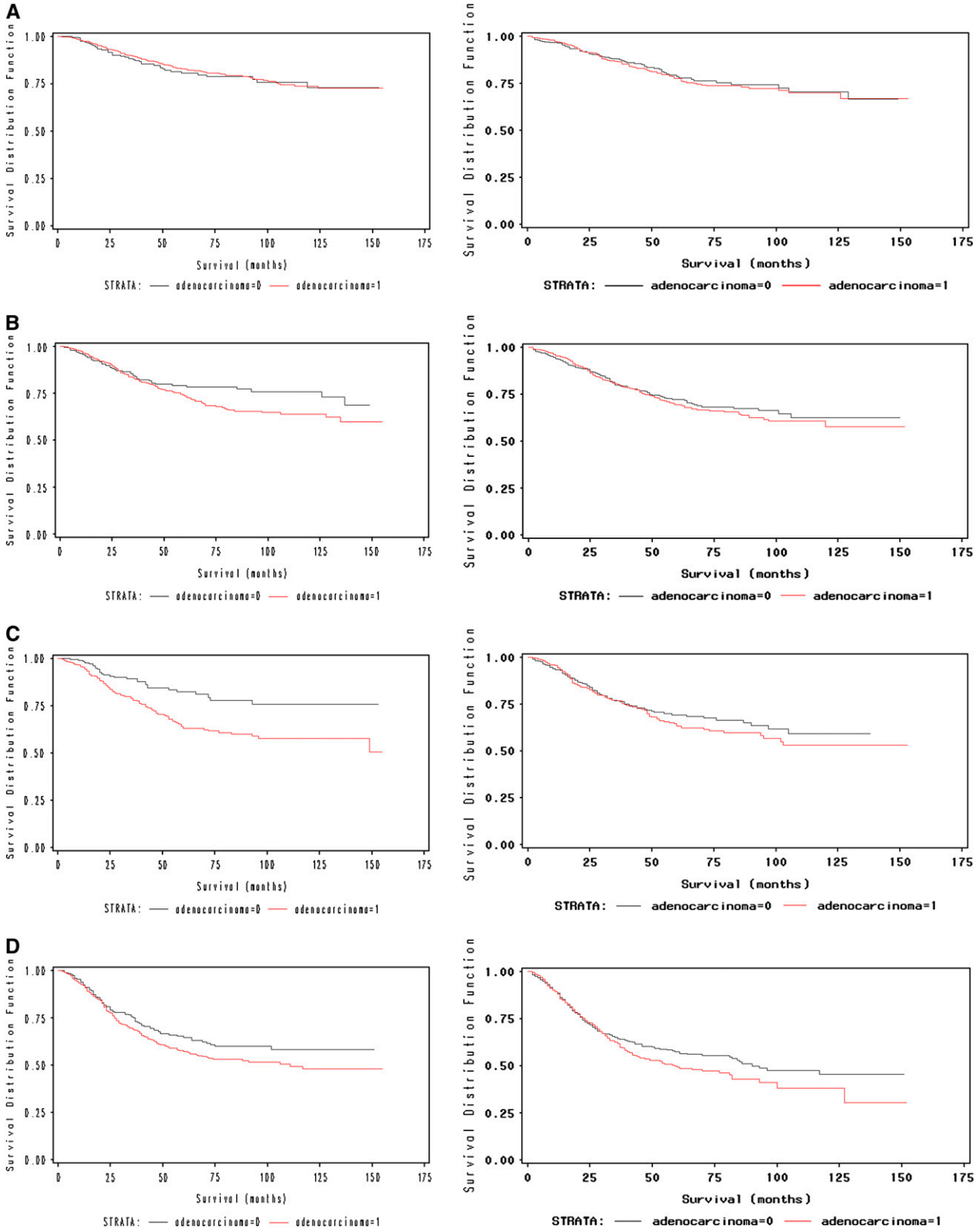

Figure 3. Kaplan-Meier curves for death due to lung cancer in patients postlobectomy stratified according to size and age. *Red* represents adenocarcinoma, *black* indicates squamous cell carcinoma. *Left side panels* show those subjects ≤65 years of age at time of diagnosis; *right side*, those >65 years of age. All *P* values are log-rank tests. (*A*) Tumors ≤2 cm in size; age ≤65, $P = 0.71$; age >65, $P = 0.78$. (*B*) Tumors >2 cm but ≤3cm in size; age ≤65, $P = 0.09$; age >65, $P = 0.66$. (C) Tumors >3 cm but ≤4 cm in size; age ≤65, $P = 0.0003$; age >65, $P = 0.39$. (*D*) Tumors >4 cm in size; age <65, $P = 0.08$; age >65, $P = 0.15$.

TABLE 2. COMPARISON OF THE ABILITY OF DIFFERENT CLASSIFICATION SYSTEMS OF NON–SMALL CELL LUNG CANCER TO PREDICT LUNG CANCER MORTALITY

			Compared with TNM		Compared with Six Size Classes	
Model	Log-Rank χ^2	*df*	Difference in χ^2	*P* Value	Difference in χ^2	*P* Value
12 classes (size and histology)	298.4016	11	119.709	<0.0001	18.5034	0.005
Six size classes	279.8982	5	101.2056	<0.0001		
TNM (two classes)	178.6926	1				

Definition of abbreviations: *df* = degrees of freedom; TNM = tumor-node metastasis.

DISCUSSION

The main finding of this study is that histologic type of NSCLC together with more precise size specifications can be used to more accurately identify patients at risk for lung cancer death after potentially curative lung cancer surgery. Larger adenocarcinomas are associated with a significantly higher chance of lung cancer mortality and much of this is due to the risk of late recurrence. The risk difference in mortality rates between adenocarcinoma and squamous cell carcinoma persists well past 5 years for tumors that are greater than 3 cm in size. In contrast, although risk of death is directly related to tumor size, the difference in mortality rates between large and small tumors decreases with time. The use of both precise size and histology greatly improved discriminatory power compared with the current TNM staging system. The inclusion of age further enhanced the benefits of the classification rule based on size and histology.

Some investigators have found that adenocarcinoma is associated with a higher risk of death and disease recurrence than squamous cell carcinoma (1, 4, 12, 13). However, other studies have failed to demonstrate any relationship between histologic types of NSCLC (2). This study is consistent with the body of evidence suggesting that adenocarcinoma does indeed carry a worse prognosis in stage I disease. Our study adds to these findings, by demonstrating that it is the late recurrences that make the difference in lung cancer–associated mortality. The hazard of death due to late recurrences of cancer after Year 2 was approximately 47% higher in those with adenocarcinoma compared with those with squamous cell carcinoma.

Clearly, long-term follow-up is needed. With the advent of more effective adjuvant chemotherapy for early-stage NSCLC, these findings become more clinically relevant, because they impact on how we select patients for potential postoperative chemotherapy. Although recent studies support the use of adjuvant platinum-based chemotherapy after complete resection of non–small cell carcinoma in patients with good performance status, patient selection criteria to identify those most likely to benefit are limited (4, 7). The JBR.10 (National Cancer Institute of Canada) trial did not include stage IA disease, whereas the IALT (International Adjuvant Lung Cancer Trial) trial and the ALPI (Adjuvant Lung Project Italy) trial did not have a high number of patients with stage IA disease (1, 3, 4). In addition, the JBR.10 trial found less of an effect size in stage IB patients and there was no interaction between stage and treatment. Our findings suggest that over the long term, patients with large adenocarcinomas (>2 or 3 cm in size depending on age) do have a significantly higher risk of recurrence than patients with squamous cell carcinoma, so it may be reasonable to take histology into consideration when making chemotherapy treatment decisions, especially in younger patients.

The impact of histology and occult micrometastases on long-term outcomes is supported by studies from Japan evaluating the efficacy of tegafur-uracil (UFT) in NSCLC (14). In a meta-analysis of six randomized controlled trials with UFT in patients who had predominantly adenocarcinoma (84%) with T1–2, N0, disease, with a mean age of 62 years, efficacy was greater on analysis of data at 7 years as compared with 5 years. The authors noted that the survival curves did not separate until the 4-year mark, and hypothesized that this might have been related to the high percentage of stage IA disease. They also noted that, whereas UFT did not have potent direct antitumor effect, the long-term administration of UFT may have been optimal for controlling micrometastases. This is consistent with our findings and suggests that it is these micrometastases that are contributing to the late recurrences of adenocarcinoma.

Recently, there has been increased interest in identification of NSCLC subgroups (15). A variety of techniques have been used, including molecular markers (16), genomic analysis (17), and gene hypermethylation (18), to mention only a few. Some of these markers also predict response to particular chemotherapy regimens

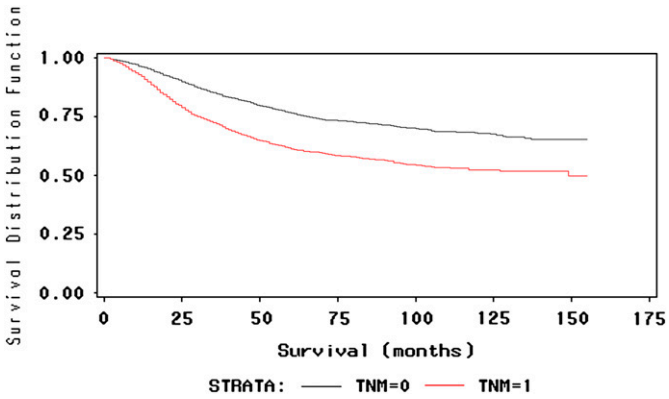

Figure 4. Kaplan-Meier curves for death due to lung cancer in patients postlobectomy according to TNM (tumor-node-metastasis) stage, either stage IA (*black*) or IB (*red*) (log-rank $P < 0.0001$).

TABLE 3. HAZARD RATIOS FOR DEATH DUE TO LUNG CANCER (n = 7,965)

Covariate	Univariate Hazard Ratios (*95% CI*)	Multivariable Model* Hazard Ratios (*95% CI*)
Year of diagnosis (per year increase)	0.964 (0.950–0.979)	0.962 (0.947–0.976)
	$P < 0.0001$	$P < 0.0001$
Age at diagnosis (per year increase)	1.017 (1.012–1.022)	1.018 (1.013–1.023)
	$P < 0.0001$	$P < 0.0001$
Male vs. female sex	1.293 (1.178–1.419)	1.233 (1.121–1.356)
	$P < 0.0001$	$P < 0.0001$
Nonwhite race vs. white	1.082 (0.952–1.230)	Not included in multivariable model
	$P = 0.23$	

Definition of abbreviation: CI = confidence interval.
* Stratified on size and histology.

TABLE 4. HAZARD RATIOS COMPARING LUNG CANCER MORTALITY FOR ADENOCARCINOMA VERSUS SQUAMOUS CELL CARCINOMA

Tumor Size (*cm*)	Unadjusted Hazard Ratio* (*95% CI*)	Hazard Ratio* Adjusted for Age (*95% CI*)	Hazard Ratio* Adjusted for Age and Sex (*95% CI*)
⩽1	0.587 (0.329–1.047), $P = 0.071$	0.653 (0.360–1.183), $P = 0.160$	0.845 (0.457–1.560), $P = 0.590$
>1 to ⩽2	1.047 (0.817–1.341), $P = 0.716$)	1.074 (0.838–1.377), $P = 0.572$)	1.137 (0.883–1.463), $P = 0.319$
>2 to ⩽3	1.123 (0.927–1.359), $P = 0.235$	1.151 (0.949–1.395), $P = 0.153$	1.172 (0.965–1.423), $P = 0.110$
>3 to ⩽4	1.350 (1.084–1.681), $P = 0.007$	1.398 (1.121–1.742), $P = 0.003$	1.468 (1.175–1.834), $P = 0.0007$
>4 to ⩽5	1.311 (1.027–1.673), $P = 0.030$	1.371 (1.072–1.754), $P = 0.012$	1.373 (1.069–1.762), $P = 0.013$
>5	1.056 (0.864–1.291), $P = 0.592$	1.166 (0.952–1.429), $P = 0.138$	1.221 (0.992–1.501), $P = 0.059$

Definition of abbreviation: CI = confidence interval.

* Hazard ratio represents the strength of association of adenocarcinoma as compared with squamous cell carcinoma for lung cancer mortality.

(19). This study demonstrates that simple and easily obtainable information that is part of the current standard of practice can also be used to improve prediction of survival after lung cancer surgery. Because these data are readily available, they should also be useful for the development of historical controls and new drug development.

Our study has several important limitations. There is the possibility that there is significant residual confounding. In particular, the association between smoking, chronic obstructive pulmonary disease (COPD), and squamous cell carcinoma is stronger than that between adenocarcinoma and smoking (20, 21). If we use all-cause mortality as the outcome measure, it is possible that smoking-related diseases, in particular COPD, but also possibly coronary artery disease and stroke, are confounding the relationship between histology and mortality. However, it is useful to note that, even if there is residual confounding from these factors, the direction of the bias would lead to an overestimate of the risk of all-cause mortality from squamous cell carcinoma, rather than adenocarcinoma. In our dataset, mortality due to COPD was rare but more common in those with squamous cell carcinoma than in those with adenocarcinoma (2.85 vs. 1.44%; relative risk, 1.98; 95% CI, 1.45–2.71; $P < 0.0001$).

Also, the SEER database does not have information on how recurrences were treated or what chemotherapy was used. Because adjuvant chemotherapy was not the standard of care during the study period for stage IA and IB NSCLC, we believe it is reasonable to believe that these patients did not receive adjuvant chemotherapy for their stage IA or IB lung cancers, but we cannot adjust for how subsequent recurrences were treated.

This may also explain the 3.6% reduction in the hazard of death with each year of diagnosis. The observed decrease might be due to improved treatment of recurrent cancers as chemotherapy improved during this time. We believe it probable that most of the patients who died of recurrent cancers in this cohort did receive chemotherapy, but we cannot assess differences or prove it with this dataset. Another possibility is that there is increased length bias because the use of computed tomography scanning has increased significantly over the time period in question. Specifically, with the explosion in the use of computed tomography imaging, there are more incidentally noted small nodules, so less aggressive nodules would be more likely to be detected than before.

In summary, this study demonstrates that there is an increased risk of lung cancer death associated with larger adenocarcinomas and that this difference persists over time. For younger patients with good performance status and no competing diseases, the long-term risks of adenocarcinoma are considerable. It is important that physicians take this into account when making decisions on chemotherapy for NSCLC after surgery. Rather than relying on simple dichotomous staging rules that ignore histology, a more complex approach is warranted. In particular, histology and precise tumor size, as well as other comorbidities, functional status, life expectancy, and patient preferences, need to be considered. In select patients, there should be a lower threshold to treat adenocarcinoma relative to squamous cell carcinoma, provided that patients have good performance status, long life expectancy, and little comorbidity.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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