Prognostic Nomogram to Predict Survival After Surgery for Synchronous Multiple Lung Cancers in Multiple Lobes

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Introduction: In the absence of metastatic disease, surgery for synchronous non–small-cell lung cancers involving multiple lobes can be curative. However, there currently exists no reliable prognostic instrument for this patient population after surgery. We undertook an analysis to examine the prognostic significance of adenocarcinoma histology and developed a prognostic nomogram.

Methods: This study was a pooled analysis of six previously reported datasets. Patients without extra-thoracic metastasis who underwent surgical resection of synchronous lung cancers in multiple lobes were included. Those with small cell cancer, carcinoid tumor, or exclusively carcinoma in situ were excluded. A multivariable Cox proportional hazards regression model was fitted to identify independent survival predictors for nomogram development.

Results: Data from 467 patients were analyzed. Adenocarcinoma was a sole histology in 253 patients (54.2%). Those with exclusively adenocarcinoma histology had a better median survival than their counterparts: 67.4 versus 36.2 months, ($p < 0.001$). Multivariable analysis incorporating histology, sex, age, maximal T-size, highest N-stage, and laterality demonstrated that having exclusively adenocarcinoma histology independently predicted an improved survival: hazard ratio 0.61 (95% confidence interval: 0.48, 0.78). Other favorable survival predictors were N0, T-size less than or equal to 3 cm, bilateral cancers, age less than 70 years, and women sex. The developed nomogram was well calibrated and demonstrated a moderate to good discrimination with a bootstrap-corrected Harrell C-statistic of 0.70.

Conclusion: Several unique features among patients with resected synchronous multiple lung cancers, including the presence of exclusively adenocarcinoma histology, are of prognostic significance. A simple nomogram incorporating these factors can be utilized to predict patient survival with acceptable accuracy.

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In the United States, lung cancer is a prevalent cancer affecting 0.08% of population[1] and as such, synchronous multiple lung cancers are not uncommon. Based on data from lung cancer screening trial, of the 484 patients with detected cancer, 35 patients (7%) had multiple lung cancers.[2] When multiple lung cancers are present at the same time without extra-pulmonary metastasis, the possibilities may include metastatic lung cancer to the lung or multiple primary lung cancers (MPLC). The treatment paradigm and prognosis of the two entities are quite different. Although MPLC is considered as an early stage disease, potentially curable by surgery, metastatic disease is considered incurable and surgery is rarely indicated.

A set of criteria have been developed to help differentiate between the two. In 1975, Martini and Melamed proposed criteria using histology and interval development of multiple lung cancers based on 50 patients.[3] MPLC can be diagnosed if the histological types of the cancers are different. When histological types are similar, MPLC can still be diagnosed if the interval development of cancers is greater than 2 years (metachronous MPLC). Otherwise, MPLC can be diagnosed if there are carcinoma in situ components, without evidence of cancer in a common lymphatic channel, and cancers must be located in a different segment or lobe. It has been estimated that the prevalence of MPLC is approximately 2% of all resected lung cancers on the basis of these criteria.[4] Though seemingly useful, the criteria are not necessarily predictive of survival and many multiple lung cancer patients do not receive surgical treatment as their overall prognosis is felt to be poor uniformly.[5]

In addition, the available staging system does not provide a reliable survival prediction for this patient population. The seventh edition of American Joint Committee on Cancer (AJCC) staging system classifies those with similar histology type as stage III or IV and those with different histology type as stage I or II[6]. However, it appears that histological type, whether similar or different, does not predict survival,[7,8] whereas tumor size, especially the maximal tumor size and nodal involvement are better predictors than histology similarity.[9–11] Interestingly, in most reports of long-term survivors after surgical resection of synchronous multiple lung cancers, the predominant histology type was adenocarcinoma.[12,13] From biological standpoint,

it is plausible that adenocarcinoma confers a better prognosis than other histological types. Adenocarcinoma is less strongly associated with cigarette smoking, which is a major cause of cardiovascular death.[14] Furthermore, adenocarcinoma often arises more distally in the airway than squamous cell carcinoma and its peripheral location may facilitate surgical resection. In addition, the incidence of adenocarcinoma histology is increasing among women and it is known that women generally have a longer life expectancy than men.[15] Finally, unlike other histology types, adenocarcinoma affords a spectrum of diseases including the lepidic subtype which has been associated with an indolent clinical course.[16]

To date, although several observational studies on the resection of multiple lung cancers are available, it is difficult to summarize the results across these studies due to the difference in the inclusion criteria and baseline patient characteristics. In addition, no prognostic instrument has yet been introduced. To this end, our group sought to improve the prognostication of synchronous multiple non–small-cell lung cancers (NSCLC) by pooling our previously published, patient-level databases.[8] In this report, we test the hypothesis that adenocarcinoma is associated with a superior survival than other histology type. We update our patient follow-up status, integrate information on their maximal tumor size in the statistical model, and construct a prognostic nomogram. Because multiple lung cancers will become an increasingly common clinical problem, along with the rise in minimally invasive surgery and lung cancer screening, we believe that a practical prognostic instrument will be timely.

MATERIALS AND METHODS

Procurement of Database

This project has been approved by the Scientific Review Committee at the H. Lee Moffitt Cancer Center. The method of database identification and procurement has been previously detailed elsewhere.[8]The Medline database was searched for literature on surgical outcomes of multiple lung cancers published during 2000–2012. The first authors of publications containing at least 10 patients were contacted to obtain individual-level patient database. Required variables were patient demography (age at surgery, sex), tumor characteristics (laterality, nodal stage, histological type), treatment (pneumonectomy), and outcomes (overall survival time). Data on tumor size were available in all but one study. This database was updated to January 2014.

Patients and Definitions

Eligible cases were identified according to a priori inclusion and exclusion criteria. Patients included in this analysis were those who underwent curative surgical resections (pneumonectomy, lobectomy, segmentectomy, or wedge resection) of at least two separate lung cancer foci in two lobes presenting synchronously, defined as cancers diagnosed simultaneously or within 2 years per Martini and Melamed criteria.[3] Those with distant metastatic disease evident by imaging studies were excluded, along with those who only had cancers in one lobe, small cell carcinoma, carcinoid tumor or all non-invasive, pure bronchioloalveolar carcinoma, also known as adenocarcinoma in situ with lepedic pattern. Histology was as supplied by the investigators from each institution. Determination of adenocarcinoma status was based on morphologic examination and when appropriate immunohistochemical staining was performed. Tumor size and nodal stage were based on pathological examination. Patients who had cancers both unilaterally and bilaterally were classified as having bilateral cancers.

Statistical Analysis

Pearson's Chi-square test and one-way analysis of variance were used to compare the difference in proportions and means between groups, respectively. Overall survival was calculated from the date of the first surgical resection to death or last follow-up date. Kaplan–Meier estimator was used to construct survival curve and to estimate median survival. In univariable analysis, Log-rank test was used to compare survival across histological types. Categorization of continuous variables followed clinical relevance: tumor size cutoff was based on AJCC T-designation[6] and age was dichotomized near the median age of patients. In multivariable analysis, Cox proportional hazards regression model was fitted, incorporating age, sex, the largest tumor size, highest N-stage, laterality, adenocarcinoma, and pneumonectomy. For regression modeling, missing data on tumor size was addressed by multiple imputation procedure based on Markov Chain Monte Carlo method.[17] Significance level was set at two-tailed p value less than 0.05.

Nomogram Development

A nomogram helps translate complex statistical models into a user-friendly graphical interface.[18] The nomogram in this study was designed to give the probability of overall survival at 2 and 5 years. Parameter estimates obtained from the above Cox proportional hazards model were used to construct

TABLE 1. Histological Characteristics of Patients with Resected Synchronous Multiple Lung Cancers

Histology Type	Number of Patients	%
One histology type present:		
Adenocarcinoma	253	54.2
Squamous cell carcinoma	54	11.6
Adenosquamous carcinoma	4	0.9
Large cell carcinoma	4	0.9
Undifferentiated or histology type other than above	3	0.6
Two histology types present		
Adenocarcinoma and squamous cell carcinoma	65	13.9
Adenocarcinoma and large cell carcinoma	28	6.0
Adenocarcinoma and adenosquamous cell carcinoma	12	2.5
Adenocarcinoma and undifferentiated/other histology	14	3.0
Squamous cell carcinoma and large cell carcinoma	11	2.4
Squamous cell carcinoma and adenosquamous cell carcinoma	6	1.3
Squamous cell carcinoma and undifferentiated/other histology	10	2.1
Large cell carcinoma and adenosquamous cell carcinoma	3	0.6
Total	467	100.0

nomogram scale.[19] The predictive accuracy of the nomogram was demonstrated by calibration and discrimination. Calibration was illustrated by a plot of patients with predicted survival (in quintile) against the actual proportion, who have died in each predicted quintile. The predicted survival probability for each patient was calculated using baseline hazard function at 2 or 5 years. Discrimination, or the ability of model to differentiate between patients with different prognosis, was demonstrated by Harrell concordance index (C-statistic), taking censored data into consideration.[20] Harrell C-statistic can be described as the probability that a subject who has died will have a higher predicted probability of dying than a subject who is still alive and may range from 0.5 (random chance) to 1.0 (perfectly discriminating model). Although no threshold exists, C-statistic between 0.70 and 0.80 is considered moderate to good and 0.80 or greater is considered excellent.[21] To reduce the bias from model over-fitting, 200 bootstrap samples with replacement were generated by computer program, and bootstrap-corrected Harrell C-statistic was obtained from full model fitted in the complete-case data set using the 0.632 bootstrapping method.[22] Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Histology Type and Patient Characteristics

Data from 467 patients were analyzed. Of these, 318 patients (68.1%) had one histology type and 149 patients (31.9%) had two histology types (Table 1). No three or greater histology types were observed in a single patient. Adenocarcinoma was a sole histology for 253 patients (54.2%), and in 119 patients (25.5%), adenocarcinoma was present along with another histology type. Overall, adenocarcinoma was the most prevalent histology type, observed in 374 patients (80.1%). Squamous cell carcinoma was the second most prevalent histology. It was present as a sole histology in 54 patients (11.6%) or present along with another histology type in 92 patients (19.7%).

Several patient characteristics were significantly associated with adenocarcinoma (Table 2). Women patients constituted 56% and 46% of cases with adenocarcinoma as a sole histology (all-adenocarcinoma) or adenocarcinoma along with another histology type (some adenocarcinoma), respectively; however, they constituted only 19% among cases with no adenocarcinoma ($p < 0.001$). The proportion of patients with small tumors (i.e., a maximal tumor size of less than or equal to 3 cm) was highest among those with some adenocarcinoma: the median maximal tumor size was 2.75 cm among patients with some adenocarcinoma, compared with 3.65 cm among those with all-adenocarcinoma and 3.45 cm among those with no adenocarcinoma, p value less than 0.001. In addition, the proportion of patients who underwent pneumonectomy was the lowest among cases with all-adenocarcinoma.

Survival Outcomes

At the time of analysis, there were 279 deaths. The median survival was 50.7 months. Among those surviving,

TABLE 2. Characteristics of Patients with Resected Synchronous Multiple Lung Cancers, Classified by the Number of Cancers with Adenocarcinoma Histology

Characteristics	Adenocarcinoma in All of the Cancers, $n = 253$ (%)	Adenocarcinoma with Another Histology Type, $n = 119$ (%)	Adenocarcinoma in None of the Cancers, $n = 95$ (%)	Total, $n = 467$ (%)	p value
Sex					<0.001
Men	110 (44)	67 (56)	77 (81)	254 (54)	
Women	143 (56)	52 (44)	18 (19)	213 (46)	
Age					0.79
<70 years	138 (54)	62 (52)	54 (57)	254 (54)	
≥70 years	115 (46)	57 (48)	41 (43)	213 (46)	
Maximal T size[a]					<0.001
≤3 cm	136 (60)	44 (48)	27 (33)	207 (52)	
>3–5 cm	67 (29)	30 (33)	36 (45)	133 (33)	
>5 cm	25 (11)	17 (19)	18 (22)	60 (15)	
Highest N-stage					0.06
N0	184 (73)	81 (68)	60 (63)	325 (70)	
N1	31 (12)	14 (12)	22 (23)	67 (14)	
N2	38 (15)	24 (20)	13 (14)	75 (16)	
Laterality					0.27
Unilateral	128 (51)	68 (57)	44 (46)	240 (51)	
Bilateral	125 (49)	51 (43)	51 (54)	227 (49)	
Pneumonectomy					<0.001
Yes	17 (7)	16 (13)	24 (25)	57 (12)	
No	236 (93)	103 (87)	71 (75)	410 (88)	

[a]Data available from 400 patients.

the median follow-up time was 51.5 months. Death within 30 days of surgery was observed in nine patients (1.9 %). When classifying patients by the number of cancers with adenocarcinoma histology, those with all-adenocarcinoma histology had the best median overall survival of all patient groups (Fig. 1*A*). The median survival among patients with all-adenocarcinoma histology was 67.4 months, compared with 39.4 months and 30.4 months among those with some adenocarcinoma and no adenocarcinoma, respectively ($p < 0.001$). When considering the status of adenocarcinoma as a binary variable, patients with all-adenocarcinoma histology had a median survival of 67.4 months, compared with the rest of the patients who had a median survival of 36.2 months ($p < 0.001$; Fig. 1*B*).

Multivariable Analysis

We performed a multivariable analysis, taking into account the differences in patient characteristics between those with exclusively adenocarcinoma and the remainders. First, we examined all variables in a univariable analysis. Sex, age, maximal T-size, highest N-stage, laterality, and histology were significantly associated with survival (Table 3). Pneumonectomy was also associated with survival, albeit of marginal significance. However, no significant survival difference by institution or by tumor count was found. Second, we performed multivariable analysis, incorporating all significant or marginally significant variables. This analysis indicated that pneumonectomy was not an independent predictor of survival. In the final model, six significant variables were retained. In the order of strength of association, these variables were highest N-stage, maximal T-size, laterality, age, sex, and adenocarcinoma histology.

To examine whether the above findings would remain robust despite a change in the definition of cancer synchronicity, a sensitivity analysis was performed by excluding patients who had the interval between their surgical resections greater than 6 months ($n = 42$). In this subgroup, the median survival

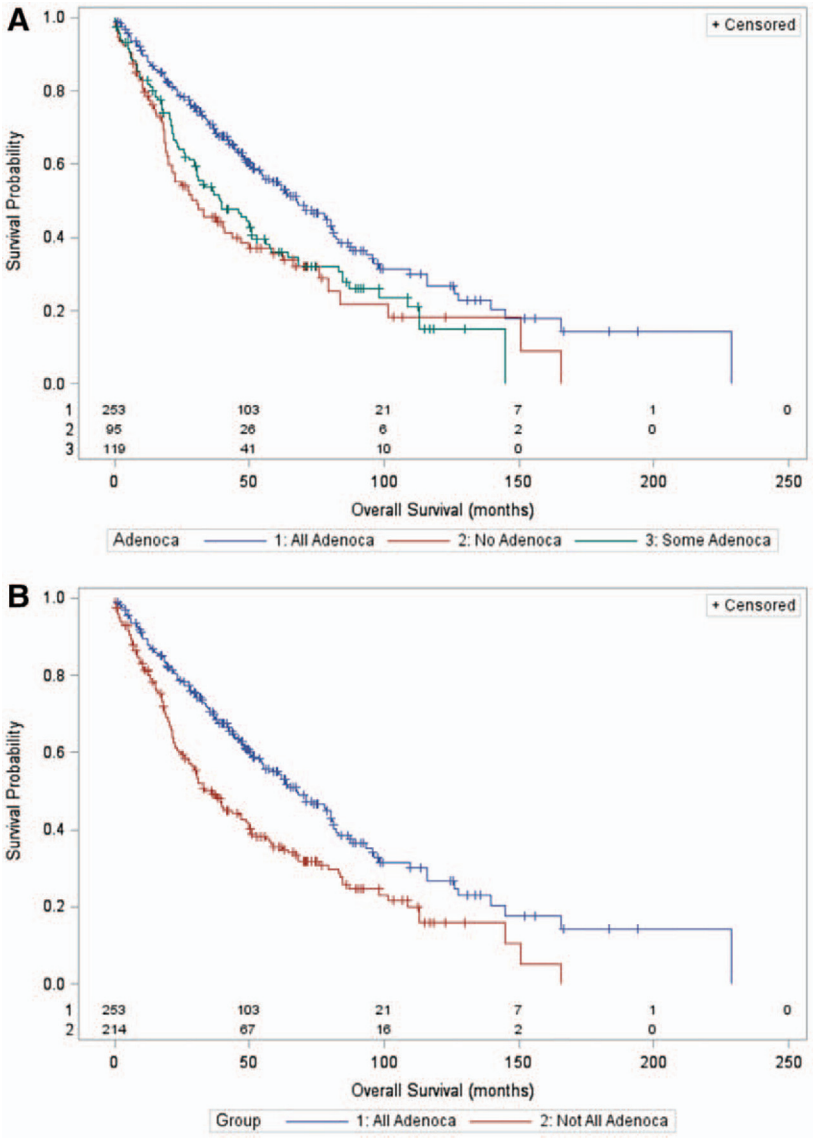

FIGURE 1. **A**, Kaplan–Meier survival estimates of patients, stratified by the number of cancers with adenocarcinoma histology. **B**, Kaplan–Meier survival estimates of patients, stratified by the presence of adenocarcinoma histology in all of the cancers

TABLE 3. Predictors of Survival After Surgery for Synchronous Multiple Lung Cancers

Variables	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	Adjusted *p*-value
Sex				
Men	1.63 (1.28, 2.08)	<0.001	1.52 (1.18, 1.97)	0.001
Women	Reference		Reference	
Age				
>70 years	1.37 (1.08, 1.73)	0.009	1.59 (1.24, 2.02)	<0.001
≤70 years	Reference		Reference	
Maximal T size				
>5 cm	2.05 (1.44, 2.92)	<0.001	1.90 (1.24, 2.90)	0.004
3 to 5 cm	1.51 (1.14, 1.99)	0.004	1.27 (0.95, 1.70)	0.11
≤3 cm	Reference		Reference	
Highest N-stage				
N2	1.98 (1.46, 2.67)	<0.001	2.14 (1.56, 2.92)	<0.001
N1	1.63 (1.17, 2.28)	0.004	1.71 (1.22, 2.42)	0.002
N0	Reference		Reference	
Laterality				
Unilateral	1.64 (1.29, 2.08)	<0.001	1.83 (1.43, 2.34)	<0.001
Bilateral	Reference		Reference	
Histology				
Not all-adenocarcinoma	1.64 (1.29, 2.07)	<0.001	1.47 (1.15, 1.89)	0.002
All-adenocarcinoma	Reference		Reference	
Pneumonectomy				
Yes	1.40 (0.99, 1.98)	0.06	-	-
No	Reference			
Number of tumors[a]:				
2	0.85 (0.57, 1.26)	0.41	-	-
>2	Reference			
Institution				
Site(s)	0.85–1.67	0.16–0.99	-	-
Reference site	Reference			

[a]Data available from 270 patients
HR, hazard ratio; CI, confidence interval limits.

was 49.9 months. Not having exclusively adenocarcinoma histology was still independently associated with an increased mortality, hazard ration (HR): 1.50 (95% confidence interval [CI]: 1.15, 1.96). Moreover, there was no substantial change in the hazard ratio estimates for other variables and the order of strength of association remained unchanged.

Nomogram and its Predictive Accuracy

Based on the identified independent survival predictors, a prognostic nomogram estimating the probability of survival at 2 and 5 years after surgery was developed (Fig. 2). N-stage emerged as the strongest survival predictor: N2 was assigned 100 points. Having all-adenocarcinoma histology was assigned 51 points. The total point derived from this nomogram may range from 0 to 431 points, corresponding to the predicted 2-year survival probability of approximately 90 and 10%, respectively, and the predicted 5-year survival probability of approximately 80 and 1%, respectively.

The resultant nomogram calibrated well. A plot of the predicted survival probability against the actual proportion surviving indicated an expected linear correlation. In accordance with the model scope, no survivor was observed in the highest predicted 5-year survival probability quintile at the time of analysis (80–100% 5-year survival probability; Fig. 3*A*). No death was yet observed in the lowest predicted 2-year survival probability quintile at the time of analysis (0–20% 2-year survival probability; Fig. 3*B*). The nomogram demonstrated a good discrimination based on the full model, with Harrell C-statistic of 0.713. An internal validation based on 200 computer-generated bootstrap samples yielded an optimism-adjusted Harrell C-statistic of 0.704.

DISCUSSION

In this report, we performed a pooled analysis of data obtained from 467 patients who underwent surgery for synchronous multiple lung cancers located in multiple lobes. We found that histology was of prognostic significance in that patients with exclusively adenocarcinoma histology had a better prognosis than others. Those with all-adenocarcinoma histology, which comprised 54.2% of patients in the study,

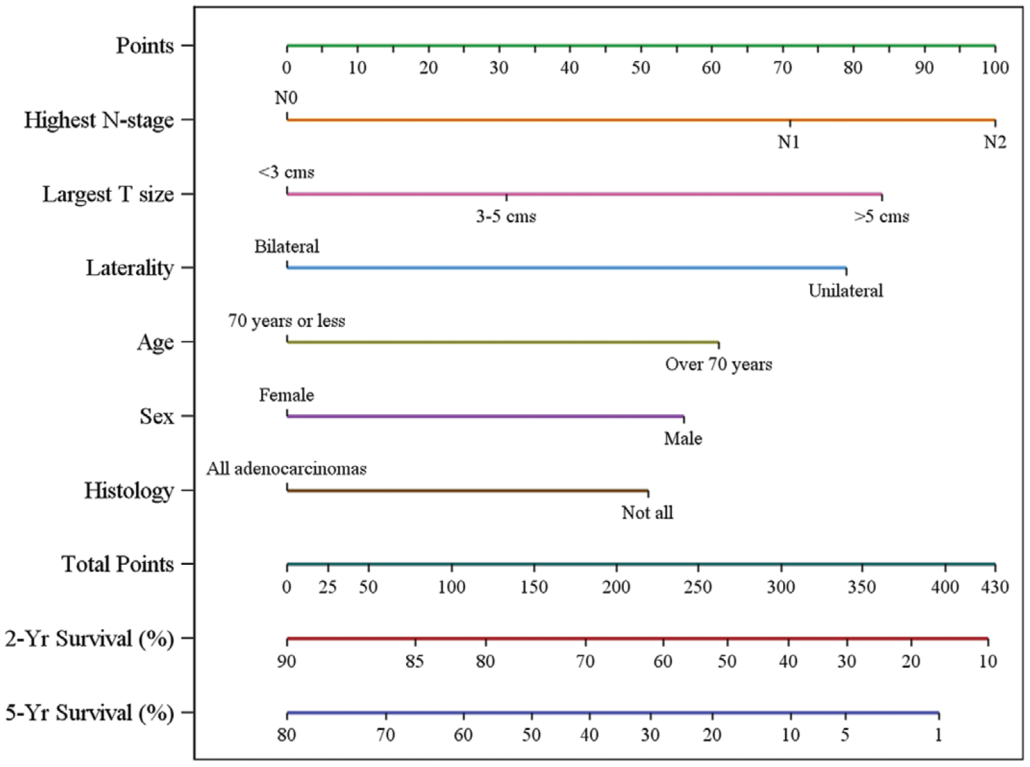

FIGURE 2. Nomogram estimating the probability of 2- and 5-year survival among patients who underwent surgical resection of synchronous multiple lung cancers: (To use the nomogram, calculate a total point by adding points associated with all observed risk factors [N1 = 71 points, N2 = 100 points, largest T-size greater than 5 cm = 84 points, largest T-size between over 3 cm up to 5 = 31 points, unilateral disease = 79 points, age greater than 70 years = 61 points, men sex = 56 points, histology not all-adenocarcinoma = 51 points] and draw a vertical line downward from the total point line to read a predicted 2- and 5-year survival probability.)

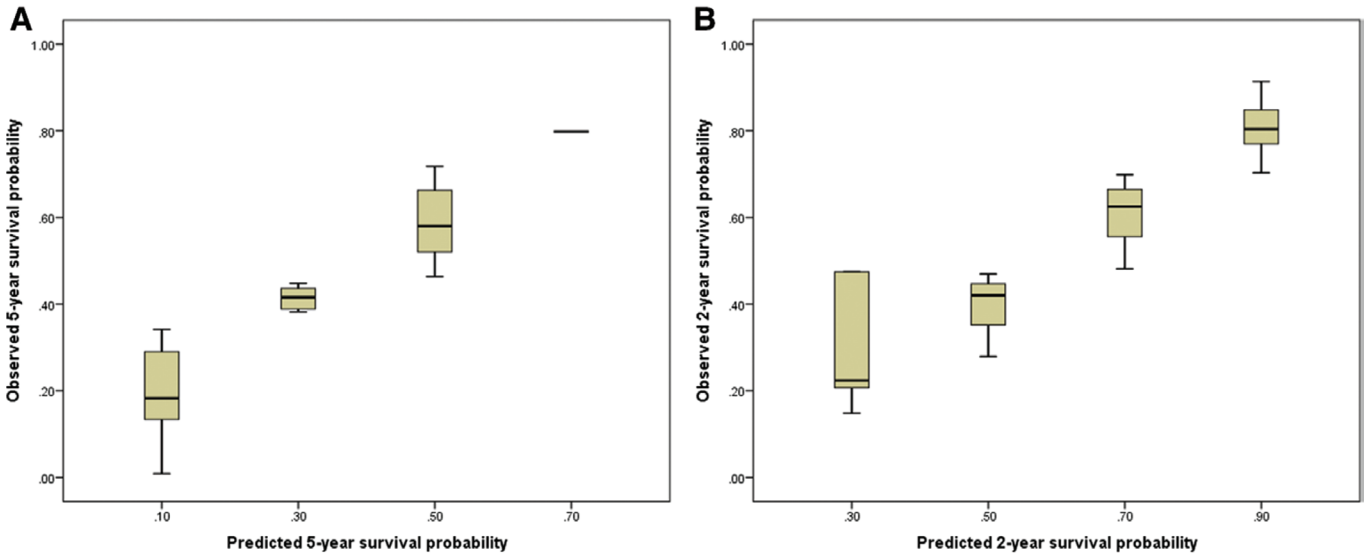

FIGURE 3. **A**, Box plot of the predicted 5-year survival probability plotted against the actual observed survival (*box* inter-quartile range; *whisker* range). **B**, Box plot of the predicted 2-year survival probability plotted against the actual observed survival (*box* inter-quartile range; *whisker* range).

experienced a 32% reduction in the risk of overall mortality. In addition, women sex, younger age, smaller tumor size, lack of nodal involvement, and bilateral cancers were good prognostic features. A nomogram predicting the probability of survival based on these factors calibrated well and demonstrated a moderate to good measure of discrimination.

The prognostic value of age, sex, tumor size, and nodal stage is not unexpected. In addition, the survival advantage of patients with bilateral cancers, compared with those with unilateral cancers, has been previously proposed to have resulted from a more complete exclusion of cases with systemic metastatic disease.[8] What could now explain the favorable survival associated with all-adenocarcinoma histology?

This association is notably independent from age, sex, tumor size, nodal stage, and cancer laterality. The absence of dose–response relationship, i.e., patients with some, but not all, adenocarcinoma do not seem to have a better survival than those with no adenocarcinoma, points to a unique biological characteristic of disease with all-adenocarcinoma histology. Data from studies of patients with single, early stage lung cancer who undergo surgical resection do not necessarily show that adenocarcinoma is associated with a better prognosis after surgery than other NSCLC histology types.[23,24] Nevertheless, it is widely accepted that there exist some minimally invasive or in-situ adenocarcinomas which confer an excellent prognosis after surgery.[16,25] These tumors have a tendency to exhibit an aerogenous or lepidic spreading pattern, often resulting in a multifocal disease.[26] Perhaps the observed favorable survival of patients with exclusively adenocarcinoma histology in our study is driven by the high proportion of patients with minimally invasive adenocarcinoma component, even though we have excluded patients with exclusively in-situ carcinoma from analysis. Although studies have estimated the prevalence of minimally invasive adenocarcinoma in resected single lung cancer ranging from 5 to 20%,[27,28] the prevalence could be higher in our study which only includes multiple lung cancers.

To the best of our knowledge, this article presents the first prognostic instrument specific for patients with resected multiple lung cancers. For patients with single lung cancer, several prognostic factors apart from AJCC stage have been identified, including tumor grade,[29,30] peripheral location,[30] lymphovascular invasion,[23] age over 70 years,[31] and pulmonary function test.[31] Our proposed nomogram does not include variables such as tumor grade, lymphovascular invasion or subtype of adenocarcinoma. Although additional information may further improve the predictive performance of the nomogram, some pathological variables may not be available pre-operatively. Another important caveat to our nomogram is that it was derived from a highly select population in the era when many patients with synchronous multiple lung cancers were not offered surgical resections. This selection bias could result in the nomogram providing an overly optimistic estimate of survival probability. However, keeping in mind the direction of this bias, the nomogram can still be useful for clinical decision making. For instance, it can be stated that a patient who has accumulated approximately 300 total points will have approximately 10% probability of survival at 5 years by an optimistic estimate.

There are other limitations in our study. We were unable to re-examine the histology type. It is possible that some patients with adenocarcinoma were misclassified as not having adenocarcinoma, thus diluting the true strength of association between having all-adenocarcinoma histology and survival. However, this misclassification was mitigated by the large specimen size typically obtained from lung resection for histological examination.[32] In addition, we were unable to obtain data on adjuvant chemotherapy or radiation treatment, although many patients were treated before adjuvant therapy era and its impact on survival is modest, affecting across all histological groups. For instance, adjuvant chemotherapy for selected patients with NSCLC has been associated with an absolute increase in survival of 4% at 5 years regardless of histology type.[33] Although in our analysis, we intend to exclude patients with distant metastatic disease, a number of patients with undiagnosed metastatic disease may have been included because a staging Positron Emission Tomography scan, which is recommended pre-operatively nowadays,[34] was not routinely performed back then. Nonetheless, based on the observed overall survival which is much better than those typical for metastatic lung cancer, the number of such patients is probably small. Finally, tumor size was measured from pathological examination which may be different from radiological measurement, especially low grade tumors which often seem smaller than they really are.[35] Although the internal validation of the nomogram showed a satisfactory performance, we are missing important information, thus an external validation will be necessary to confirm its validity across populations.

In summary, several unique characteristics of patients who present with multiple NSCLC can be used to predict survival after surgical resections. Having an exclusively adenocarcinoma histology portends a good prognosis. This information may be useful for clinical decision making and for hypothesis generating in future study.

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