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

