The International Association for the Study of Lung Cancer Staging Project

Prognostic Factors and Pathologic TNM Stage in Surgically Managed Non-small Cell Lung Cancer

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Purpose: To assess the impact of cell type, age, and gender in addition to pathologic tumor, node, metastasis (TNM) stage in surgically managed stage I-IIIA non-small cell lung cancer (NSCLC) cases from the international staging database of the International Association for the Study of Lung Cancer.

Material and Methods: From the 67,725 cases of NSCLC submitted to the staging database, 9137 surgically managed cases were selected for which all the following variables were available: pathologic stage, age, gender, and specific histologic cell type. Performance status and smoking history were examined in subsets. Methods used were Cox proportional hazards regression and recursive partitioning and amalgamation (RPA) analyses.

Results: Pathologic TNM stage, age, and gender were all independently prognostic for survival. The bronchioloalveolar carcinoma (BAC) subtype had superior survival over other cell types despite the potential for heterogeneity in this group. Adjusted comparisons revealed a small survival advantage for squamous cell carcinomas over non-BAC adenocarcinoma histology and also over large cell, though the effect appeared to be limited to the male patients. RPA revealed the importance of TNM stage primarily, and age was prognostic within stage groups. Cell type was not found to add prognostic value in the RPA analysis. Prognostic groups were formed based on the RPA output, and the prognostic value of these groupings was validated using the North American Surveillance, Epidemiology, and End Results Registries. Performance status and smoking history were prognostic in the subsets where data were available. Effects of other variable were not influenced by the inclusion of smoking status in regression models.

Conclusions: Age and gender are confirmed as important prognostic factors in surgically resected NSCLC. Cell type is less important, although the small population of cases classified as BAC have a survival advantage over other histologies, and there may be a small survival advantage for squamous cell carcinomas over non-BAC adenocarcinomas. Imbalances between stage, gender, and cell type at presentation may lead to a misleading result with respect to cell type in unadjusted analyses. Pathologic TNM category is the most important prognostic factor in this analysis.

Key Words: Non-small cell lung cancer, TNM stage, Pathologic stage, Prognostic factors, Histology, Cell type, IASLC Lung Cancer Staging Project.

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The International Association for the Study of Lung Cancer (IASLC) International Staging Committee has submitted proposals for revision of the tumor, node, metastasis (TNM) descriptors[1–4] and stage groupings[5] for lung cancer in the forthcoming (7th) Edition of the International Union Against Cancer and American Joint Committee on Cancer TNM Classification of Malignant Tumors. These proposals were developed using a very large database that was specifically collected from individual databases for that purpose. As part of this effort, the Prognostic Factors Subcommittee of the International Staging Committee reported on the role of other prognostic factors, in addition to stage, with respect to survival in 12,428 clinically staged cases of non-small cell lung cancer (NSCLC).[6] Age, gender, and performance status were all found to be prognostic for survival after adjustment for stage of disease. Cell type was found to be only minimally prognostic within the non-small cell types, with the squamous cell carcinoma cell type having a slightly superior survival overall after adjustment for other factors. However, the effect of cell type only appeared important in the stage IIIA cases.

Here, we examine primarily a subset of those prognostic factors (cell type, age, and gender) in 9137 pathologically

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staged NSCLC surgically managed cases selected from the IASLC database. The large number of cases and relatively homogenous group with respect to management (surgery as part of definitive treatment in all cases) allowed us to explore the prognostic impact of cell type in greater detail than has been possible in the analyses of single institution series or of population-based registries. The relative prognoses for the adenocarcinoma and squamous cell histologies have been reported with various results. In consideration of the potential for disproportionate representation of the different cell types within patient groups, particular care was taken to explore the relationship with respect to survival between stage, cell type, and gender.

METHODS

The methodology of the IASLC Lung Cancer Staging Project and the major proposals have been reported.[2–5,7] All data were retrospective, and, by mutual agreement, were transmitted to Cancer Research And Biostatistics (CRAB) as coded data without identifiable private information, with appropriate regulatory permission from the contributing sites. The project was reviewed and determined to be exempt from further human subjects review by CRAB's institutional review board.

Population

In total, 100,869 cases were submitted to the international database, of which 81,015 remained eligible for analysis after exclusion of cases outside the study period (1990–2000), those with unknown histology, those not newly diagnosed at the point of entry and those with inadequate information on stage, treatment or follow-up. Of the eligible cases, 67,725 cases were of non-small cell histology. Of these, 15,236 were pathologically staged, surgical cases with sufficient T, N, and M descriptor information to reclassify according to the IASLC proposals for the 7th edition of TNM. From this group, 9137 stage I-IIIA cases were identified as having come from databases that distinguished the bronchioloalveolar carcinoma (BAC) subtype from the other adenocarcinomas as a separate category wherever it was identified and reported by the local pathologist. The time frame for these cases mostly predates the 1999 3rd edition of WHO guidelines for the classification of lung tumors,[8] so that many cases classified as BAC were potentially adenocarcinoma with a BAC component, rather than pure BAC without invasion. Although there was no central histopathological review of cell type and we therefore cannot be certain that the allocation of cell type was consistent across groups, especially in identifying BAC, the recognition of a separate category for BAC or adenocarcinoma with BAC features was felt to be important.

Age, gender, and cell type were available for all of these cases. Performance status was unavailable in two thirds of the cases; therefore, this factor was not included as a factor in the primary analysis but was explored in a subset. Because all of these cases were candidates for surgery, performance status typically did not exceed 1 on the Zubrod scale in those cases where performance status was provided. Smoking history was also unavailable for 54% of cases; therefore it was explored separately as well. Patients who were documented as having received neoadjuvant chemotherapy were not included in these analyses. Cases with notation of chemotherapy at some time point after surgery (in about 8.5% of the cases where the data were provided) were allowed.

TABLE 1. Geographical Representation of Submission Types

	Total Cases	Clinical Trial	Consortium	Registry[a]	Series
Asia	1135	0	0	0	1135
Australia	1383	0	0	0	1383
Europe	4818	10	1851	1880	1077
North America	1801	466	0	0	1335
All regions	9137	476	1851	1880	4930

[a] Category includes surgical registry and population-based registry.

Cases included in the primary analysis were from 27 separate databases representing 18 countries. The largest contributions were from the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S, 1851 cases) and the Norway Registry (1737 cases), which collected surgical cases specifically. The majority of cases were from surgical series or hospital consortia submitting surgical cases to a central registry. A small proportion of cases (143 cases) were from population-based registries (collecting cases from all treatment modalities) and 476 were from clinical trials (Table 1). Of the 9137 cases included in this analysis, 1950 had also been included in the previous analysis of clinically staged cases.

Statistical Analysis

Survival was measured from the date of surgery until death due to any cause, and median survival was calculated by the Kaplan-Meier method. Prognostic groups were assessed by Cox regression analysis on overall survival, using the SAS system for windows version 9.0 PHREG procedure. In regression analyses, stage and histology categories were modeled categorically using indicator variables. For ease of interpretation, age was considered as a dichotomous categorical variable with a cutpoint of 70. Although the cutpoint for age was 75 in the previous paper from this group, there was a smaller proportion of cases that were over age 75 in the current surgical subset. Thus, a cutpoint of 70 was chosen, which is consistent with the age cutpoint frequently cited for clinical trials in "elderly" patients. The decision to use a dichotomous age variable was reinforced by the fact that when regression models were adjusted by age as a continuous variable for comparison, the resulting hazard ratios for cell type, stage, and gender were the same to within ± 0.03. Significance testing for binary variables (age and gender) was done using the Wald statistic. Comparisons of individual levels of stage and histology also used a Wald test for each individual hypothesis. Because of the number of variables used and models considered, the threshold for statistical significance was adjusted to 0.01.

Recursive partitioning and amalgamation (RPA) analyses[9] were performed to generate tree-based models by stage (proposed version 7 TNM) plus the key prognostic factors: age, gender, and cell type. The tree algorithms were per-

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