Local recurrence after surgery for non–small cell lung cancer: A recursive partitioning analysis of multi-institutional data

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Objective: To define subgroups at high risk of local recurrence (LR) after surgery for non–small cell lung cancer using a recursive partitioning analysis (RPA).

Methods: This Institutional Review Board–approved study included patients who underwent upfront surgery for I-IIIA non–small cell lung cancer at Duke Cancer Institute (primary set) or at other participating institutions (validation set). The 2 data sets were analyzed separately and identically. Disease recurrence at the surgical margin, ipsilateral hilum, and/or mediastinum was considered an LR. Recursive partitioning was used to build regression trees for the prediction of local recurrence-free survival (LRFS) from standard clinical and pathological factors. LRFS distributions were estimated with the Kaplan-Meier method.

Results: The 1411 patients in the primary set had a 5-year LRFS rate of 77% (95% confidence interval [CI], 0.74-0.81), and the 889 patients in the validation set had a 5-year LRFS rate of 76% (95% CI, 0.72-0.80). The RPA of the primary data set identified 3 terminal nodes based on stage and histology. These nodes and their 5-year LRFS rates were as follows: (1) stage I/adenocarcinoma, 87% (95% CI, 0.83-0.90); (2) stage I/squamous or large cell, 72% (95% CI, 0.65-0.79); and (3) stage II-IIIA, 62% (95% CI, 0.55-0.69). The validation RPA identified 3 terminal nodes based on lymphovascular invasion (LVI) and stage: (1) no LVI/stage IA, 82% (95% CI, 0.76-0.88); (2) no LVI/stage IB-IIIA, 73% (95% CI, 0.69-0.80); and (3) LVI, 58% (95% CI, 0.47-0.69).

Conclusions: The risk of LR was similar in the primary and validation patient data sets. There was discordance between the 2 data sets regarding the clinical factors that best segregate patients into risk groups. (J Thorac Cardiovasc Surg 2013;146:768-73)

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An accurate understanding of risk (eg, risk of recurrence) is essential in the field of oncology. Estimates of risk guide the development of clinical trials exploring alternative treatment strategies but are also used when considering treatment programs for individual patients. In specialties that deal with local modalities, more precise risks are particularly helpful (eg, risk of *local* recurrence). This is complicated statistically because of the issue of competing risks.[1] Nonetheless, possessing a reasonable appreciation of such is critical in surgical and radiation oncology practice.

Lung cancer remains the leading cause of cancer mortality in the United States.[2] Disease recurrence resulting in death is common despite complete surgical resection, even in patients with early-stage disease. Recurrences are generally subdivided into those developing at local sites (surgical margin and regional draining lymph nodes) and those developing at distant sites. Although adjuvant chemotherapy can potentially decrease the risk of both local and distant recurrence, the risk of local recurrence can also be reduced with the use of postoperative radiation therapy.

Understanding the risk of local recurrence in resectable non–small cell lung cancer (NSCLC) has 4 primary challenges. First, although overall recurrence rates are generally reported in randomized lung cancer trials, patterns of failure are often not described. This can lead to a general unawareness of recurrence patterns, which has relevance to the choice of adjuvant treatment modalities. Second, various definitions of local recurrence have been used in the literature.[3] This creates difficulty when one compares rates of local recurrence among different studies.[3,4] Third, although multiple risk factors for local recurrence have been observed using multivariate modeling, there are inconsistencies between studies. Finally, estimating the aggregate risk in

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Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
LR = local recurrence
LRFS = local recurrence-free survival
LVI = lymphovascular invasion
NSCLC = non–small cell lung cancer
RPA = recursive partitioning analysis

an individual patient, or population, based on the presence or absence of numerous potential factors is a challenge.

With these issues in mind, using 2 independent databases of lung cancer patients undergoing surgery for NSCLC, we estimated the distribution of local recurrence-free survival (LRFS) (using a practical definition of local recurrence), performed multivariate analyses to assess risk factors for local recurrence, and finally performed recursive partitioning to better understand the risk of local recurrence in defined cohorts of lung cancer patients.

METHODS

The retrospective collection of data for this study was approved by the Institutional Review Board of each of the individual participating institutions. The primary data set included all patients who underwent upfront surgery for I-IIIA NSCLC at Duke University (Durham, NC) between 1995 and 2008. The validation data set included patients from the following institutions: University of North Carolina (Chapel Hill, NC), Penn State Hershey Cancer Institute (Hershey, Pa), Beth Israel Deaconess Medical Center (Boston, Mass), and the Veterans Administration hospitals in Boston, Mass, and Denver, Colo, including patients who underwent surgery between 1996 and 2008. For both data sets, patients who received preoperative chemotherapy and/or radiation therapy, presented with synchronous primary tumors, or died in the immediate postoperative period (30 days) were excluded. Patients with superior sulcus tumors or chest wall invasion were excluded because their patterns of local recurrence are different than patients with disease confined to the lung parenchyma and regional lymph nodes. Because the primary objective of the study was to evaluate the risk of local recurrence, we also excluded patients who had positive surgical margins or who received adjuvant postoperative radiation therapy. Because the effect of chemotherapy on local recurrence is not clear, patients receiving adjuvant chemotherapy were included.

Disease recurrence at the surgical resection margin, ipsilateral hilum, and/or mediastinum was defined as a *local recurrence*. This definition was used because it encompasses the anatomic sites that are included in a typical postoperative radiation field. All other sites of recurrence, including the supraclavicular fossa and contralateral hilum, were considered distant recurrences. Patterns of recurrence were assessed by follow-up imaging studies supplemented with invasive procedures, such as bronchoscopy, as clinically indicated.

Statistical Analyses

The primary and validation data sets were analyzed separately and identically. Recursive partitioning was used to fit regression trees for the prediction of LRFS, defined as the time from surgery to local recurrence, with distant recurrences ignored and deaths censored. The candidate predictors for both trees were sex, age, surgery type (wedge/segmentectomy vs lobectomy/pneumonectomy), histology (squamous/adenosquamous cell carcinoma, large-cell carcinoma, adenocarcinoma, and NSCLC not otherwise specified), lymphovascular space invasion (yes/no), pleural invasion (yes/no), number of hilar lymph nodes sampled, stage using the American Joint Committee on Cancer, 7th edition, classification (IA, IB, IIA, IIB, or IIIA, treated as a continuous variable), and adjuvant chemotherapy (yes/no). Other predictors were not included in the analysis, either because they had many missing values in the secondary data set (eg, surgical approach [open vs thoracoscopic] and grade) or because they were measures of the same construct as pathologic stage and were highly correlated with pathologic stage (eg, T-stage, N-stage, size of the primary tumor, and number of hilar nodes involved). We used stage as the candidate predictor instead of one of its correlates because stage had by far the largest univariate association with LRFS. Extent of mediastinal lymph node sampling was not included because the available data in the 2 databases were different (number of stations sampled vs number of lymph nodes sampled).

Recursive partitioning is a statistical method that groups patients into distinct cohorts based on maximizing the value of log-rank tests for the clinical end point of interest (in this case, LRFS). The first 2 cohorts are defined by assessing all possible dichotomizations of all predictor variables, whether categorical or continuous, to find the one dichotomization that produces the largest log-rank test statistic. The method then repeats this assessment within each of these 2 cohorts so that 1 of these 2 cohorts is further split into 2 smaller subgroups. The method proceeds in this manner until a complex stopping rule is met. For each cohort, 5-year LRFS rates are estimated.

Recursive partitioning was done with R's rcart function (The R Foundation for Statistical Computing, Vienna, Austria). Overgrown trees were developed using 10 cross validations and then pruned down to a selected number of nodes. To select the number of nodes to retain, we plotted the mean of cross-validation errors from models of all sizes against their corresponding ''complexity parameters.'' We then noted the lowest-lying point in the plot (or, in practice, the leftmost of 2 or 3 similar low-lying points) and noted its complexity parameter value. Because each complexity parameter value is uniquely linked to a given number of nodes, the selected complexity parameter value determines the recommended number of nodes. For both trees, either 2 or 3 nodes were considered appropriate using this procedure.

The Kaplan-Meier product limit method was used to estimate 5-year LRFS rates. The proportional hazards model was used to determine the predictors of LRFS. By using the same 9 predictor variables as were used in the recursive partitioning analyses (RPAs), the model was fit by using a backwards elimination procedure with a significance level to stay in the model of 0.40.[5] Predictors that were retained in the model were not assessed for statistical significance, but their *P* values were used to show the strength of evidence against the null hypothesis.

RESULTS

The primary data set included 1411 patients, 199 of whom developed an LR, whereas the validation data set included 889 patients, 146 of whom developed an LR. The median follow-up among patients without LR was 26 months (range, 3 days to 175 months) and 33 months (range, 6 days to 175 months) in the two data sets, respectively. The primary and validation data sets had similar LRFS distributions (Figure E1). The data sets had 5-year LRFS rates of 77% (95% confidence interval [CI], 0.74-0.81) and 76% (95% CI, 0.72-0.80), respectively. Patient characteristics and surgical/pathological details are found in Table E1. The 2 cohorts were generally similar, although there were statistically significant differences in many of the factors given the many patients included in the analysis, despite identical inclusion and exclusion criteria.

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