Beyond Margin Status: Population-Based Validation of the Proposed International Association for the Study of Lung Cancer Residual Tumor Classification Recategorization

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ABSTRACT

Introduction: The International Association for the Study of Lung Cancer’s (IASLC’s) proposal to recategorize the residual tumor (R) classification for resected NSCLC needs validation.

Methods: Using a 2009 to 2019 population-based multi-institutional NSCLC resection cohort from the United States, we classified resections by Union for International Cancer Control (UICC) and IASLC R criteria and compared the distribution of R classification variables and their survival associations.

Results: Of 3361 resections, 95.3% were R0, 4.3% were R1, and 0.4% were R2 by UICC criteria; 33.3% were R0, 60.8% were R-uncertain, and 5.8% were R1/2 by IASLC criteria; 2044 patients (63.8%) migrated from UICC R0 to IASLC R-uncertain. Median survival was not reached, 69 (95% confidence interval [CI]: 64–77), and 25 (95% CI: 18–36) months, respectively, for patients with IASLC R0, R-uncertain, and R1 or R2 resections. Failure to achieve nodal dissection criteria caused 98% of migration to R-uncertainty, metastasis to the highest mediastinal node station, 5.8%. Compared with R0, R-uncertain resections with mediastinal nodes, no mediastinal nodes, and no nodes had adjusted hazard ratios of 1.28 (95% CI: 1.10–1.48), 1.47 (95% CI: 1.24–1.74), and 1.74 (95% CI: 1.37–2.21), respectively, suggesting a dose-response relationship between nodal R-uncertainty and survival. Accounting for mediastinal nodal involvement, the highest mediastinal station involvement was not independently prognostic. The incomplete resection variables were uniformly prognostic.

Conclusions: The proposed R classification recategorization variables were mostly prognostic, except the highest mediastinal nodal station involvement. Further categorization of R-uncertainty by severity of nodal quality deficit should be considered.

Keywords: Lung cancer; Staging; Resection margin; Complete; Incomplete; Lymph node

Introduction

Although surgical resection provides the main pathway to cure for most patients with early-stage NSCLC, a large proportion suffer disease recurrence and die of their disease. The residual tumor (R)

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classification of the Union for International Cancer Control (UICC) indicates the likelihood of residual disease after surgical resection. Incomplete resection, currently defined as residual disease at the resection margin, is associated with a high risk of recurrence, progression, and mortality, compared with complete (R0) resection. However, this definition of incomplete resection ignores the risk in cases in which margins are uninvolved, but great doubt remains about disease left behind, such as after suboptimal nodal examination.

To address this problem, the International Association for the Study of Lung Cancer (IASLC) proposed a more expansive definition of incomplete resection (R classification recategorization), including creation of a new category of R-uncertain resections, which have negative margins but a high risk of residual disease. These proposals need validation. R classification recategorization reported strong association with survival in a predominantly Japanese data set with little contribution from North American institutions and was supported by a retrospective analysis from a single Italian institution. We evaluated the prognostic value of the proposed R classification descriptors in a population-based multi-institutional cohort from a region of high lung cancer incidence and mortality in the United States.

We hypothesized that, given the prevalence of suboptimal nodal examination, it would be the most common cause of reclassification into the new R-uncertain category and it would be associated with poor survival in a dose-dependent manner. We examined the distribution of uncertain and incomplete resections stratified by cause, including gradations of poor nodal evaluation, and compared their survival implications.

**Materials and Methods**

**Study Population**

With approval of the Institutional Review Boards of all participating hospitals and the University of Memphis, we analyzed the Mid-South Quality of Surgical Resection (MS-QSR) cohort, a unique population-based data set involving 12 hospitals in four contiguous Dartmouth Hospital Referral Regions in East Arkansas, North and Central Mississippi, and West Tennessee, with five or more annual curative-intent resections for lung cancer, including more than 95% of the resections in the catchment area. The data set is continually updated in real time by trained data abstractors using source clinical data from all participating institutions, and survival updates are made through each institution’s Tumor Registry at 6-month intervals. The current analytical data set includes first resections for NSCLC from 2009 to 2019 with overall survival information updated in May 2019 for all subjects.

**Definitions of Completeness of Resection**

The traditional UICC R classification definition broadly categorizes resections as R0 (having no evidence of cancer at the tissue resection margin), and incomplete (having cancer evident at the resection margin). Incomplete resections are divided into two subcategories—those with microscopic (R1) or macroscopic (R2) evidence of disease at the tissue resection margin. The IASLC has proposed three broad categories: complete, uncertain, and incomplete. Complete resection is now defined as the combination of negative margins, adequate nodal dissection (either systematic nodal dissection or lobe-specific nodal dissection), absence of extracapsular extension of nodal metastasis, and absence of metastasis in the highest mediastinal lymph node resected. Incomplete resection includes any invasive cancer at the resection margin, extracapsular lymph node extension, nonresection of known nodal disease, and positive pleural or pericardial fluid cytology. Uncertain resections have margins negative for invasive cancer, but any combination of inadequate nodal dissection, involvement of the highest resected mediastinal lymph node, carcinoma in situ at the bronchial resection margin, and positive pleural lavage cytology.

**Definition of Adequate Nodal Dissection**

Systematic nodal dissection involves resection of lobar, interlobar, and hilar lymph nodes along with a minimum of three mediastinal nodal stations, including the station 7 (subcarinal) lymph nodes. In addition to evaluation of the hilar, interlobar, and lobar nodes, lobe-specific nodal dissection requires evaluation of station 7 and at least two of three other stations— station 2R (right upper paratracheal), station 3 (prevascular or retrotracheal), and station 4R (right lower paratracheal) for right upper or middle lobe tumors; stations 4R, 7, 8 (paraeosophageal), and 9 (pulmonary ligament) for right lower lobe tumors; stations 5 (subaortie), 6 (para-aortic), and 7 for left upper lobe tumors; and stations 7, 8, and 9 for left lower lobe tumors.

**Study Outcomes and Covariates**

The primary outcomes were distribution and survival of patients according to R classification system. Secondary outcomes were survival according to specific R classification variables. We examined the associations between R classification and patient-level demographic, disease, and treatment characteristics. Demographic covariates included age at the time of operation, sex, race (white, black, other), type of health insurance coverage, and smoking status (never [consumption of fewer than 100 cigarettes in a lifetime], former [quit smoking more than 1 year before operation], active, or...
Disease covariates included tumor histology, grade, size, stage (using the eighth edition of the American Joint Committee on Cancer/UICC TNM system). We included the sum of known comorbidities as a covariate in the proportional hazards model. Treatment characteristics included the extent (pneumonectomy, bilobectomy, lobectomy, segmentectomy, or wedge) and technique (open, robotically assisted, video-assisted) of resection and the evaluation of lymph nodes from specific anatomical locations. We used the IASLC nodal staging map to identify intrathoracic lymph node stations. Because we could not reliably identify the highest mediastinal lymph node per se, we used involvement of lymph nodes in the highest mediastinal lymph node station as a surrogate in analyses examining the survival implications of the highest involved lymph node.

**Statistical Methods**

Categorical variables are summarized with frequency (percent) and continuous data are summarized with means and SD or median (first quartile, third quartile). We compared groups with the chi-square test, t test, or Wilcoxon-Mann-Whitney test, as appropriate. We defined survival time (in months) as the time from operation to either death or last follow-up (for censored patients). We calculated overall survival estimates with the Kaplan-Meier method and compared survival curves between groups using the log-rank test. We used Cox proportional hazards models to estimate crude and adjusted hazard ratios with 95% confidence intervals (CIs). Consistent with IASLC analyses, we adjusted hazard ratios for age at operation, sex, race, primary insurance, histology, extent of resection, total comorbidities, and pathologic T-category. To evaluate the impact of short follow-up periods on survival comparisons, we performed additional analyses in which we excluded resections from 2016 to 2019. Detailed results from the additional analyses are included in the supplemental material. The proportional hazards assumption was evaluated graphically with log(-log) survival plots. A p value less than 0.05 was considered statistically significant. All analyses were conducted using SAS software (SAS Institute Inc., Cary, NC).

**Results**

**R Classification Redistribution**

In the cohort of 3361 resections from 2009 to 2019, 3203 (95.3%) were R0, 143 (4.3%) were R1, and 15 (0.4%) were R2 by UICC criteria, whereas, using the proposed IASLC criteria, 1119 (33.3%) were R0, 2044 (60.8%) were R-uncertain, and 198 (5.9%) were either R1 or R2 (Table 1). The greatest R category migration was from UICC R0 to IASLC R-uncertain: 63.8% of UICC R0 resections were R-uncertain. Failure to achieve recommended pathologic nodal staging criteria was the cause of uncertainty in 98% of patients, and metastasis in the highest mediastinal lymph node was the next most common cause, in 5.8%. Carcinoma in situ at the bronchial margin and positive pleural lavage cytology were infrequent in this cohort (<1%). Forty resections (1.2%) migrated from R0 to R-incomplete: 18 because of extracapsular extension of lymph node metastasis, 14 because of failure to resect biopsy-proven lymph node metastasis, eight because of positive pleural or pericardial fluid cytology.
Comparative Patients’ Demographic, Disease, and Treatment Characteristics Across R-Categories

By both UICC and IASLC criteria, women who had incomplete resection, irrespective of whether by UICC or IASLC criteria [Supplementary Tables 1A, 2A]. No other demographic characteristic, including age, race, insurance, smoking status, and number of comorbidities, was associated with the occurrence of incomplete resection. Advancing clinical T and N (but not M) category, aggregate clinical stage, extent of resection, open resection (compared with minimally invasive resection techniques), and pathologic T-category were all strongly associated with likelihood of incomplete resection (Supplementary Tables 1B and 2B).

Survival Impact

Postoperative mortality at 30, 60, 90, and 120 days was statistically significantly worse in patients who had incomplete resection, irrespective of whether by UICC or IASLC criteria (Supplementary Tables 1B and 2B). After a median duration of follow-up of 43 months, 3-year overall survival rates of patients with R0, R1, and R2 resections by UICC criteria were 69%, 40%, and 55%, respectively; 5-year survival rates were 57%, 30%, and 47%, respectively. Median overall survival after R0, R1, and R2 resections was 77 months (95% CI: 72–86), 25 months (95% CI: 17–36), 39 months (95% CI: 9–NA), respectively (Supplementary Fig. 1).

With the IASLC R classification recategorization, the 3-year survival rates for R0, R-uncertain, R1/R2 resections respectively were 75%, 67%, and 42%; the 5-year survival rates were 64%, 54%, and 33%. Median survival was not reached for R0, 69 months (95% CI: 64–77) for R-uncertain, and 25 months (95% CI: 18–36) for R1/R2 resections (Fig. 1). These survival differences remained statistically significant in fully adjusted models (R-uncertain versus R0 adjusted hazard ratio [aHR]: 1.36 [1.19, 1.56]; R1–R2 versus R0 aHR: 2.18 [1.75, 2.71]). Because of the small sample size for R2 (n = 15), we combined the R1/R2 categories. To further evaluate these survival relationships, we stratified the cohort by pathologic nodal status, analyzing the pN0 (i.e., node-negative) subcohort separately from those with node-positive (pN1, pN2, pN3) disease. The survival relationships among R0, R-uncertain, and R1/R2 remained consistent (Figs. 2A and B).

Evaluation of Individual R Recategorization Variables

Next, we examined the survival implications of each of the proposed IASLC R classification variables with sufficient sample size for meaningful analysis. R0 resections with lobe-specific nodal dissection had similar survival to those with systematic nodal dissection not meeting the more anatomically stringent lobe-specific definition (HR: 1.06 [0.84, 1.33]; aHR: 1.07 [0.85–1.35]; p = 0.5409; Fig. 3).

Patients with R-uncertain resections because the highest mediastinal lymph node station was involved had substantially worse survival than patients who were R-uncertain because of failure to achieve systematic nodal dissection (HR: 1.50 [1.00, 2.31]). However, because those with positive highest mediastinal nodal involvement are, by definition, mediastinal node-positive, we further compared them with the subsets of mediastinal node-positive patients who had R0 resection, and mediastinal node-positive patients with R-uncertainty because of failure to achieve nodal dissection criterion only (i.e., with uninvolved “highest mediastinal node station”). The median survival of R0 with mediastinal nodal involvement, R-uncertain with highest mediastinal nodal station involved, and R-uncertain with mediastinal nodal involvement other than the highest station was 37 (95% CI: 27–77) months versus 32 (95% CI: 21–62) months versus 39 (95% CI: 18–55) months, aHR (with R0 as reference) were 1.0, 1.08 (95% CI: 0.71–1.67; p = 0.7126) and 1.07 (0.61–1.87; p = 0.8203), respectively (Fig. 4). Because of small sample size, we were unable to evaluate the survival impact of positive pleural lavage cytology or bronchial margin carcinoma in situ.

Compared with patients with R0 resections, patients with incomplete resection who had only positive margin (aHR: 2.08 [1.64–2.64]; Supplementary Fig. 2A), positive pleural or pericardial fluid cytology (aHR: 2.05 [0.91–4.65]; Supplementary Fig. 2B), and extracapsular extension alone (aHR: 3.03 [1.70–5.41]; Supplementary Fig. 2C) had worse survival. The 14 patients with only known lymph node disease not resected had aHR 1.32 (0.42–4.12; Supplementary Fig. 2D). There was no significant difference in survival among patients with only one of each of the four defining variables for incomplete resection, p = 0.7033 (Supplementary Fig. 3).

Exploratory Further Recategorization of R-Uncertain Resections by Severity of Nodal Evaluation Deficit

To test the hypothesis that extremes of poor nodal staging partially have their adverse survival effect through nonremoval of oligometastatic lymph node disease, we further recategorized the R-uncertain population into sequentially more extreme subsets of poor nodal staging: 1331 resections (65.1%) had at least one...
mediastinal lymph node examined, 505 (24.7%) had at least one lymph node but none from the mediastinum (mediastinal NX), and 208 (10.2%) had no lymph nodes examined (pNX). In the whole cohort of 3361 resections, 33.3% were R0, 39.6% R-uncertain with at least one mediastinal lymph node, 15% R-uncertain with mediastinal NX, 6.2% R-uncertain with pNX, and 5.9% R1/R2. There was a sequential increase in the crude and adjusted hazard of death across these five groups, \( p < 0.0001 \) (Fig. 5).

![Kaplan-Meier Survival Curves](image)

<table>
<thead>
<tr>
<th>(months)</th>
<th>Median Survival</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
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<tbody>
<tr>
<td>R-Complete</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>R-uncertain</td>
<td>69</td>
<td>64</td>
<td>77</td>
</tr>
<tr>
<td>R-Incomplete</td>
<td>25</td>
<td>18</td>
<td>36</td>
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<th>Hazard Ratio</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
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<tbody>
<tr>
<td>R-Complete</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>R-uncertain</td>
<td>1.41</td>
<td>1.23</td>
</tr>
<tr>
<td>R-Incomplete</td>
<td>2.74</td>
<td>2.21</td>
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<th>Adjusted Hazard Ratio</th>
<th>95% lower CI</th>
<th>95% upper CI</th>
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<tr>
<td>R-Complete</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>R-uncertain</td>
<td>1.36</td>
<td>1.19</td>
</tr>
<tr>
<td>R-Incomplete</td>
<td>2.18</td>
<td>1.75</td>
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**Figure 1.** Cohort survival stratified by IASLC R classification: complete; uncertain; and incomplete. “R-incomplete” combines microscopically and grossly incomplete resections. Hazard ratio adjusted for: age at operation, sex, race, primary insurance, histology, extent of resection, total comorbidities, and pathologic T-category.
Sensitivity Analysis
In additional survival analyses, we limited the cohort to the 2301 resections from 2009 to 2015, to ensure the opportunity for a minimum of 3 years follow-up after surgical resection. The results were very similar to our primary analyses (Supplementary Figs. 4–11).

Discussion
Despite curative-intent resection, substantial proportions of patients suffer disease recurrence and die, suggesting failure of surgical extirpation of disease. Disease recurrence at the bronchial margin, ipsilateral hilum, and mediastinum is probably the strongest evidence of incomplete resection, occurring either alone or concurrently with distant failure in 26% to 60% of patients with recurrent disease.12-14 Although invasive disease at the tissue resection margin (the traditional definition of incomplete resection) provides the greatest hazard for death, it is a relatively infrequent occurrence.5 Uncertain resection because of suboptimal nodal evaluation, being considerably more frequent, increased the hazard for the greatest number of patients after curative-intent resection. This observation is especially important because suboptimal nodal evaluation is susceptible to corrective intervention and, left unaccounted for, may profoundly confound comparisons of lung cancer survival statistics across time and geography.15,16

Moreover, despite intuitive logic, involvement of lymph nodes in the highest mediastinal station, although seemingly more hazardous than suboptimal nodal staging, actually did not have an independent survival impact once the fact of mediastinal nodal metastasis was taken into account. Although the highest mediastinal lymph node itself, the variable actually proposed by the IASLC, is not specifically identified in our database, we used the station as a surrogate. Despite this limitation, our

Figure 2. Survival stratified by IASLC R classification: (A) pathologic N0 resections; (B) pathologic node-positive resections. “R-incomplete” combines microscopically and grossly incomplete resections. Hazard ratio adjusted for: age at operation, sex, race, primary insurance, histology, extent of resection, total comorbidities, and pathologic T-category.
analysis suggests the need for further validation of this R-uncertain variable before adoption as a measure of potential incompleteness of resection. We were unable to test the survival impact of the other two R-uncertain variables, bronchial margin carcinoma in situ and positive pleural lavage cytology, which occurred too infrequently for meaningful analysis. The four incomplete resection variables (margin involvement, extracapsular extension, positive pleural or pericardial fluid cytology, and nonresection of known lymph node disease) seemed of generally similar prognostic significance, although sample size constraints with the latter two limited our analysis.

In general, we corroborate the prognostic value of the IASLC’s proposed R classification recategorization, except for the “positive highest mediastinal lymph node” variable. Similar to reports from Japan, we found that patients who underwent lobe-specific nodal dissection had similar survival with those who had systematic nodal dissection.\textsuperscript{17} Our analysis confirmed poor nodal staging as the greatest cause of uncertainty about the completeness of resection. We found the adverse survival association of R-uncertainty in both pathologic node-negative and node-positive resections. In previous work within this population, we reported that 12% of pN0 resections had intrapulmonary lymph nodes with

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<th>(months)</th>
<th>Median Survival</th>
<th>95% lower CI</th>
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<tr>
<td>Systematic minus lobe-specific nodal dissection</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lobe-specific</td>
<td>NA</td>
<td>NA</td>
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<th>Hazard Ratio</th>
<th>95% lower CI</th>
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<tbody>
<tr>
<td>Systematic minus lobe-specific nodal dissection</td>
<td>1.0 (reference)</td>
<td>*</td>
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<tr>
<td>Lobe-specific (crude)</td>
<td>1.06</td>
<td>0.84</td>
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<tr>
<td>Lobe-specific (adjusted)</td>
<td>1.07</td>
<td>0.85</td>
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**Figure 3.** Survival of IASLC R0 resection patients with systematic vs lobe-specific nodal dissection.
metastasis identifiable by hematoxylin and eosin light microscopy in the discarded resection specimen.\textsuperscript{18} We subsequently demonstrated the adverse survival impact of missed lymph node metastasis.\textsuperscript{19} This provides insight into the etiology of the danger of R-uncertainty in the pN0 population, suggesting the additional influence of

![Kaplan-Meier Survival Curves](image)

**Figure 4.** Survival of patients with positive highest mediastinal lymph node station v R0- with positive mediastinal lymph node v R-uncertain with positive “other than highest” mediastinal lymph node station.

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<th>Variable Description</th>
<th>Median Survival (months)</th>
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<th>95% upper CI</th>
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<tr>
<td>R-0, + mediastinal lymph node</td>
<td>37</td>
<td>27</td>
<td>77</td>
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<tr>
<td>R-un, + highest mediastinal lymph node</td>
<td>32</td>
<td>21</td>
<td>62</td>
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<tr>
<td>R-un, + mediastinal node, not highest</td>
<td>39</td>
<td>18</td>
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**Hazard Ratio**

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<tr>
<td>R-0, + mediastinal lymph node</td>
<td>1.0 (reference)</td>
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<tr>
<td>R-un, + highest mediastinal lymph node</td>
<td>1.10</td>
<td>0.72</td>
<td>1.66</td>
</tr>
<tr>
<td>R-un, + mediastinal node, not highest</td>
<td>1.21</td>
<td>0.70</td>
<td>2.08</td>
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**Adjusted Hazard Ratio**

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<td>R-0, + mediastinal lymph node</td>
<td>1.0 (reference)</td>
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<tr>
<td>R-un, + highest mediastinal lymph node</td>
<td>1.08</td>
<td>0.71</td>
<td>1.67</td>
</tr>
<tr>
<td>R-un, + mediastinal node, not highest</td>
<td>1.07</td>
<td>0.61</td>
<td>1.87</td>
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Figure 5. Survival of cohort with R-uncertain category stratified by quality of nodal evaluation.
the thoroughness of pathologic examination on inaccurate risk stratification in the R-uncertain population. 20

We also suggest the potential value of further subcategorizing the R-uncertain population on the basis of the dose of uncertainty emanating from the enormity of the pathologic nodal staging quality deficit, by demonstrating that R-uncertain resections with evaluation of any mediastinal lymph nodes have superior survival compared with those without examination of any mediastinal nodes, which in turn have superior survival compared with those without examination of any lymph nodes (pNX). 6,21,22 Further categorization of the R-uncertain population in this way would be relatively simple, and profoundly impactful by heightening awareness of poor nodal staging as an eminently preventable cause of potentially incomplete resection, thereby calling attention to the need for quality improvement. Postulates for the adverse survival impact of R-uncertainty include simple misclassification of risk, missed opportunity for beneficial adjuvant therapy, but also the danger from oligometastatic lymph node disease left behind. In reality, combinations of these possibilities probably exist in these populations, although their implications for corrective intervention differ.

The striking improvement in survival of the R0 population from the UICC classification (median 76 months) to the IASLC classification (median not reached) may be an example of the Will Rogers phenomenon. 23 More thorough staging can inflate stage-stratified survival statistics because less obviously high-risk patients such as those with less clinically obvious nodal metastasis (with inherently better zero-time prognosis) are recategorized with other more overtly high-risk patients, thereby raising the survival of the node-positive group, while concurrently raising the survival of the residual node-negative group because of enrichment for true freedom from nodal involvement. This purely statistical phenomenon does not change individual and aggregate patients’ survival odds or mortality risk, despite the improved stage-stratified survival. It might explain the dose-response relationship between the quality of pathologic nodal staging and survival in the R-uncertain population.

The failure of the landmark American College of Surgeons Oncology Group Z0030 trial to demonstrate a survival benefit from mediastinal lymphadenectomy over a rigorously performed systematic sampling procedure, despite discovery of unexpected mediastinal nodal metastasis in 4% of lymphadenectomy recipients, heightened skepticism about the theory of beneficial resection of oligometastatic lymph node disease. 24,25 Nevertheless, a recent meta-analysis of five major randomized controlled trials, including Z0030, has suggested that mediastinal nodal dissection might yet provide better survival than systematic sampling. 26 Moreover, the systematic sampling procedure performed in Z0030 was rigorous and would meet the standards required by the IASLC for categorization as R0, suggesting that the difference between the two arms of that trial is not germane to the R-uncertainty classification. Striking improvement in the aggregate survival of patients who undergo surgical resection with interventions to improve nodal staging quality, which eliminate the occurrence of pNX and mediastinal NX resections, suggests that more than the Will Rogers phenomenon is at play here. 27

Limitations

Our study has certain limitations, including the retrospective nature of this analysis, which opens up the possibility of unknown biases, small numbers of certain subsets foiling any attempt at robust analysis, e.g., carcinoma in situ at the resection margin, pleural lavage cytology (parts of R-uncertain), positive pleural or pericardial fluid cytology, nonresection of known lymph node disease (components of incomplete resection). The data set does not include information on disease recurrence or cause of death, therefore precluding analysis of relapse-free survival, location of disease recurrence, or cause-specific mortality. We have already acknowledged the limitation in the data set which precludes reliable identification of the highest mediastinal lymph node specifically, forcing us to compromise by using the more reliably identified highest involved mediastinal nodal station instead in our analysis. Finally, in advocating for consideration of the dose of lymph node evaluation uncertainty, we have not addressed the issue of whether or not thorough nodal evaluation is necessary for patients with known low-risk radiologic variants such as small malignant subsolid nodules or histologic variants such as adenocarcinoma in situ or minimally invasive adeno-

A major strength of this study is that we have analyzed a population-based, multi-institutional North American cohort, which is very different from the nonpopulation-based, predominantly Japanese cohort previously analyzed by the IASLC, or the single-institutional Italian cohort, which are the only existing attempts to test the IASLC R classification recategorization effort. 6,9 In addition, the MS-QSR has considerably more anatomical details about examined lymph nodes than are found in most publicly available data sets, and since January 2013, the MS-QSR data have been entered in prospective fashion, although only data available from clinical records are entered and there is no direct contact with patients or clinicians.
In conclusion, the proposed IASLC R classification recategorization is mostly valid and likely to help focus attention on the problem of poor nodal examination. However, involvement of the highest mediastinal lymph node may not be adversely prognostic beyond the fact of mediastinal nodal involvement. In addition to the standard attribution of survival differences from improved nodal staging to improved stage redistribution and the Will Rogers phenomenon, we hypothesize a therapeutic value to surgical removal of occult or oligometastatic lymph node disease. Emphasizing the survival deficit of R-uncertainty provides additional opportunity for quality improvement especially in the thoroughness of nodal evaluation. The IASLC staging committee should consider subcategorizing R-uncertainty by marking particularly adverse subsets of poor nodal evaluation (pNX, mediastinal NX) in the ninth edition of the staging system. These extreme states, pNX and mediastinal NX, are readily identified, have profound survival implications, and can confound survival comparisons among different populations of surgically resected patients with NSCLC.

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Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at [https://doi.org/10.1016/j.jtho.2019.11.009].

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