Editorial

Improving post-resection risk stratification in non-small cell lung cancer: 'wit, whither wander you?'

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With an annual worldwide burden of 1.6 million new cases and 1.4 million deaths, and with the rapid penetration of tobacco use into some of the most population-dense regions of the world including East and South Asia, lung cancer, the greatest oncologic public health challenge of this age, will remain so for generations to come (1). Despite encouraging progress in our knowledge of cancer biology which has provided a rich harvest of increasingly more effective drug treatments for patients with advanced disease, the stark reality is that the aggregate 5-year overall survival (OS) of all patients diagnosed annually with lung cancer remains only about 18% at best (2).

The vast majority of these survivors are patients with non-small cell lung cancer (NSCLC) who have had curative-intent resection for early stage disease. Unfortunately, a high proportion of recipients of curative-intent resection die or see their disease recur within 5 years (3,4). Unresectable recurrent NSCLC behaves like stage IV disease, and most such patients die within 5 years of recurrence (5). Therefore, there remains great interest in accurate postoperative risk-stratification, in order to identify patients whose recurrence risk and survival probability can be improved by adjuvant therapy (6).

Adjuvant therapy after complete resection of NSCLC has a 5-year OS benefit ranging from 4% to 15% (7-9). However, the inherent risk of adjuvant therapy restricts the benefit to patients with residually high postoperative risk. This is currently most accurately defined by the presence of lymph node metastasis, local extensiveness (T3 and T4), and (with weaker evidence) bulky disease (9). Accurately identifying patients with high residual postoperative risk is an ongoing challenge, given the disconcerting disparity in survival of patients categorized within identical pathologic nodal stage groups (10). The theoretical causes of this within-TNM stage survival disparity have been categorized as: poor sensitivity of the current TNM system; suboptimal implementation of TNM staging processes; and biologic disparity of disease beyond the representative capacity of the TNM system (6).

Because pathologic TNM staging depends on hematoxylin and eosin (H&E) light microscopy, there has been interest in exploring the first hypothesis (improving the prognostic value of TNM by improving the sensitivity of detecting occult metastasis) by using immunohistochemistry (IHC) and polymerase chain reaction (PCR) to detect more subtle tumor presence at potential sites of metastasis. The report of the mature results of CALGB 9761 (Alliance) is the most recent effort in this direction (11).

In this study, 298 patients who received complete surgical resection for pathologic stage I NSCLC between 1997 and 2002 had primary tumor and lymph nodes assayed for occult metastasis using IHC for cytokeratin AE1/AE3; 256 patients also had real-time reverse transcriptase PCR (RT-PCR) to assay for carcinoembryonic antigen. There was no difference in OS or disease-free survival (DFS) between the 14% of patients with IHC-positive lymph nodes and patients who were IHC-negative. In multivariate analysis adjusting for age, performance status, sex, race, the presence of weight loss ≥5%, histology, tumor size and receipt of adjuvant therapy, N1 lymph node IHC positivity was associated with a hazard ratio of 1.12 (95% CI, 0.61–2.59; P=0.53), and N2 positivity by IHC was associated with a hazard ratio of 2.04 (95% CI, 1.14–3.66; P=0.017). Although 69% of patients had PCR-positive lymph nodes,

this was not associated with survival.

What should we make of these somewhat disappointing results from a prospective multi-institutional study involving patients from 11 US academic institutions and with central analysis of IHC and RT-PCR? It helps to contrast this study with a larger multi-institutional study, the American College of Surgeons Oncology Group (ACOSOG) Z0040 trial (12). That study, also prospective, included a larger number of institutions and patients, including patients with resectable stage I–IIIB disease. In analysis restricted to the pN0 subset of 580 patients and without stratification by the pN-category of IHC-positive lymph nodes, the IHC-positivity rate was 22%, and IHC positivity was associated with a hazard ratio of 1.63 (95% CI, 1.13–2.36; P=0.009) for DFS and 1.59 (95% CI, 1.13–2.23; P=0.007) for OS. This result was consistent in a multivariable analysis adjusting for age, sex and histology (12).

Both studies accrued patients from the late 1990s to the early 2000s, used centralized tissue processing and two independent, blinded pathologists for histologic review, and similar methods to resolve discordance between pathologists. They were similarly limited by not including PET/CT scans in the preoperative workup. Z0040, using antibodies to AE1 and CAM 5.2, had a 22% IHC-positive rate in pN0 specimens while CALGB 9761, using antibodies to AE1/AE3, had a 14% positive rate, raising questions about the sensitivity of the IHC analysis in the CALGB study. Although systematic nodal examination was mandated, only 31% of patients in the CALGB study had all the mandated lymph node stations examined. Indeed, 26% of resections had 2 or more missing nodal stations (11). The thoroughness of hilar and intrapulmonary lymph node examination was not reported in either study. However, judging from a re-analysis of a different trial, ACOSOG Z0030, it was probably suboptimal in both studies, reflecting contemporary pathology practice (13,14).

This begs the question: how well applied was the TNM staging system in these two studies? There is increasing evidence of a worldwide heterogeneity in the thoroughness of pathologic nodal staging, the most recent evidence coming from analysis of the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project. In that report, 5-year survival for patients who had received curative-intent resection for pN0 NSCLC ranged from 54% in Europe to 79% in Asia (represented by Japan and South Korea), and the pN1 survival ranged from 34% to 54% (10). Thoroughness of examination, using the number of lymph nodes examined as a surrogate, has been strongly linked with survival (15-17). Specifically, the thoroughness of mediastinal nodal sampling (to search for N2 or N3 metastasis) and the thoroughness of retrieval of intrapulmonary lymph nodes (to search for N1 metastasis) have been directly linked with survival (13,17-19). This observation holds true, even in ACOSOG Z0030, in which mediastinal nodal dissection and systematic nodal sampling provided equivalent survival in patients with hilar and mediastinal node-negative NSCLC (13,20).

If IHC of H&E-negative lymph nodes, by increasing the sensitivity of detecting metastasis in however few lymph nodes are provided for examination, can overcome limitations in the thoroughness of lymph node retrieval, it would be worth the effort to change pathology practice to include it as a component of routine evaluation of pN0 (IHC for N1 and N2 nodes) or pN1 (IHC for N2 nodes) NSCLC. However, examination of inadvertently discarded intrapulmonary lymph nodes reveals that although 12% of pN0 resections have missed metastasis detectable by H&E staining (14), no patients with H&E-negative lymph nodes (when including the examination of discarded nodes) had IHC positive lymph nodes (Osarogiagbon, Sareen, Wang, *et al.*, unpublished data). This suggests that IHC testing might not overcome the problem of incomplete gross dissection of lymph nodes for routine histologic examination.

The intercontinental survival differences between Asian pN0 and pN1 resections and those from America, Australia and Europe, will naturally raise questions about biologic drivers of postoperative NSCLC survival disparities (the third hypothesis). As illustrated by differences in the prevalence of Epidermal Growth Factor Receptor mutations, biology almost certainly plays a role in within-stage survival differences. The problem, as we have previously articulated, is that mud from heterogeneous application of the TNM staging method significantly inhibits discovery in this direction (6).

Putting the CALGB 9761 report within the context of emerging knowledge, it seems prudent to recommend improvement in the quality of routine pathology practice, including the thoroughness of mediastinal, hilar and intrapulmonary nodal examination. The relationship between cancer biology and outcome differences is very interesting, probably significant, but will remain difficult to tease out until the overall standard of application of TNM is raised significantly above current levels. RT-PCR, as used in CALGB 9761, seems too sensitive and insufficiently specific for clinical use. Although data suggesting the clinical utility of IHC are very intriguing, widespread adoption, on the

basis of existing evidence, is likely to encounter significant resistance among pathologists.

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