The Pathologic Nodal Staging Quality Gap: Challenge as Opportunity in Disguise

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The minority of patients who undergo curative-intent resection for NSCLC represent the overwhelming majority of long-term survivors of lung cancer. Nevertheless, barely half of recipients of curative-intent lung cancer resection survive up to 5 years.[1] Postoperative mortality rates are in the low single digits, but a large proportion die of recurrent lung cancer.[2] Although unheralded biological characteristics probably drive most of the disparate cancer outcomes between patients with ostensibly similar disease, the quality of surgical resection also has an impact. For example, resection with positive margins, associated with a high recurrence and cancer-specific mortality risk, varies between institutions and surgeons, even after accounting for patient-level differences.[3] The risk-adjusted margin positivity rate therefore provides a robust quality benchmark.[4] Less obvious is resection with suboptimal lymph node evaluation. Because pathologic nodal stage is a good surrogate for the burden of malignancy, lymph node metastasis also predicts the likelihood of aggressive disease biology and the possibility of occult distant metastatic disease. Although the therapeutic benefit from lymphadenectomy—specifically the surgical removal of oligometastatic lymph node disease—is debated, there is no doubt that poor pathologic nodal staging is strongly associated with adverse outcomes in populations of patients who undergo surgical resection.[5]

In this edition of the *Journal of Thoracic Oncology*, Heiden et al.[6] weigh in with additional evidence to support this notion. They analyzed 9749 primary surgical resections for American Joint Committee on Cancer and Union for International Cancer Control seventh edition stage I NSCLC from 2006 to 2016 in the U.S. Veterans Health Administration health care system, to assess the quality of pathologic nodal evaluation. They examined the rates of attainment, and the associated outcomes, of two versions of the American College of Surgeons Commission on Cancer (CoC) quality measures for lung cancer surgery: the old count-based benchmark, evaluation of more than 10 lymph nodes in resections for stage I/II, and the new Operative Standard 5.8 which requires evaluation of lymph nodes from at least one hilar/intrapulmonary and three mediastinal nodal stations.[7] Using patients who had no lymph nodes examined (pathologic NX resections) for reference, they reported on the following four specific end points: recurrence-free survival, their primary end point; overall survival; pathologic nodal upstaging; and recurrence within 6 months of surgery. Among several interesting findings are the following: 34% met count-based criteria and 26% met station-based criteria, including 18% who met count-based but not station-based criteria, 10% who met station-based but not count-based criteria, and 16% who met both criteria; 11% of resections were pathologic NX; attainment of station-based quality criteria alone (Operative Standard 5.8, the new CoC quality measure), but not count-based criteria (the old CoC measure), was associated with improved recurrence-free survival; both criteria were associated with improved overall survival and higher rates of pathologic nodal upstaging; and neither was associated with lower recurrence within 6 months of surgery.

This rigorous evaluation supports the global effort to improve the quality of lung cancer surgery. It should heighten awareness of the ongoing need for interventions to improve surgical quality as a means of improving population-level lung cancer outcomes, including the CoC's effort to benchmark performance at accredited institutions.[7] It reinforces the urgency of the International Association for the Study of Lung Cancer (IASLC) effort to redefine the completeness of resection

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(R-factor) by including aspects of quality.[5,8,9] The main practical innovation in the R-factor redefinition is the creation of the R-uncertain category. These are resections with negative margins but residual ambiguity about the completeness of tumor removal, caused in most cases by suboptimal lymph node evaluation.[5,10] Populations of patients reclassified as R-uncertain have significantly worse survival than patients who remain R0 in the IASLC's more stringent definition.[5,10]

More than a decade after the ACOSOG Z0030 trial revealed no survival benefit from mediastinal lymph node dissection compared with a fastidiously performed systematic sampling procedure, the challenge of achieving the optimal nodal evaluation for pathologic staging remains.[11–13] On this challenge hinge important issues such as progress in clinical care delivery, patient survival, and research discovery. Suboptimal nodal evaluation, including the extremes of poor quality—pNX, nonexamination of mediastinal lymph nodes, failure to examine specific lymph node stations (such as stations 10 and 7) that are the recognized way-stations of onward metastasis—is problematic for at least the following three putative reasons: underestimation of residual risk leading to undertreatment, which takes on greater significance with increasingly effective adjuvant therapy; loss of any inherent benefits from removing oligometastatic lymph node disease (such resections may be de facto R1 or R2, hence R-uncertain); and, possibly most dire of all, the inhibition of discovery.

The staging system guides understanding and communication of the extent of disease, prognosis, and treatment. Its poor application inhibits risk stratification, treatment selection, and research. To illustrate the prevalence of the problem, the N category of the lung cancer TNM staging system has remained static since the third edition, whereas the T and M categories have been iteratively improved.[14–16] Data heterogeneity has constrained the N category analyses, potentially inhibiting the discovery of novel stage-independent prognostic factors and stage-based adjuvant treatments. At a minimum, it imposes inefficiency by increasing the sample size needed to detect small differences in outcomes because of imbalances between comparison groups; at worst, it raises the danger of type II (false-negative) errors, in which imbalance between comparison groups submerges differences in outcomes, potentially causing the erroneous rejection of effective treatment.

Not every patient with lung cancer truly needs an elaborate pathologic nodal evaluation. Unfortunately, we cannot reliably identify such patients because rigorous research into this matter has been inhibited by the prevalence of poor pathologic nodal staging practice. Conceptually, patients who undergo surgery for early-stage lung cancer may be grouped into the following four population subsets on the basis of the quality of surgery and recurrence-free survival: group 1—good quality surgery and good outcomes (desirable for all); group 2—good quality surgery and poor survival (indicating adverse cancer biology); group 3—poor quality surgery and good outcomes (indicating favorable cancer biology); and group 4—poor-quality surgery and poor outcomes (indicating an opportunity for quality improvement). Patients in groups 2 and 3 are particularly interesting for discovery of the biological drivers of disparate outcomes. Group 2 patients, if prospectively identified, would be the ideal population for studying innovative approaches to improve curative-intent treatment, including adjuvant therapy. Patients in group 3 would be ideal subjects for testing safer, less morbid, deintensified treatments such as parenchyma-sparing resections, less extensive nodal evaluations, and noninvasive approaches to curative-intent treatment. Unfortunately, a lot of current research is focused on processes and policy interventions to eliminate group 4.

The bottom line: We need a reliable, robust, and readily accessible means of identifying residual disease at the individual person level. Current surgical quality guidelines and benchmarks are useful in quantifying risk in groups of patients, but not at the individual person level. Patients with early-stage disease who experience disease recurrence and early death after oncologically sound resection and those who remain disease free despite seemingly poor-quality resections remind us of this limitation. The ability to detect minimal residual disease at the time of surgery, whether by circulating tumor DNA, cell-free DNA, or other molecular means, may solve this problem, potentially enabling reliable identification of future risk of recurrence at the single person level.[17] Such a "yes" or "no" test would open up the floodgates of discovery by allowing clinical trialists to enrich their studies for the right risk patients, reducing the number of patients needed to test innovative treatments, increasing the likelihood of efficiently conducting and completing such studies.

Poor pathologic nodal staging inhibits our progress toward a world in which lung cancer is routinely cured. Heiden et al.[6] remind us of the enormity of the opportunity still before us. Their robust analysis of this unique U.S. national data set further emphasizes the near universality of the pathologic nodal staging quality gap. Their use of recurrence-free survival as the primary end point is particularly valuable in connecting the pathologic nodal staging quality gap to a lung cancer surgery-specific outcome, which unlike overall survival (the only available end point in most large databases) is less confounded by competing mortality risks. Their process for identifying recurrence, well explained and reasonable, limits the criticism that recurrence is difficult to

reliably identify in retrospective analyses.[5,6] This work will help the IASLC Staging and Prognostic Factors Committee's work in producing the ninth edition of the lung cancer TNM staging system. The N-Descriptors and R-Factor Subcommittees will find this article especially useful. The American College of Surgeons and the CoC will be reassured that they are on the right track with Operative Standard 5.8.

Finally, this detailed analysis of a large, relatively new data set in this arena, by corroborating the prevalence and adverse prognostic implications of suboptimal pathologic nodal staging, should encourage all stakeholders interested in overcoming the century-long worldwide lung cancer pandemic—including policymakers, device makers, clinical trial designers, institutional and program administrators, purveyors of quality benchmarks, patients with lung cancer, and advocacy groups—to redouble their efforts to ensure the equitable dissemination of best practices so patients benefit, irrespective of where they go to seek care.

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