

Predicting survival of patients with resectable non-small cell lung cancer: Beyond TNM

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Glendower: I can call spirits from the vasty deep.

Hotspur: Why, so can I, or so can any man

But will they come when you do call for them? (1)

We need better risk stratification tools in lung cancer. With an annual worldwide population of 1.6 million individuals diagnosed and 1.4 million killed, lung cancer is the most lethal cancer in humans (2). The overall 5-year survival rate is only about 16%, but this varies from 73% in patients ostensibly with the earliest stage, IA, to 2% in those with stage IV (3). The vast majority of long term survivors of non-small cell lung cancer (NSCLC) have had surgery as part of their treatment. Currently, for these patients (most of whom have had distant metastasis excluded), the most powerful prognostic factor is the N-category of the TNM staging system: The status of their intrapulmonary, hilar and mediastinal lymph nodes. However, 29% of patients with stage IA disease and 48% of patients with node-negative disease die within five years, most with distant recurrence (4).

Why are these results so poor? There are at least three, somewhat interconnected, plausible reasons: Biologic heterogeneity; the limitations of our current staging/prognostic tools; and poor application of our current best prognostic tool, the TNM staging system. In recent years, there has been greater recognition of the biologic heterogeneity of NSCLC. For example, we now recognize the importance of histology in predicting response (5) and safety (6) of certain systemic treatments; and the existence of 'driver' mutations that are

both prognostic and predictive of response to certain specific treatments (7-9). There are many ongoing efforts to develop biologic identifiers of risk differences in patients with resectable NSCLC in this age of molecular medicine. Despite a few missteps, the hypothesis undergirding these efforts seems valid. Nevertheless, most of the evidence so far has come from poorly validated, small, retrospective studies (10).

The work by Kratz, He, *et al.* from Michael Mann and David Jablons' group at the University of California San Francisco, is a major new contribution to this field (11). They developed a 14-gene signature panel, consisting of 11 cancer-related genes and 3 reference genes, from a training sample of 361 non-stage-restricted non-squamous NSCLC resection specimens from the University of California San Francisco. They then rigorously validated the candidate gene signatures in blinded fashion, in 2 different populations: A community-based series of 433 resections for stage I non-squamous NSCLC from Northern California, and a cohort of 1,006 resections for stage IA-IIIB non-squamous NSCLC from the China Clinical Trials Consortium. Unlike most other previous reports which used fastidiously collected flash-frozen tissue, Kratz, He, *et al.* used formalin-fixed, paraffin-embedded specimens, dramatically increasing the practicality of their assay. Their results are stellar. The combination of gene signatures proved to be independently prognostic irrespective of TNM stage grouping. It was prognostic in stage I, II and III patients. The prognostic value was significantly greater than certain clinical risk stratification criteria proposed by the US National Comprehensive Cancer Network for stage I resections. Furthermore, it was similarly effective in the Northern California and Chinese validation populations. No doubt, this study represents a major breakthrough in the use of gene signatures for risk stratification of lung cancer. The successful use of formalin-fixed, paraffin-embedded specimens brings this technology much closer to the clinic; the robustness of the validation sample size and discriminatory effect suggest that, this time, 'these spirits will come when we do call for them'.

Are we now ready to adopt Kratz, He, *et al.*'s unique panel in triaging between patients who can be served with surgical

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resection as the sole treatment modality, and those who need adjuvant therapy (the crux of that matter at stake here)? The answer to this question, of course, is 'no'. There are limitations to this study that need to be pointed out.

Setting aside the fact that this report excludes patients with squamous cell histology, who represent about 30-40% of the whole NSCLC resection population, we still need validation in a prospective cohort. As with all studies so far, the Kratz, He, *et al.* study is another retrospective series, albeit the largest and most rigorously validated one performed to this date. Importantly, although the study ostensibly addresses the first two plausible explanations for the poor overall results of resection for node-negative NSCLC (heterogeneous tumor biology and limitations of the TNM staging system), it does not directly address the third scenario raised above: Heterogeneity in application of the TNM staging system. How significant is this problem? Put bluntly, pathologic nodal staging of lung cancer is often very poor. In the US, for example, 40-50% of lung resections do not provide any mediastinal lymph nodes for examination (12-14); the number of mediastinal lymph nodes examined is often very low (13,14); only about 8% of patients undergo a resection with systematic lymph node examination (15); even worse, examination of hilar and intrapulmonary lymph nodes is also often suboptimal. The median number of N1 lymph nodes examined in the US is about 3-5 (14,16). The majority of intrapulmonary lymph nodes are left unexamined: In a re-dissection study of remnant lung resection specimens after completion of the official pathology report, we found 150% more lymph nodes discarded than were examined; there were discarded lymph nodes in 90% of patient specimens; and, most disturbing, 12% of patients said to be pathologic node-negative had one or more discarded lymph nodes with metastasis (Ramirez RA, *et al.* Journal of Clinical Oncology, in press). The most extreme illustration of the poor overall quality of pathologic nodal staging is the finding that 18% of US resections for NSCLC have no lymph nodes examined, a phenomenon we have termed 'pathologic NX' (13,17,18).

These failures of routine care occur in the face of cumulative evidence of the independently prognostic value of the number of examined lymph nodes in patients with pathologic N0 disease (17,19,20), and the number of positive lymph nodes in patients with node-positive disease (21-24). They reflect quality deficits in the combined efforts of surgeons and pathologists, with dire consequences for patient survival (18,25). To complicate matters further, the American College of Surgeons Oncology Group (ACOSOG) Z0040 trial confirms prior reports of the negative prognostic implication of micro-metastatic lymph node disease, detected by immunohistochemical staining of lymph nodes negative by light microscopy (26). Put simply, if we don't look, we won't find lymph node metastasis.

What does this all mean in the context of the report by Kratz, He, *et al.*? Because application of our best-validated prognostic

tool- the TNM system- is poor, validation of prognostic gene signatures should be done in cohorts of patients in whom the TNM staging system has been applied optimally and thoroughly. At a minimum, all studies attempting to test or validate gene signatures must report the thoroughness of pathologic lymph node staging - the number of lymph nodes examined from N1 and N2 stations; the number of positive lymph nodes detected, etc. Their statistical analyses must adjust for these factors. The only way around this obstacle would be to test candidate gene signatures in prospective trials in which equivalent sets of patients, stratified for quality of pathologic lymph node staging, are randomized to conventional staging or staging by gene signature. High risk patients on both arms can then be offered post-operative adjuvant therapy, in a bid to determine the prognostic and predictive value of such candidate gene signatures. Kratz, He, *et al.* indicate their interest in conducting a prospective validation study. It would be important to take these tenets into consideration in the design of any such study. Clearly, the optimal study will be cumbersome, expensive and will require a lengthy period of follow-up.

However, the U.S. Southwest Oncology Group (SWOG) is setting up a trial, titled 'Strategies to Improve Lymph Node Examination of Non-small cell lung Tumors (SILENT)', in which lung resections with two interventions (the use of a special hilar/mediastinal lymph node specimen collection kit in the operating room; and a special thin-section pathology examination protocol) designed to improve pathologic lymph node staging are compared to lung resections with conventional operative specimen collection and pathology examination. The intervention arm of this trial would provide a suitably fastidiously staged cohort of patients for prospective validation of prognostic gene signatures, as an interim step towards the definitive prospective randomized trial suggested above.

In summary, the report by Kratz, He, *et al.* is likely to be a monumental landmark in our progress towards uniformly high rates of cure for surgically resectable NSCLC by providing a means for better identification of individual patients' risk. However, it cannot be the final word. We need to prospectively validate the panel in a cohort with uniformly thorough pathologic lymph node staging, in order to determine if it truly adds anything over and above the optimal use of the TNM staging system. When is stage I NSCLC not stage I NSCLC? When the pathologist did not examine lymph nodes with cancer. Molecular signatures from the primary tumor have the potential to simplify prognostication and clinical effort in risk stratification: Low risk patients may someday be spared the rigors of mediastinal lymph node examination, high risk patients may someday be routinely offered pre-operative systemic therapy, irrespective of their clinical TNM stage group. However, a lot of work remains to be done before we can arrive at this juncture. Not the least of which is to optimize the thoroughness of application of the TNM

system, which is still our best-validated prognostic tool.

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