Editorial

Meet the new boss: lung cancer staging

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Lung cancer staging remains a moving target. Since the first TNM staging system was established by Mountain and colleagues there have been seven revisions (1,2). A jaded viewer may understandably feel that these revisions have proven to be refinements more than paradigm shifts. Attempts to incorporate novel technologies or genomic platforms have proven inadequate or worse, and have not changed standard of care for non-small cell lung cancer (NSCLC) (3-6). Heineman and colleagues explore NSCLC staging with an emphasis on how stage affects decision to administer adjuvant chemotherapy in the review article, "*Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy*". Although a new 8th edition of NSCLC staging has been published, it is not in effect yet and all existing data uses the Union Internationale Contre le Cancer (UICC) and American Joint Committee on Cancer (AJCC) 7th edition. Heineman and colleagues present data on clinical staging accuracy, compared to the gold standard surgical pathologic staging. Largely, we believe that the community at large and our institution in particular support and share most of their recommendations.

Lung cancer treatment options have dramatically changed and advanced since the first TNM cancer staging system first was published in 1977, and recent evidence suggests that the once dismal mortality is starting to improve (7).

Similarly, the staging has become more specific with each iterative edition. As such, now more than ever, an understanding of staging guidelines and implications is vital for all thoracic physicians. Surgical upstaging occurs when a preoperative clinical stage II case has confirmed central mediastinal disease (N2 or higher) resulting in pathologic stage IIIa (or higher). In the recently published data from CALGB 9761, the surgical upstaging rate in a prospectively gathered series from North America remains quite high, again arguing for the necessity of quality surgical staging including nodal sampling of the mediastinum in all patients when medically possible (8).

Clinical stage I disease

Heineman and collaborators submit that stage I disease is the most straightforward in terms of staging accuracy and treatment consensus. Adjuvant chemotherapy for Stage IA disease is not recommended (9). These patients possess node-negative tumors less than 3 cm in size without invasion of adjacent mediastinum or close proximity to major vessels. However, current recommendations include optional (moderate evidence) platinum-based adjuvant chemotherapy for tumors larger than 4 cm (9), based on *post hoc* retrospective analysis of the data from CALGB 9633 (10). In their review, Heineman and colleagues do not recommend adjuvant chemotherapy for the patients with larger stage IB tumors. Current American Society of Clinical Oncology (ASCO) guidelines allow for adjuvant chemotherapy in this population. Similarly, the final results of CALGB 9633 demonstrated an overall survival benefit for carboplatinum and paclitaxel arm for Stage IB larger

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tumors (10). Moreover, the lung cancer-specific death rate still favored the arm that received adjuvant chemotherapy, raising the specter of chemotherapy toxicity blunting the survival advantage of adjuvant therapy. Currently, the LACE-Bio consortium is investigating this phenomenon across all the adjuvant trials (11).

Postoperative radiotherapy in stage I is currently supported solely for resected disease with positive margins, although second attempt at surgical resection is favored when possible (9,12). This conclusion clearly stated in the current review is supported by multiple retrospective studies and meta-analyses. Indeed, the often-referenced post-operative radiotherapy (port) analysis determined there was likely a detriment to radiation therapy when routinely used in the adjuvant setting in stage I and II resected NSCLC (13).

Clinical stage II disease

Because risk of N2 disease (contralateral mediastinal adenopathy that results in upstaging to stage IIIa or higher) is high in many clinical stage II patients, pathologic mediastinal staging prior to surgical resection is nearly always recommended. Consequently, accuracy of clinical stage II disease improves, and is more likely to match postoperative pathologic staging. Nonetheless, unanticipated pathologic stage II disease can and does appear. This is particularly important in patients with smaller tumors (T1) (8). These clinical stage IA patients may have as high as 14% unexpected higher stage nodal disease including hilar and bronchial lymph node involvement. Such a T1N1(pIIA) tumor will have a strong recommendation for adjuvant chemotherapy as borne out by all the major adjuvant chemotherapy studies except CALGB 9633, which included only stage I patients (9). In particular, the seminal National Cancer Institute of Canada (NCIC) JBR10 study demonstrated a clear and sustained survival benefit for adjuvant chemotherapy to stage II patients with N1 positive disease (14).

Clinical stage III disease

We agree with the authors' endorsement to employ multidisciplinary thoracic oncology consensus to distinguish potentially resectable clinical stage III NSCLC from unresectable disease. Prior to surgical resection, we also perform invasive mediastinal staging on all cIII as they recommend. Most importantly, whenever possible, pathologic confirmation of mediastinal involvement is crucial when it affects the decision to offer surgical resection. Given the high false positive rate of PET/CT, clinical evidence (without pathologic confirmation) of mediastinal disease in a patient with suspected stage IIIa NSCLC may over-stage and deny therapy to good surgical candidates. The role of surgery, of course, remains controversial and is often determined on an institutional basis. The intergroup trial evaluating chemotherapy and radiation as pre-operative versus definitive therapy for stage IIIA disease left more questions than it resolved (15). Once again, an unplanned retrospective analysis revealed that patients undergoing lobectomy appeared to have a better survival than those that underwent definitive chemotherapy and radiation alone, while patients requiring pneumonectomy fared worse than those receiving only chemotherapy did and radiation did (15). This propels the recommendation for further refinement of criteria for surgery (i.e., nodal size, number of stations, genomic markers) for stage III disease. Aggressive nodal staging as recommended by Heineman and colleagues is critical for appropriate multimodality management and diagnosis of the stage III NSCLC patient.

Conclusions

Accurate staging is important for assessing prognosis and delivering therapy of NSCLC, and is most challenging in stages II and III. Mediastinal staging in particular has become safer and more widely available with proliferation of endoscopic techniques, including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and esophageal endoscopic ultrasound (EUS). As the 8th and newest edition of NSCLC staging guidelines is implemented, we agree that accurate staging may become more difficult, but remains critical. Timely and complete staging is the standard of care for all patients, including older patients who may not get the benefit of the doubt from skeptical thoracic physicians who hold nihilistic views regarding lung cancer mortality. Along those lines, the important issues related to treatment of NSCLC not covered in this review include the explosion of targeted therapies. Nonetheless, patient autonomy and individual patient factors will continue to require that treatment plans use guidelines as a suggestion but make room for personalized medicine. A multimodality team approach as detailed by Heineman and colleagues will clearly serve patients best interests in the care of NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Chansky K, Detterbeck FC, Nicholson AG, et al. The IASLC Lung Cancer Staging Project: external validation of the revision of the TNM Stage Groupings in the Eighth Edition of the TNM Classification of lung cancer. J Thorac Oncol 2017;12:1109-21.
2. Mountain CF. A new international staging system for lung cancer. Chest 1986;89:225S-33S.
3. McCook A. Duke fraud case highlights financial risks for universities. Science 2016;353:977-8.
4. Potti A, Mukherjee S, Petersen R, et al. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med 2006;355:570-80.
5. Potti A, Mukherjee S, Petersen R, et al. Retraction: A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med 2011;364:1176.
6. Tang H, Wang S, Xiao G, et al. Comprehensive evaluation of published gene expression prognostic signatures for biomarker-based lung cancer clinical studies. Ann Oncol 2017;28:733-40.
7. Richards TB, Henley SJ, Puckett MC, et al. Lung cancer survival in the United States by race and stage (2001-2009): Findings from the CONCORD-2 study. Cancer 2017;123 Suppl 24:5079-99.
8. D'Cunha J, Herndon JE 2nd, Herzan DL, et al. Poor correspondence between clinical and pathologic staging in stage 1 non-small cell lung cancer: results from CALGB 9761, a prospective trial. Lung Cancer 2005;48:241-6.
9. Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA completely resected non-small-cell lung cancers: american society of clinical oncology/cancer care ontario clinical practice guideline update. J Clin Oncol 2017;35:2960-74.
10. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.
11. Shepherd FA, Lacas B, Le Teuff G, et al. Pooled analysis of the prognostic and predictive effects of TP53 Comutation Status combined with KRAS or EGFR Mutation in early-stage resected non-small-cell lung cancer in four trials of adjuvant chemotherapy. J Clin Oncol 2017;35:2018-27.
12. Bezjak A, Temin S, Franklin G, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol 2015;33:2100-5.
13. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352:257-63.
14. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.
15. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.

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