Commentary

Implications of the lymph nodal ratio in resected N1 non-small cell lung cancer

Vivek Verma[1], Steven H. Lin[2]

[1]Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE, USA; [2]Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Correspondence to: Steven H. Lin, MD, PhD. Department of Radiation Oncology, the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 097, Houston, TX 77030, USA. Email: shlin@mdanderson.org.

Comment on: Li Q, Zhan P, Yuan D, *et al.* Prognostic value of lymph node ratio in patients with pathological N1 non-small cell lung cancer: a systematic review with meta-analysis. Transl Lung Cancer Res 2016;5:258-64.

Submitted Oct 11, 2016. Accepted for publication Oct 24, 2016.
doi: 10.21037/tcr.2016.11.65
View this article at: http://dx.doi.org/10.21037/tcr.2016.11.65

Comment

The management of early-stage non-small cell lung cancer (NSCLC) with clinically positive N1 lymph nodes (LNs) involves surgical resection if technically and medically feasible (1,2). Thereafter, many of these patients will be confirmed as pathologically N1, without involvement of N2 mediastinal nodal stations. However, it is well-recognized that N1 NSCLC represents a diverse and heterogeneous population, with varying rates of recurrence and survival (3). Hence, the goal of ongoing investigation has been to better delineate prognostic groups within this relatively ambiguous cohort, so as to optimally treat patients at various risk levels.

Several prognostic factors have been reported for N1 NSCLC in various studies. These include the size and histologic grade, which are noted tumor-related factors associated with regional lymphatic involvement (4). However, arguably more important factors are those that pertain to LN spread. A 450-patient study from France demonstrated that the number of metastatic nodal stations also was predictive of overall survival (OS) (5). The authors further noted that stations 12–14 are involved more through direct extension, but station 10 becomes involved through frank metastasis and thus was most associated with worse OS. These data were echoed by a study from Japan of pT1-2N1 NSCLC that observed a 5-year OS of 60% for segmental bronchial nodal disease versus just 20% for main bronchial nodal involvement (6).

These compelling data also bring forth the question of whether the likelihood of being categorized into such prognostic nodal factors is, in itself, dependent on another variable—namely, the number of LNs resected. This is not a novel notion in other neoplasms; for instance, standard practice of an axillary LN dissection in breast cancer is to remove at least ten nodes, because data has demonstrated inferior outcomes with suboptimal dissections (7). This is not only because nodal dissections in both breast and lung cancers can be considered therapeutic to a certain degree, but also because of the central notion that the likelihood of discovering more pathologic LNs is predictably related to how many nodes are dissected. As such, there have been numerous reports demonstrating a prognostic effect of the so-called "lymph node ratio" in pancreatic (8), head and neck (9), and colon malignancies (10).

In the article accompanied by this commentary, Li *et al.* demonstrate using meta-analytic methodology that LNR is an effective method with which to prognostically stratify the heterogeneous N1 NSCLC population (11). Therein, 6,130 total patients with examined LNRs were analyzed for outcomes, the largest cohort evaluating this parameter to date. The pooled hazard ratio for (worse) OS with high LNRs was 1.53, and for disease-free survival (as reported in three papers) was 1.64. Importantly, there was no substantial heterogeneity between studies, indicating consistent results and reliable conclusions. It is acknowledged that nearly two-thirds of the pooled patients came from one study, and a difficulty in interpreting the data were that each study utilized different interval definitions of what constituted a "high" LNR. Nevertheless, a salient message

of the article is that LNR should indeed be more utilized as potentially relating to prognosis in this population, and just as importantly, further experiences should seek to report individual LNRs as part of the presented data. Doing so would facilitate the reporting of future meta-analyses with even larger sample sizes and more awareness of the prognostic role of LNR in N1 NSCLC.

There are multiple reflections to be gained from this report. First, it is currently unknown whether involvement of proportionally greater LNs is more indicative of worse tumor biology (e.g., rapid transit time between LNs) or a greater time period between mutagenesis and pathologic diagnosis. The elucidation of the genetic basis of many NSCLCs, with subsequent efforts at targeted therapies, could be related to propensity for subclinical nodal spread. Next, it should be questioned whether more extensive nodal dissections should be "required" in this cohort (or potentially even in N2 disease, by extrapolation), similar to the recommended "requirement" of at least ten removed LNs in axillary LN dissections for breast cancer. Though no guidelines on this issue in NSCLC exist (1), a further volume of work is needed to bring this issue to the forefront of thoracic surgical oncology. Though prospective trials are always preferred, retrospective validations of the five studies examined by Li *et al.*, as well as comparisons of outcomes, are encouraged (especially in high-volume centers).

Regarding ramifications on treatment, it has been demonstrated that postoperative radiotherapy (PORT) for pathologic N1 disease has been associated with a survival detriment (12). However, criticisms against these data remain, such as the use of antiquated radiotherapy techniques and issues with patient selection and staging. It was further demonstrated that PORT may not be detrimental when given alone, but potentially so when added to adjuvant chemotherapy (13). In light of the data presented by Li *et al.*, it may be worth re-evaluating whether PORT may be beneficial in patients with higher LNRs. In addition to the use of modern techniques and precise image guidance, selection of a study subpopulation already at higher risk of death may be most advantageous to show whether PORT may improve outcomes. Similarly, it is also important to consider what kind of effects adjuvant chemotherapy has in patients with higher versus lower LNRs (and if so, whether changes in regimens and/or doses potentially impact outcomes in various subpopulations).

These results have been utilized in a compelling recent study that hypothesized on the prognostic effect of using both LNR and the current pathological LN classification (14). Using this methodology, 700 N1 patients were divided into prognostic groups that effectively stratified actual prognosis in a manner heretofore not demonstrated with other forms of nodal-based classification. Moreover, the authors posited that PORT benefited pN2 patients with high LNRs but not those with low LNRs. Though these data are the first of their kind, further corroborative work will be greatly needed in order to confirm the conclusions set forth by the report.

It follows, then, that perhaps LNR may be a factor worth consideration in the upcoming eighth edition of the American Joint Cancer Commission's TNM staging guidelines (3,15). Though it is more likely that definitions of N2 disease will be further stratified on account of more data thereof, we recommend that LNR be taken into account as part of personalized risk stratification. The noted difficulty of categorizing intrinsically heterogeneous patients into prognostic categories is largely a result of a lack of personalized risk modeling. Though there are several factors that can aid in such, we agree that LNR should be one of several considerations, and with further study in the future, may be considered increasingly important.

In summary, the article herein has demonstrated in a meta-analytic manner that LNR is indeed prognostic in N1 NSCLC, and together with other candidate factors, will help to further create subgroups of a distinctly heterogeneous N1 NSCLC population. It is hoped that using these stratification schemes, differential treatment options may be applied to groups at various risk levels, so as to more sensitively and accurately provide treatment in the future.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: SH Lin has research funding from Elekta, STCube Pharmaceuticals, Peregrine, and Roche/Genentech, has served as consultant for AstraZeneca, and received honorarium from US Oncology and ProCure. V Verma has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer. Version 4.2016. Available online: http://www.nccn.org/professionals/physician_gls/PDF/nsclc.pdf
2. Bott MJ, Patel AP, Verma V, et al. Patterns of care in hilar node-positive (N1) non-small cell lung cancer: A missed treatment opportunity? J Thorac Cardiovasc Surg 2016;151:1549-1558.e2.
3. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:1675-84.
4. Liu CY, Hung JJ, Wang BY, et al. Prognostic factors in resected pathological N1-stage II nonsmall cell lung cancer. Eur Respir J 2013;41:649-55.
5. Mordant P, Pricopi C, Legras A, et al. Prognostic factors after surgical resection of N1 non-small cell lung cancer. Eur J Surg Oncol 2015;41:696-701.
6. Matsuoka K, Sumitomo S, Misaki N. Prognostic factors in patients with pathologic T1-2N1M0 disease in non-small cell carcinoma of the lung. J Thorac Oncol 2007;2:1098-102.
7. Sosa JA, Diener-West M, Gusev Y, et al. Association between extent of axillary lymph node dissection and survival in patients with stage I breast cancer. Ann Surg Oncol 1998;5:140-9.
8. Riediger H, Keck T, Wellner U, et al. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. J Gastrointest Surg 2009;13:1337-44.
9. Chen CC, Lin JC, Chen KW. Lymph node ratio as a prognostic factor in head and neck cancer patients. Radiat Oncol 2015;10:181.
10. Vaccaro CA, Im V, Rossi GL, et al. Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. Dis Colon Rectum 2009;52:1244-50.
11. Li Q, Zhan P, Yuan D, et al. Prognostic value of lymph node ratio in patients with pathological N1 non-small cell lung cancer: a systematic review with meta-analysis. Transl Lung Cancer Res 2016;5:258-64.
12. 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.
13. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695-701.
14. Ding X, Hui Z, Dai H, et al. A Proposal for Combination of Lymph Node Ratio and Anatomic Location of Involved Lymph Nodes for Nodal Classification in Non-Small Cell Lung Cancer. J Thorac Oncol 2016;11:1565-73.
15. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.

Cite this article as: Verma V, Lin SH. Implications of the lymph nodal ratio in resected N1 non-small cell lung cancer. Transl Cancer Res 2016;5(Suppl 6):S1167-S1169. doi: 10.21037/tcr.2016.11.65