Editorial

Surgery in microscopically pathological N2 non-small cell lung cancer: the size of lymph node matters

Ming-Ching Lee[1,2], Chung-Ping Hsu[1,2]

[1]Division of Thoracic Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan; [2]School of Medicine, National Yang-Ming University, Taipei, Taiwan

Correspondence to: Chung-Ping Hsu, MD, FCCP. Division of Thoracic Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan. Email: cliffhsu@gmail.com.

Provenance: This is an invited Editorial commissioned by the Section Editor Min Zhang (The First Affiliated Hospital of Chongqing Medical University, Chongqing, China).

Comment on: Garelli E, Renaud S, Falcoz PE, *et al*. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2016;50:322-8.

Submitted Dec 31, 2016. Accepted for publication Jan 03, 2017.
doi: 10.21037/jtd.2017.02.46
View this article at: http://dx.doi.org/10.21037/jtd.2017.02.46

The optimal therapeutic intervention of pathologic N2 (pN2) non-small cell lung cancer (NSCLC) is still controversial. The argument and the debate about the selection of patients for multimodality therapy, the role of surgery, the choice of neoadjuvant treatment and sequential therapies have continued for years. To assess the prognostic factors of pN2 NSCLC patients who receive curative intent surgery, Garelli and colleagues recently reported that the status of microscopic mediastinal lymph nodal (N2) metastasis, which means a tumor aggregate ranging from 0.2 to 2 mm in size, was associated with better prognosis than macroscopic status (1). After retrospectively reviewing the clinical records of 982 unselected pIIIA-N2 NSCLC patients who underwent curative intent surgery over a period of 10 years [1996–2015], the 5-year overall survival (OS) rate of microscopic status N2 patients was 39%, as compared to the 21% for macroscopic status (P<0.01). Although the patients with and without induction therapy were both enrolled in this study, the microscopic status clearly demonstrated as a favorable prognostic factor in univariate and multivariate analyses.

Microscopic N2 represents a subgroup with better prognosis in NSCLC was not a new idea. In 1994, Green and Lilenbaum proposed the "minimal N2" feature by the definition of the pN2 patients with no detection of N2 disease by preoperative CT scan and mediastinoscopy. Patients with minimal N2 feature that can be resected completely could achieve a 5-year survival rate of more than 30%, close to T3N1 disease (2). In 2000, Andre *et al.* reported the subclassification of minimal N2, that no mediastinal LN enlargement (<10 mm) at preoperative CT scan or enlarged mediastinal LN whose mediastinoscopy is negative, could well predict better outcome in the pN2 patients. The 5-year OS rates of minimal N2 and clinical N2 patients were 34% and 9% respectively (P=0.002) (3). Subsequently, additional terminologies including "unanticipated", "unforeseen", "unsuspected", "incidental" and "surprise" N2 have been used for any patients with pathologic N2 LN involvement but not suspected or documented preoperatively. If patients with surprise microscopic N2 disease, the 5-year survival rate is approximately 26–27% compared with 15% in selective macroscopic N2 patients after surgical resection (4). Comparing with conventional definition of size of mediastinal LN by 10 mm, the referred article used 2 mm as upper limit of microscopic status. The meticulous definition of microscopic status of mediastinal LN may elucidate the better 5-year survival rate, reaching to 39%, which was observed in the referred article.

Conversely to the surprise microscopic pN2 (+) with outcomes predominantly determined by fate or tumor-associated factors that we are not able to predict preoperatively, the surgical benefit in persistent microscopic N2 after induction therapy had raised more attentions. Ideally, the surgery was preserved for partial or complete response after induction therapy and for patients who are

in good performance and can tolerate radical resection. Unfortunately, the current standard techniques for clinical restaging such as repeat computer tomography and mediastinoscopy after induction therapy have not been accurate in clinical setting. Beside the microscopic status which was proposed in the referred article, Dooms *et al.* demonstrated the magnitude in changes of glucose avidity of the primary site of lung cancer after induction therapy, measured by serial positron emission tomography (PET) scan, correlate with pathologic response (5). In addition, the combination of microscopic mediastinal LN by histologic assessment and reduction of maximal standardized uptake value (SUV_{max}) over 60% could become as important tools in evaluating which patients as candidate for surgery after induction therapy for stage IIIA–N2 NSCLC. Afterwards, Barnett *et al.* reported the utility of PET imaging targeting to mediastinal nodal site by similar definition (reduction of SUV_{max} >60%) could better predict tumor response after induction therapy (6). Both articles show the usefulness of PET scan to improve radiographic measures of therapeutic response and attempting to optimize pre-surgical assessment after induction therapy. Although the referred article did not provide the data of PET imaging in the cohort, we will wonder whether the microscopic N2 status correspond to the patients with the most reduction of SUV_{max} after induction treatment. However, it will be interesting to find the correlation between these two parameters even though the SUV interpretation is hampered by difficulty in partial volume correlation for mediastinal lymph node of less than 15 mm and interference by central location of primary tumor in some patients. Based on the finding from recent reports and referred article, we may conclude that the survival is more acceptable in the microscopic N2 patients and the resection is nevertheless with sufficient benefit.

Beyond the size of mediastinal lymph node, features such as single versus multiple lymph node involvement, level of station, skip metastases, lymph node ratio, extracapsular spread of lymph node, and <10% tumor cells in LN (another definition of microscopic pN2) had been proposed to better stratify the persistent N2 patients and correlated with different clinical impaction in the past decade. In line with recent reports, the International Association for the Study of Lung Cancer's lung cancer staging project recommended that physicians should record the number of metastatic lymph nodes (or stations) and to further classify the N2 category into N2 at a single station without N1 involvement ("skip" metastasis, N2a1), N2 at a single station with N1 involvement (N2a2), and N2 at multiple stations (N2b) (7). However, among the patients with microscopic status in the referred article, the number of N2 LN involved, skip metastases and extracapsular spread were not significantly different by multivariate analysis. Therefore, one can speculate that microscopic status is a more important prognostic factor than others.

Currently, the best adjuvant therapy of microscopic pN2 is not conclusive. In general, adjuvant chemotherapy or concurrent chemoradiotherapy might be the reasonable choice and radiotherapy alone should be reserved for cases with unclear resection margins. This concept was further supported by the referred article. However, the subgroup analysis showed the best OS in microscopic pN2 cases was obtained by simple follow-up opposite to macroscopic pN2 patients by adjuvant chemo-radiotherapy. Even though the exactly percentage of the treatment naïve microscopic pN2 patients who did not receive any further adjuvant treatment after radical resection was not provided in this article, the authors challenged the concept of the adjuvant therapies should be provided for all pN2 (+) NSCLC after curative intent surgery and concluded by suggesting the adjuvant therapy seems to be detrimental in this subgroup patients with the size of pN2 (+) less than 2 mm. Nevertheless, the recurrence pattern of microscopic N2 patient should be carefully evaluated in future. In addition, further prospective clinical trials continue to be essential to answer these questions.

Although the best treatment of pN2 NSCLC had been discussed controversially in past decades, we should not accept a dogmatic view of no surgery in this complexity and heterogeneity setting. Choosing wisely of microscopic N2 patients for surgery, particularly for those cases where complete resection is possible with low morbidity and mortality, is essential. With the advancement of diagnostic technology, surgical technique, and neo- or adjuvant treatment, the prognostic benefit of surgery from intensified locoregional control and avoiding consequentially distant metastases could be expected in microscopic N2 NSCLC patients.

Acknowledgements

None.

Footnote

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

References

1. Garelli E, Renaud S, Falcoz PE, et al. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. Eur J Cardiothorac Surg 2016;50:322-8.
2. Green MR, Lilenbaum RC. Stage IIIA category of non-small-cell lung cancer: a new proposal. J Natl Cancer Inst 1994;86:586-8.
3. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 2000;18:2981-9.
4. Detterbeck F. What to do with "Surprise" N2?: intraoperative management of patients with non-small cell lung cancer. J Thorac Oncol 2008;3:289-302.
5. Dooms C, Verbeken E, Stroobants S, et al. Prognostic stratification of stage IIIA-N2 non-small-cell lung cancer after induction chemotherapy: a model based on the combination of morphometric-pathologic response in mediastinal nodes and primary tumor response on serial 18-fluoro-2-deoxy-glucose positron emission tomography. J Clin Oncol 2008;26:1128-34.
6. Barnett SA, Downey RJ, Zheng J, et al. Utility of Routine PET Imaging to Predict Response and Survival After Induction Therapy for Non-Small Cell Lung Cancer. Ann Thorac Surg 2016;101:1052-9.
7. 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.

Cite this article as: Lee MC, Hsu CP. Surgery in microscopically pathological N2 non-small cell lung cancer: the size of lymph node matters. J Thorac Dis 2017;9(2):230-232. doi: 10.21037/jtd.2017.02.46