



The current only location-based nodal classification in NSCLC may be inadequate

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Response to: Lee C, Guel DA, Weksler B. Is there a role for upfront surgery in patients with N2 disease and good prognostic features? J Thorac Dis 2019;11:S1199-201.

Submitted Jun 04, 2019. Accepted for publication Aug 03, 2019.

doi: 10.21037/jtd.2019.08.24

View this article at: <http://dx.doi.org/10.21037/jtd.2019.08.24>

We thank Dr. Lee and colleagues for their valuable comments on our article. Dr. Lee discussed the results of three randomized studies evaluating the role of surgery compared to radiation therapy after induction therapy in patients with N2 disease and concluded that there was no difference in overall survival (OS) between the two treatment groups (1-3). However, as per the available national data, a few patients with clinical N2 disease still sometimes receive upfront resection (4,5).

A direct lymphatic metastasis from a primary tumor to the upper mediastinal lymph node or aortic window lymph nodes is sometimes recognized in pN2 (6). As for pN2 disease, patients with N2 and without N1 disease (skip N2) have a longer survival than those with N2 and N1 disease (7). However, up to date, few reports about clinical N2 disease by current preoperative examinations, including thin-section CT or positron emission tomography, have been. We evaluated the results of upfront resection in patients with clinical selective N2 disease by current preoperative examinations.

We classified patients into Group A and Group B by the following two criteria: (I) clinical skip N2 disease and (II) primary tumor in the right upper lobe or left upper segment. Thirty-nine were eligible for these two criteria. They were classified into Group A and the other group of 55 patients was classified into Group B. Our study showed that 25 (64.1%) patients had pN2 disease in Group A. Of these, 13 (52.0%) had pathological N2 disease without N1. The 5-year OS of patients with pN2 disease in Group A was 54.5% (8). They had a better prognosis than previous

reports (1,4,5).

The 5-year OS suggested a better prognosis for patients in Group A than for those in Group B ($P=0.039$) in univariate analysis. Moreover, Group A was an independent prognosis factor ($HR=1.99$, 0.030) in multivariate analysis. These results show that upfront resection for patients with selective clinical N2 disease may be acceptable.

The patients need to receive invasive examinations such as mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) if they receive induction therapy before resection. The metastasis of mediastinal lymph node should be pathologically definite as N2 disease. These invasive examinations are related with complications and increase the hospital time or cost. Our study showed that 22 (23.4%) had pathological N0 or N1 disease (8). Even if these patients had received EBUS-TBNA of the mediastinal lymph nodes before surgery, they would have been re-classified as having N0 or N1 disease and subsequently receive upfront resection.

A prospective randomized trial will help clarify the superiority of upfront resection over standard chemoradiotherapy in patients with clinical selective N2 disease. However, such a trial would be difficult, given the small number of patients.

Finally, the current nodal staging of solid tumors in other areas of the body, such as esophagus, stomach, colorectum, kidney, or breast is categorized by the number of metastatic lymph nodes (9). And categorizing the number of metastatic lymph nodes for nodal classification in non-small cell lung cancer (NSCLC) has been also recently reported (10). The

current only location-based nodal classification in NSCLC may be inadequate. For instance, the group of patients with skip N2 disease was different compared to the group of patients with other pN2 diseases. We would need to revise nodal classification in NSCLC in future.

Acknowledgments

We thank Dr. Lee and colleagues for their interest in our article and wish them well.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is 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.

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Cite this article as: Maniwa T. The current only location-based nodal classification in NSCLC may be inadequate. *J Thorac Dis* 2019;11(8):E131-E132. doi: 10.21037/jtd.2019.08.24