



# Local control of locally advanced (N2) non-small cell lung cancer: when and how?

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*Comment on:* Kim MP, Correa AM, Hofstetter WL, *et al.* Occult stage IIIA-N2 patients have excellent overall survival with initial surgery. *J Thorac Dis* 2018;10:6670-6.

Submitted Feb 22, 2019. Accepted for publication Mar 27, 2019.

doi: 10.21037/jtd.2019.04.26

View this article at: <http://dx.doi.org/10.21037/jtd.2019.04.26>

In patients with locally advanced (N2) non-small cell lung cancer (NSCLC), surgery alone results in dismal prognosis despite of its localized presentation by definition (1). As most locally advanced lung cancers are large and centrally located, extensive resection is expected for complete tumor removal. The incidence of postoperative complications is generally high, and functional impairments are often encountered after extensive surgery. Even if patients recover well following complicated surgery, oncologic outcomes are poor because of the high rate of distant failures (2). Therefore, invasive mediastinal staging is widely adopted in many centers for all potentially operable NSCLC patients to identify N2 NSCLC patients and to avoid risky and ineffective surgery (1). The European Society of Thoracic Surgeons guidelines strongly recommend invasive mediastinal staging in the presence of 1 or more of the following criteria: central location of lesion, tumor size >3 cm, or suspicion of N1 nodes (3).

Studies by Roth *et al.* (4) and Rosell *et al.* (5) are clinical landmark on the treatment of locally advanced NSCLC. These authors hypothesized that preoperative chemotherapy would maximize the effectiveness of surgery by controlling the microscopic systemic disease before surgery. They demonstrated improved survival and neoadjuvant therapy followed by surgery became one of the good treatment options. Subsequent randomized controlled trials (RCTs) and meta-analyses supported the use of neoadjuvant therapy followed by surgery in N2 NSCLC patients (6,7). However, the prognosis of N2 NSCLC is still worse than expected,

even though it has been improved with the thoughtful multidisciplinary approach including surgery.

Meanwhile, advances in radiation therapy led improved local control with minimized toxicity (8). Several studies have investigated the use of radiotherapy as an alternative to surgery (9,10). Also, the emergence of newer systemic therapies, such as targeted therapy and immunotherapy, opens up a new chapter in lung cancer treatment. In 2018, durvalumab maintenance treatment following definitive chemoradiotherapy, without surgery, for stage III NSCLC yielded excellent outcomes (11). The favorable results of checkpoint inhibitor therapy in advanced lung cancer treatment encouraged the assessment of checkpoint inhibitor treatment in earlier stages of lung cancer (12). Moreover, the negative attitude to surgery was reflected in the staging revision for NSCLC. For instance, by changing T3N2 from IIIA in the seventh edition to IIIB in the eighth edition of the American Joint Committee on Cancer (AJCC) staging for NSCLC, the proportion of patients indicated for surgical treatment was reduced (13).

What then is the best treatment strategy for locally advanced NSCLC in this era of various treatment modalities? The concept of multimodal treatment based on the consensus on that the chosen modalities should control both local and systemic disease. However, the optimal combination and sequence have long been debated. Even if surgery is included in the treatment program, deciding extent of resection is also a challenging issue. "Can outcomes following extensive resection still be better than

those following minimal resection in this era of improved chemotherapy and radiotherapy?” These issues are debated and difficult to resolve.

Although it is not the first study on this subject matter, the study by Kim *et al.* (14) is valuable in providing clues to help answer the questions, as it more clearly demonstrated the previous observation. This study showed that occult stage IIIA–N2 patients, who were examined using fluorodeoxyglucose positron emission tomography (FDG-PET) or positron emission tomography-computed tomography (PET-CT), had a 5-year overall survival (OS) of 48% and a median survival of 49 months. These results are excellent compared to those of patients of the same stage in the seventh edition of AJCC staging for NSCLC (24%). Our group reported that the median OS was 75.2 months and a 5-year OS rate was 62.7% in patients with unsuspected N2 lung adenocarcinoma (15). Patients with N2 involvement were single-station without N1 involvement, the so-called skip metastasis, and showed an excellent 5-year OS of 69% and a recurrence-free survival of 44.8%. Furthermore, adjuvant therapy was significantly associated with longer recurrence-free survival. These results are important as well-selected patients with N2 lung cancer had excellent prognosis after complete resection followed by the appropriate adjuvant therapy.

As is evident from the above results, since surgical resection in well-selected patients is still the most reliable method of tumor removal and the best chance of cure, all NSCLC patients should be thoughtfully considered for surgery. It is paradoxical that expanding the indication for surgery may be appropriate in this era of improved non-surgical treatment.

To achieve improved prognosis with increasing the use of surgery, first of all, it is necessary to perform safe and effective surgery. Most importantly, a distinction must be made between patients who will benefit from surgery and those who may not. In other words, patients predicted to have good prognosis with surgery should be included and high-risk patients who may have negative surgical outcomes should be excluded. There are many studies on surgical morbidity and mortality in N2 lung cancer patients (15–18). Higher surgical mortality and poorer prognosis were observed in older patients or those who underwent pneumonectomy. Many studies have been conducted on the diagnosis and prognostic factors of N2 NSCLC due to the heterogeneity of the N2 NSCLC patient group. It is therefore possible to differentiate good prognosis groups, such as the microscopic and single-station group, from

poor prognosis groups, such as the bulky and multi-station group, among N2 NSCLC patients (19–21).

Secondly, it is necessary to study treatment failure, and the recurrence pattern and dynamics are useful for understanding the potential causes of treatment failure. Analysis of recurrence patterns and dynamics will provide insight into the actual differences between treatment strategies and clues for exact timing and treatment modality (22,23).

Furthermore, advancements in diagnostic techniques such as PET-CT and endobronchial ultrasound provide relatively accurate information on the diagnosis of mediastinal lymph node metastasis, such as the site of the involved nodes, the number of involved nodes, and the extent of tumor involvement within the nodes. However, this is not enough to win the war on lung cancer. More advanced non-invasive diagnostic techniques such as liquid biopsy, which shows disease burden (24), may be used in the not-too-distant future with consideration for the status of host immunity in treatment planning. This will help in the decision to conduct surgery and in the planning of personalized optimal treatment combinations and the sequence of multi-modality therapy.

The optimal combination and sequence of surgery, chemotherapy and radiotherapy should be assessed by multi-institutional large-scale RCTs to improve treatment outcomes in locally advanced NSCLC patients. Although it may be an arduous task, a global consortium of professionals from all relevant medical and scientific specialties should work resolutely on this subject matter.

### Acknowledgements

The authors are grateful to Drs. Junghee Lee and Hong Kwan Kim for their valuable contributions to the scientific discussion and manuscript preparation.

### Footnote

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

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**Cite this article as:** Park BJ, Kim J. Local control of locally advanced (N2) non-small cell lung cancer: when and how? *J Thorac Dis* 2019;11(Suppl 9):S1169-S1171. doi: 10.21037/jtd.2019.04.26