Editorial

Is there a role for upfront surgery in patients with N2 disease and good prognostic features?

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Comment on: Maniwa T, Shintani Y, Okami J, *et al.* Upfront surgery in patients with clinical skip N2 lung cancer based on results of modern radiological examinations. J Thorac Dis 2018;10:6828-37.

Submitted Mar 10, 2019. Accepted for publication Mar 18, 2019.
doi: 10.21037/jtd.2019.03.68
View this article at: http://dx.doi.org/10.21037/jtd.2019.03.68

Patients with clinical stage IIIA-N2 non-small cell lung cancer (NSCLC) often pose a challenge to surgeons. The wide variability in patient management and outcomes is attributed in part to variability in tumor histology, size, location, and extent of N2 disease. This has spurred interest in identifying the optimal treatment of this heterogeneous group and whether all patients should be treated uniformly. The landmark study by Rosell *et al.* (1) demonstrated the inadequacy of surgery alone in the treatment of patients with N2 disease. The use of surgery alone in the treatment of patients with N2 has been put to rest.

Three randomized studies addressed the role of surgery after induction therapy in patients with N2 disease. The RTOG 89-01 treated patients with induction chemotherapy (cisplatin, vinorelbine, and mitomycin) and then randomized patients to surgery or 65 Gy of radiation therapy. The study accrued poorly and only 73 patients were evaluable. There was no difference in survival between the surgery and the radiation group. van Meerbeeck and the European Organisation for Research and Treatment Cancer-Lung Cancer Group (2) analyzed patients with N2 disease who had a good radiological response to three cycles of platinum-based therapy. Patients who did not respond to chemotherapy were excluded. Patients were randomized to either surgery or 60 to 62 Gy of radiation therapy. There was no difference in survival between the two groups. The RTOG R9309 (3) treated patients with N2 disease with two cycles of cisplatin and etoposide concurrent with 45 Gy of radiation. Patients who did not progress were randomized to either surgery or continued radiation to 61 Gy. Although the surgical arm had a superior progression-free survival, overall survival was not different between the two groups. Finally, a metanalysis published in the *Journal of Thoracic Disease* (4) that included the three mentioned studies failed to demonstrate a survival advantage for the surgical arm.

To further complicate matters, the PACIFIC trial (5) randomized patients with inoperable stage IIIA and IIIB treated with definitive chemo-radiation therapy to durvalumab a PDL-1 inhibitor or placebo. Survival for patients treated with durvalumab was 66.3% compared to 55.6% in the placebo group at 24 months. Survival in the durvalumab group is very respectable considering the relatively poor prognosis of unresectable patients with stage IIIA and IIIB. The National Comprehensive Cancer Network (NCCN) guidelines (6) incorporated the results of the PACIFIC trial early. The current recommendations for patients with N2 disease (irrespective of resectable or not resectable) are definitive chemoradiotherapy followed by one year of durvalumab (category 1) or for patients deemed resectable preoperative chemotherapy with or without radiation and if no progression surgical resection (category 2B).

Another complicating matter in the discussion of the best treatment for N2 disease is the heterogeneity of the disease. Previous work has shown that patients with single station N2 disease had better survival than those with multilevel N2 disease (7,8). Andre *et al.* (9) identified four negative prognostic factors in patients with N2 disease including the presence of clinical N2, multistation N2 disease, more advanced tumors (T3 and T4), and lack of neoadjuvant therapy. Other studies have shown that tumors in the upper

lobes (in particular left upper lobe), and clinical N0 disease (skip metastases) had a better prognosis (7,10).

In the December issue of the *Journal of Thoracic Disease*, Maniwa and colleagues (11) reported on a multi-institutional retrospective study aimed at investigating outcomes of patients with clinical N2 disease with skip metastases in particular in upper lobe tumors. All patients had a chest computed tomography (CT) and positron emission tomography (PET). Criteria for clinical N2 disease included nodes with more than 10 mm in the shortest diameter on CT or increased metabolic activity on PET. There were 94 eligible patients with clinical N2 NSCLC who underwent R0 resection with either lobectomy or pneumonectomy and systematic or lobe-specific lymph node dissection. Only two patients had pathologic confirmation of N2 disease before surgery. The majority of the tumors were adenocarcinomas, and most patients underwent lobectomy (90.4%). Eighty-three patients (88.3%) presented with clinical single station N2 disease and 50 patients (53.2%) had clinical skip N2 disease. The authors divided the cohort into two groups. Group A (n=39) had tumors in the upper lobes and skip N2 metastases. Group B (n=55) encompassed all other patients.

Concordance between the clinical and pathological N stage was seen in 74.5%, and importantly nearly a quarter of the cohort was N0 or N1 by pathology. In the whole group, overall 5-year survival was 47.9%. In patients with pathologic N0 or N1 5-year survival was 74.9% and in those with pathologic N2 disease, the survival was 41.2%. Group A had a 5-year survival of 64% and group B of 37%. When analyzing only upper lobe tumors, there was no difference in survival between patients with skip metastases and those without skip metastases. Multivariable analysis of factors associated with overall survival showed that group A (upper lobe tumors with skip N2 metastases) was associated with better survival. The authors conclude that upfront surgery may be a good option for selected patients with clinical N2 disease.

Maniwa and colleagues (11) attempt to tease-out patients with clinical N2 disease that may benefit from surgery upfront. It is undeniable that the survival for patients with upper lobe disease and skip metastases was respectable at 64% at five years. However, the authors did not report how many of these patients had pathologic N2 disease. If the proportion of patients with pathologic N2 disease in the whole cohort translates to this group, 25% of patients had N0 or N1 disease. We also know from previous work that in patients with N2 disease those with upper lobe disease and single station skip metastases are the ones with better prognosis. It is unknown if chemoradiation therapy followed by immunotherapy could have provided similar survival in group A patients. So far, randomized trials have not been able to show a survival advantage for patients undergoing surgery even in better prognostic groups (2).

Clinical staging of the mediastinum is fraught with errors. Even in the modern era of chest imaging CT and PET are inaccurate. PET CT is a significant advance in chest imaging but its sensitivity for detecting positive mediastinal nodes is 50–85%, and the specificity is 74–93% (12-14). Accurate preoperative surgical staging of the mediastinum is critical for proper clinical decision making. Identification of patients with multistation disease and patients with N3 disease will significantly change the therapeutic options for patients and will have a high impact on prognosis. For example, a patient with a T3 tumor with N2 disease is currently classified as stage IIIB and because of poor prognosis surgery should not be offered up front. If the same patient has N3 disease, the current stage is IIIC where survival curves are very close to patients with stage IV disease (15).

It will serve surgeons and patients well to follow existing guidelines. Careful staging of the mediastinum with invasive methods, multidisciplinary discussion, and avoidance of surgery upfront in patients with N2 disease, should not be ignored. Until randomized trials in patients with N2 disease and good prognostic features (such as single station N2 disease in upper lobe cancer) compare surgery upfront to the current standard of care, preoperative neoadjuvant therapy or definitive chemoradiation followed by durvalumab should remain the mainstay of therapy for N2 disease.

Acknowledgements

None.

Footnote

Conflicts of Interest: Benny Weksler, MD is a proctor for Intuitive Surgery and speaker for AstraZeneca. The other authors have no conflicts of interest to declare.

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Cite this article as: 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(Suppl 9):S1199-S1201. doi: 10.21037/jtd.2019.03.68

