Editorial

Surgery for stage IIIA-N2 non-small cell lung cancer: the jury is still out!

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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 18, 2019. Accepted for publication Apr 02, 2019.
doi: 10.21037/jtd.2019.04.36
View this article at: http://dx.doi.org/10.21037/jtd.2019.04.36

Stage IIIA-N2 non-small cell lung cancer (NSCLC) comprises a very heterogeneous group of locally advanced tumors for which optimal treatment strategies remain highly controversial although results of large randomized controlled trials are available (1). In general, recommended treatment for pathologically proven, clinical stage IIIA-N2 NSCLC consists of concomitant chemoradiotherapy (CRT) (2). However, the prognosis for this patient group remains poor (3). The role of surgery in the multimodality setting is intensively debated and different treatment recommendations have been proposed. However, more recent evidence suggests that in selected patient groups neoadjuvant treatment followed by surgery yields good long-term survival with limited morbidity (4). Despite the advances in mediastinal staging and imaging techniques, a number of these patients are treated by surgical resection initially, and are found to have N2 disease only at the final pathological examination (5). This so-called "occult N2" or "surprise N2" disease occurs in around 4–10% of stage T1 and T2 tumours (6,7). The present retrospective study investigates survival and mortality rates of patients with occult N2 disease treated with initial surgery, and optimal treatment for patients with N2 disease discovered during mediastinal staging but without evidence of N2 disease on imaging studies (8). A total of 101 patients operated between 2000 and 2013 were included, which represents 3.6% of all patients who underwent lobectomy, bilobectomy or pneumonectomy during the same time period. In 30% of patients, lymph nodes >1 cm were found on chest computed tomographic (CT) scanning. Thirteen percent of patients had multilevel N2 involvement. On positron emission tomography (PET)-CT scanning 24% had positive N2 nodes. Invasive staging was performed in 43%. Most patients underwent lobectomy (83%). Adenocarcinoma was the major pathological type (72%). Adjuvant chemoradiation was completed in 86% of cases. Five- and 10-year overall survival rates were 48% and 24%, respectively. On multivariate analysis, age and peripheral vascular disease were associated with worse survival, underscoring the importance of comorbidity on final outcome. The authors conclude that patients with occult N2 disease treated with initial surgery have excellent 5-year survival rates. Furthermore, they suggest that for patients with a negative mediastinum on PET and CT scanning, but with positive N2 nodes on endobronchial ultrasound (EBUS), surgery as a first strategy in multimodal therapy should be investigated further (8).

A number of randomized controlled trials have been performed in patients with stage IIIA-N2 NSCLC. Rosell *et al.* and Roth *et al.* have shown that induction chemotherapy followed by surgical resection improved overall survival (OS) compared to surgery alone (9,10). Both trials date from 1994 and were performed in an era in which staging was predominantly done via chest CT scans and mediastinoscopy. Modalities such as PET and EBUS were not routinely used, and minimally invasive surgical procedures and radiotherapy (RT) techniques were less developed as well. The general findings of these trials have been confirmed by more recent studies (11-13). However, heterogeneous patient populations have been included and

pathological proof of N2 disease was not always available.

Currently, it is generally agreed that multimodality therapy including variable regimens of chemotherapy, RT and surgery, is indicated in stage IIIA-N2 NSCLC. Several phase III trials have specifically investigated the role of surgery for stage IIIA-N2 NSCLC in a multimodal setting. The European Organisation for Research and Treatment of Cancer (EORTC) 08941, Intergroup (INT) 0139, and the ESPATUE trial are the largest randomized trials that have included pathologically proven stage IIIA-N2 disease (14-16). The EORTC trial compared surgical resection to RT after induction chemotherapy. The results of this trial showed that OS and progression-free survival (PFS) were similar for both treatment groups (14). The INT 0139 trial had a slightly different set-up by using CRT as induction therapy and comparing definitive CRT to induction CRT plus surgical resection (15). The results also showed similar OS rates for both treatment groups; however, PFS was notably better in the surgical arm. The ESPATUE trial included both stage IIIA and stage IIIB and used chemotherapy followed by CRT as induction therapy (16). After this initial treatment, patients were randomized to receive a concurrent CRT boost or surgery. OS and PFS were similar for both treatment groups and the authors concluded that both are acceptable strategies for this patient population.

Although these trials suggest that surgery is an acceptable strategy within a multimodal approach for patients with stage IIIA-N2 NSCLC, there have been difficulties in defining for which subgroup surgery is most suitable. Several meta-analyses have been published in the last few years to resolve this issue. In 2015, McElnay *et al.* published a meta-analysis that investigated bimodality and trimodality regimens including 6 randomized trials with a total number of 868 patients (17). For both bimodal and trimodal treatment approaches, OS was not significantly different between surgery and RT after induction chemotherapy or CRT. There was a 13% survival advantage for patients treated with surgery in the trimodality regimen; however, this difference did not reach statistical significance. It should be highlighted that patients in both treatment arms had resectable disease. In the 2017 meta-analysis published by Pöttgen *et al.*, 6 randomized trials were included that compared surgery with RT as local treatment modalities for stage III NSCLC (18). OS was not different between the surgical and definitive RT arms. In the concurrent CRT trials, survival tended to have an excess early mortality before 6 months in the surgical arm. No significant difference was found regarding PFS in both arms. The authors concluded that both surgical resection and definitive RT after induction therapy are valid treatment strategies for this heterogeneous patient population. However, they emphasize that each case should be carefully evaluated by a multidisciplinary team (MDT) to select the optimal, individualized therapeutic regimen. Two other meta-analyses from 2015 comparing surgery to definitive RT after induction treatment, were also not able to find any significant difference in OS (19). More recently, a meta-analysis consisting of 2,158 patients from 18 randomized trials was published comparing surgery, chemotherapy, RT, and different treatment combinations (20). In this study, the authors concluded that neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy or RT seemed to be the most optimal treatment approach in terms of OS rates for patients with stage IIIA-N2 NSCLC. The role of adjuvant radiotherapy in completely resected N2 disease is currently evaluated in the phase III LungART study (21).

Despite the increasing number of trials and meta-analyses published on the treatment of stage IIIA-N2 NSCLC, it remains difficult to find specific pretreatment predictive and prognostic factors to select patients for surgical treatment. Conflicting results in these studies create uncertainty regarding which factors should especially be taken into consideration when deciding on the treatment approach. Obtaining a macroscopic and microscopic complete resection is the major goal of surgical treatment. In the majority of studies, no distinction is made between the different types of N2 disease, e.g., single station versus multilevel involvement. In the 8th 'tumor, node, metastasis' (TNM) classification published by the International Association for the Study of Lung Cancer (IASLC), the definitions of the N descriptors remained unchanged and no new subcategories were proposed in this latest version (22). However, for further detailed analysis, the authors recommended to subdivide N2 disease into three subcategories: N2a1, N2a2, and N2b. In N2a1, also known as "skip N2" disease, there is invasion of a single N2 nodal station without N1 involvement. N2a2 is defined as involvement of a single N2 nodal station with N1 involvement as well. Lastly, N2b is defined as invasion of multiple N2 nodal stations. Studies on skip N2 metastases indicate that this entity probably has a different prognosis compared to "non-skip" N2 disease (23). Further prospective studies are necessary to confirm the clinical significance of skip N2 disease.

There is no doubt that the jury is still out regarding the

optimal treatment and the role of surgery for stage IIIA-N2 NSCLC. Besides questions regarding the initial treatment of N2 disease, there is also uncertainty regarding the best therapeutic approaches for patients with locoregional recurrence of NSCLC without distant metastases after concurrent or sequential CRT. The concept of "salvage surgery", which was traditionally used as a therapeutic option in the management of anorectal cancers, has gained popularity in thoracic surgery as well. Although large patient series and studies are lacking, it seems that in a highly selected group of patients, salvage surgery is feasible and acceptable survival rates can be obtained in dedicated centers with extensive thoracic surgery experience. This also applies to stage III NSCLC with locoregional recurrent disease for which no other treatment options remain (24).

In the near future, new modalities such as immunotherapy and molecularly targeted therapies will change the landscape and offer clinicians more tools in deciding treatment regimens. A number of recent trials have shown that these therapies can provide significant survival benefits and can safely be used for smaller subsets of lung cancer patients, mostly with advanced disease (25). The ongoing Spanish NADIM trial evaluates induction chemotherapy combined with immunotherapy for stage IIIA-NSCLC. Preliminary results were presented at the 2018 World Conference on Lung Cancer in Toronto (abstract OA 01.05). In 30 patients a major pathological response defined as <10% viable tumor cells in the resected specimen, was observed in 80% which is a remarkably high figure.

Clear definitions of which subsets of patients would benefit most from these therapies are not available yet. This will certainly remain an important topic in upcoming international meetings. Moreover, these therapies will very likely be incorporated into multimodality regimens as well, creating ever more complicated therapeutic approaches and more methodological difficulties for future researchers. At this time, it is clear that the road to consensus lies far ahead of us. However, the evolution in diagnostic techniques and treatment strategies will definitely offer researchers more and better tools to answer some of these important questions. Some fascinating developments are to be expected in the near future!

Acknowledgements

None.

Footnote

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

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Cite this article as: Berzenji L, Beckers P, Van Schil PE. Surgery for stage IIIA-N2 non-small cell lung cancer: the jury is still out! J Thorac Dis 2019;11(Suppl 9):S1153-S1156. doi: 10.21037/jtd.2019.04.36

