

## New classification—new problems to solve

Marcin Zieliński<sup>1</sup>, Robert Kwiatkowski<sup>2</sup>

<sup>1</sup>Department of Thoracic Surgery, Pulmonary Hospital, Zakopane, Poland; <sup>2</sup>Radiation Therapy, Katowice Oncological Center, Katowice, Poland  
Correspondence to: Marcin Zieliński, MD, PhD Department of Thoracic Surgery, Pulmonary Hospital, Ul. Gładkie 1, 34 500 Zakopane, Poland.  
Email: marcinz@mp.pl.

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Treatment of non-small cell lung cancer (NSCLC) has undergone a significant evolution during the last two decades. Currently, the progress is visible especially in chemotherapy. Due to the introduction of the new personalized molecular-targeted therapies survival and the quality of life has improved. In the future, it will probably lead to change the advanced NSCLC in a chronic, long-lasting disease (1). However, currently there is no evidence, that NSCLC could be cured with chemotherapy. The other area of progress is radiotherapy. The use of stereotactic body radiotherapy (SBRT) created the alternative for surgery for early-stage tumors with the survival rates comparable to the results of surgery (2,3). At present, this type of therapy is accepted for the treatment of medically inoperable patients, the role of this modality is less clear in the operable patients.

Nevertheless, surgery is still a gold standard of the treatment of NSCLC (3). The critically important issue is staging of NSCLC enabling a choice of the optimal treatment for individual patients. This problem was raised by Heineman and colleagues, who presented a comprehensive review on the clinical staging of NSCLC, with special attention paid to the therapeutic implications (4). The Authors correctly distinguished individual algorithms for stage I, II and III NSCLC and clearly underlined the differences in the therapeutic approach for each stage. Unfortunately, the authors were too optimistic about the 5-year survival rate for all NSCLC patients. According to the recent data, the mean 5-year survival of patients with NSCLC for the whole European Union is only 13.2%, with

the highest rate 17.9% achieved in Austria (5). These highly unsatisfactory numbers show how much is to be done in the future.

The shortcoming of the article of Heineman *et al.*, explainable due to the shortage of new data is the use of the 7<sup>th</sup> edition of the TNM instead of the 8<sup>th</sup> one introduced in 2016 (6). The 8<sup>th</sup> edition is an expression of the new, changed view on staging of NSCLC. It is not possible to analyze all these changes in detail in this short Editorial, but we would like to give an example illustrating complexity of changes connected with the new classification. Tumors of diameter >7 cm were called T2 according to the 6<sup>th</sup> classification, T3 according to the 7<sup>th</sup> edition and T4, currently (6,7). It means that if such tumors were accompanied by N0, they would be stage I, according to the 6<sup>th</sup> edition, stage IIB, according to the 7<sup>th</sup> edition and stage IIIA, now. In consequence, what about the indication for adjuvant chemotherapy in such patients? Historically, according to the 6<sup>th</sup> edition there was no indication, but nowadays there is no clear answer based on the 7<sup>th</sup> and, especially the 8<sup>th</sup> edition. According to the 7<sup>th</sup> edition patients with pathological stage II (N1) were the candidates for adjuvant chemotherapy, but there were no established indications for the stage II (N0) (3). Are there currently any indications for adjuvant chemotherapy based on pathologic T stage alone (T2a and higher categories)?

These unsolved questions show how the philosophy of management of NSCLC has changed. There has been a transition from ultra-extensive surgical procedures supplemented with radiotherapy in some patients, practiced

with variable success in the 1980s and 1990s to the modern era of growing popularity of minimally invasive video-assisted thoracic surgery (VATS) procedures for early-stage cancer and multimodality treatment, with or without surgery for the advanced tumors. The example given above illustrates also the change of opinion of what is the definition of an advanced tumor now and how it affects the management—is a patient with T4 tumor still a candidate for upfront surgery even if it is technically operable? Should neoadjuvant chemotherapy or, maybe neoadjuvant chemo-radiotherapy be proposed in such cases?

What is our view on the role of surgical treatment in patients with stage IIIA and IIIB according to the 8<sup>th</sup> edition—for example for such cases as T3N2 (stage IIIA)—for example, a tumor with diameter of 5.5 centimeters and a single N2 node? Or in stage IIIB, with a tumor of diameter 8 centimeters and a single N2 node?

Obviously, there are more questions than answers in regard to NSCLC staging according to the 8<sup>th</sup> edition of TNM classification.

The next difficult problem raised by Heineman *et al.* is a staging and treatment of stage IIIA NSCLC (according to the 7<sup>th</sup> edition—it is even less clear with the 8<sup>th</sup> edition).

The latest American College of Chest Physicians (ACCP) guidelines recommended that two alternative treatment modalities for stage IIIA NSCLC, with discrete N2 involvement identified preoperatively were either definitive chemoradiation therapy or induction chemotherapy followed by surgery (8). In the last case, a proper selection of patients for surgical treatment was based on the primary staging and the repeated staging (restaging) after neoadjuvant therapy.

Restaging of the mediastinal nodes is a pivotal part of multimodality treatment of stage IIIA NSCLC. In several studies it was found that the results of survival in patients with residual metastatic nodes much inferior in comparison to the patients in whom the nodes are N0-1 after neoadjuvant therapy. This is especially pronounced in patients with residual multi-level metastatic nodes (9).

Heineman *et al.* mentioned two major studies, the North-American RTOG 9309 and the European EORTC 08941 trials comparing the results of multimodality treatment with/without surgery in patients undergoing induction therapy followed by definitive radiotherapy (10,11).

In both studies the survival rates were significantly better in patients in whom downstaging to N0-1 was achieved with in comparison to the patients with persistent N2 disease. In this selected group of patients with yN0-1 disease there

was a significant benefit of surgical treatment combined with induction chemotherapy, or chemo-radiotherapy in comparison to the group of patients treated with chemo-radiotherapy without surgery. Unfortunately the number of patients with persistent N1-3 nodes after induction treatment was exceedingly high in RTOG 9309 Study (51.8%) and in the EORTC 08941 study (73%), which most probably has affected the survival rates of the whole groups.

Therefore, any decision about surgery after neoadjuvant therapy should be based on the reliable restaging. Unfortunately, all techniques most commonly used for restaging of NSCLC after induction therapy have relatively low diagnostic yield in discovery of the persistent mediastinal metastatic nodes.

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### Footnote

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

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