Letter to the Editor

Invited letter to the editor on the editorial on "*Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy*"

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Response to: Begnaud A, Kratzke RA. Meet the new boss: lung cancer staging. J Thorac Dis 2018;10:1329-31.
Zieliński M, Kwiatkowski R. New classification—new problems to solve. J Thorac Dis 2018;10:S1067-9.

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It is with great interest that we took notice of the expert knowledge on staging of non-small cell lung cancer (NSCLC) and the implications on adjuvant chemotherapy expressed in the two invited editorials on our previously published article entitled "*Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy*" (1). We read the reviews entitled "*New classification—new problems to solve*" by Dr. Zieliński and Dr. Kwiatkowski (2) and "*Meet the new boss: lung cancer staging*" by Dr. Begnaud and Dr. Kratzke (3) and would like to respond to the issues that have been raised.

Both editorials point out the use of the 7th edition of the TNM instead of the new 8th edition of the TNM, which was introduced in 2016 (4). In our review we have deliberately chosen the 7th edition of the TNM because this has been used from 2009 until 2016 and most recent literature on staging NSCLC uses this 7th edition. The 8th edition has been introduced in 2016 but its use has not been implemented worldwide yet. It is not possible to describe the impact of clinical staging and implications on adjuvant chemotherapy in the new edition, when there are ample studies describing this. Dr. Zieliński and Dr. Kwiatkowski described a very interesting phenomenon and we would like to thank them for pointing this out: there is an interesting shift in tumour stage when comparing the staging systems, meaning that a tumour with a diameter >7 cm and no involvement of lymph nodes used to be T2 and stage I according to the 6th edition, T3 and stage IIB according to the 7th edition and T4 and stage IIIA according to the 8th edition. The TNM classification is largely based on survival differences between stage groups and apparently, the impact of tumour size on overall survival is increasingly gaining acknowledgement (4).

We do not support the statement that there are no established indications for adjuvant chemotherapy in stage II (N0) patients and believe however that there are indications for adjuvant chemotherapy for patients based on pathological T stage alone, as stated in our article. The article of Howington *et al.* that is referred to by Dr. Zieliński and Dr. Kwiatkowski makes an important comment on a subanalysis on stage II (N0) patients in the CALGB 9633 and that they may benefit from adjuvant chemotherapy in larger N0 tumours (>5 cm) (5,6). This is supported by the more recent data from the updated American Society of Clinical Oncology (ASCO) guidelines, that states that adjuvant cisplatin-based chemotherapy is recommended in patients with completely resected stage IIA, IIB or IIIA disease (7). Next to this there is some evidence from two trials that even supports the use of adjuvant chemotherapy in patients with tumours smaller than 4 cm and N0 disease (8,9). Our recommendation with a cut-off value of 5 cm (stage IIA in the 7th edition of the TNM) might even be called tentative in regard to the CALGB 9633 subanalysis, that recommends adjuvant chemotherapy in patients with a tumour >4 cm (which is still stage IB in the 7th edition of the TNM) (6). In this respect Dr. Begnaud

and Dr. Kratzke are right in stating that the cut-off should be 4 cm, although they also righteously state that this is based on a post hoc retrospective analysis of these data. We agree that the option of adjuvant chemotherapy should be considered in patients with a resected stage IB tumour (in the 7th edition of the TNM) that is larger than 4 cm. In the new edition of the TNM this will be more clear since stage IIA tumours are >4 cm in the 8th edition of the TNM (4).

Another difficult issue that all reviewers point out is what to do with locally advanced NSCLC, especially restaging after induction therapy. Accuracy of staging seems to decrease in higher stages, where correct staging is of vital importance. Therefore, mediastinal N2 node involvement should always be cytologically or histologically proven before induction therapy can be initiated, especially since Positron emission tomography-computed tomography (PET-CT) has a tendency to over-estimate mediastinal involvement (10). Restaging after induction therapy poses an even more difficult task, since accuracy of diagnostic modalities decreases after induction therapy. We do agree with Dr. Zieliński and Dr. Kwiatkowski's statement that one should make a subdivision between yN0-1 and yN2 disease. The first group should be treated with surgery after induction therapy since there is a prognostic benefit. In the last group, it is unclear if additional surgery after induction therapy improves survival (11,12).

In conclusion, lung cancer staging remains a controversial topic and a new edition of the TNM poses additional challenges. Facing so many challenges in the staging and treatment of lung cancer, there is certainly no time for nihilism. Instead, we should be optimistic and make a global ongoing effort to improve the outcome for lung cancer patients. An open scientific debate is the way forward and therefore the critical appraisal of our work by the reviewers is greatly appreciated.

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Footnote

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

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