Editor's note:
In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

Controversies on Lung Cancer: Pros and Cons

Rebuttal from Dr. Decaluwé and Dr. Dooms

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We congratulate Drs. Obiols and Call for their excellent argumentations to consider a preoperative exploration of the mediastinal lymph nodes in order to avoid futile anatomical lung resections. As they rightly pointed out, preoperative invasive mediastinal nodal staging is not routinely indicated in clinical stage IA non-small cell lung cancer (cStage-IA NSCLC). Nevertheless, the authors suggested specific indications in which preoperative invasive mediastinal nodal staging might be indicated for cStage-IA NSCLC: centrally located tumor; adenocarcinoma histology; high FDG-uptake on PET; tumor size (≤2 *vs.* 2.1–3.0 cm); or a combination of these factors.

First, our paper did address the test characteristics of either preoperative endosonography (EUS/EUS) or preoperative cervical mediastinoscopy for systematic mediastinal nodal sampling and staging in cStage-IA NSCLC. Their poor sensitivity (25–50%) to detect mediastinal nodal disease does not greatly increase the accuracy or the negative predictive value of PET-CT in cStage-IA NSCLC.

Second, we would like to comment on the raised clinical factors that might affect the indication to perform a preoperative mediastinal nodal staging. A prediction model (based on 938 patients; Farjah *et al.*) for pathologic N2 disease in lung cancer with a negative mediastinum by PET-CT did test two different definitions for tumor centrality, and found no relationship between centrality of the primary tumor and an increased risk of pN2 disease (1). We believe that there is substantial uncertainty about the true relationship between centrally located c-Stage-IA and pN2 disease. Although we agree that adenocarcinoma histology has been found as a risk factor for pN2 disease by several authors, we would like to raise the consideration that the information on histology is often not available preoperatively in the setting of a cStage-IA tumor. Besides the issues regarding standardization of SUV value of the primary tumor we would like to raise two additional considerations that complicate its clinical use. It seems reasonable to hypothesize that there is no true cut-off point for SUV (below which the pN2 risk drops almost to zero and above which the pN2 risk raises >10%), but rather a transition zone where the pN2 risk gradually increases. In addition, several studies have shown that squamous cell carcinoma generally generate higher FDG uptake compared to adenocarcinoma, and that SUV values were found to be positively correlated with tumor size. Ultimately, clinical tumor size is probably the most relevant predictive parameter to consider. Koike *et al.* reported a 3.9% *vs.* 10.6% risk for pN2 in ≤2 *vs.* 2.1–3.0 cm, respectively, in a cStage-IA patient cohort with a negative hilum and mediastinum mainly by CT only (2). Farjah *et al.* reported a 6.8% *vs.* 11.9% risk for pN2 in ≤2 *vs.* 2.1–3.0 cm, respectively, in a slightly different patient cohort with a negative mediastinum by PET-CT (1).

Given the overall low prevalence (<10%) of mediastinal nodal disease in the context of cStage-IA, we believe that a multicenter prospective study is still warranted to evaluate a prediction model for pN2 disease, but unless randomized

its potential impact on overall survival will remain unclear.

In conclusion, we agree with the authors that a preresectional lymphadenectomy (e.g., by VAMLA) is indicated in cStage-IA tumors in combination with VATS lobectomy to achieve a radical lymphadenectomy.

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Footnote

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

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