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

Cons: should a patient with stage IA non-small cell lung cancer undergo invasive mediastinal staging?

Herbert Decaluwé[1,2], Christophe Dooms[3]

[1]Department of Thoracic Surgery, University Hospitals KU Leuven, Leuven, Belgium; [2]Department of Clinical and Experimental Medicine KU Leuven, Leuven, Belgium; [3]Department of Respiratory Diseases, University Hospitals KU Leuven, Leuven, Belgium
Correspondence to: Christophe Dooms, MD, PhD. Department of Respiratory Diseases, University Hospitals KU Leuven, Herestraat 49, 3000 Leuven, Belgium. Email: Christophe.dooms@uzleuven.be.

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Rationale for mediastinal nodal staging

In patients with (suspected) NSCLC and absence of metastases, current treatment guidelines are at large based on the extent of intrathoracic nodal disease. The rationale for preoperative invasive mediastinal nodal staging is to identify with the highest certainty and the lowest morbidity those patients with mediastinal nodal disease, as upfront surgery is not indicated in patients with mediastinal nodal disease (1).

More accurate staging in clinical stage IA NSCLC can lead to better survival outcomes, only if the information obtained leads to a change in treatment that can lead to better survival outcomes, and if the change in treatment occurs frequently enough. Randomized controlled trials in stage IA NSCLC did demonstrate that 5-year overall survival is similar when induction therapy followed by resection for cStage-IA was compared to resection followed by adjuvant chemotherapy for pStage-IA (2,3) .

To find the number of invasive staging procedures needed to be performed to save one extra live at 5 years, one can simulate the number needed to undergo invasive staging to find one additional patient with mediastinal disease, in combination with the 5-year survival benefit of avoiding upfront surgery (in patients identified to have found mediastinal disease) *vs*. surgery with adjuvant treatment (in patients with unsuspected N2 disease). The number needed to undergo invasive staging to detect an extra patient with mediastinal disease is calculated from, first, the prevalence of unsuspected N2 disease in cStage-I NSCLC after PET-CT imaging and second, the sensitivity of invasive mediastinal staging.

Prevalence of unsuspected mediastinal nodal disease in PET-CT clinical stage IA NSCLC (TNM 7)

If the 2014 ESTS guidelines for preoperative mediastinal nodal staging are followed rigorously, the rate of unsuspected N2 disease at surgery is as low as 5.5% with a negative predictive value of 0.91 (4).

According to these 2014 ESTS guidelines, preoperative invasive mediastinal nodal staging of (suspected) NSCLC can be discarded if all following three criteria apply: primary tumor located in the outer third of the lung AND primary tumor with largest diameter measured ≤3 cm, AND absence of intrathoracic lymph node(s) on CT and PET (1). The rationale is that in this situation the pretest probability having mediastinal nodal disease is <10%. Indeed, the rate of unsuspected pathologic mediastinal nodal disease

varied from 2.9% to 7.6% (5-7). Interestingly, Call *et al.* recently reported from a prospective database that for any cT1a-bN0 (TNM7) the rate of unsuspected pathologic mediastinal nodal disease was only 6.4%, confirming what was reported in the meta-analysis by Wang *et al.* for any cT1N0 (TNM6) (8,9). This low rate of N2 disease supports that invasive preoperative evaluation of the mediastinal lymph nodes is not required in clinical stage IA based on PET-CT. In Obiols *et al.*, 134 patients underwent direct surgical resection with systematic nodal dissection based on recommendations of the ESTS guidelines (4). Unsuspected pathologic mediastinal nodal disease was found in 7.5%, in whom single-station pN2 occurred in 80% and none had extracapsular invasion. Five-year survival rates were 86% in the absence of mediastinal nodal disease, while 41% in the presence of mediastinal nodal disease.

Sensitivity of invasive mediastinal staging

Currently, minimally invasive endoscopic techniques (EBUS-TBNA and EUS-FNA) and cervical mediastinoscopy are considered as preoperative staging algorithms (1). Two recent studies reported a sensitivity of 35% and 41%, respectively, for EBUS-TBNA to detect mediastinal nodal disease in patients with clinical N0 disease by PET-CT (10,11). The sensitivity and negative predictive value of mediastinoscopy is investigator dependent and accounts for the reported heterogeneity of 0.32 to 0.97 and 0.8 to 0.99 respectively (8). The sensitivity of cervical mediastinoscopy to detect pN2 was 45% in a large retrospective series on 291 patients with clinical stage I NSCLC on CT scan (12). More recently, a large cohort study on 577 patients with clinical stage cT1-2N0M0 based on PET scan found pN2 in 8.3% of patients, of whom a small subgroup (9.5%) underwent an invasive preoperative mediastinal staging by mediastinoscopy (13). Its overall sensitivity was 50% (95% CI, 26–74%). Similarly, Fernandez *et al.* evaluated the utility of mediastinoscopy in clinical stage I lung cancer after PET-CT. The prevalence of occult mediastinal nodal disease was low at 5.6%, and the sensitivity of mediastinoscopy to detect occult mediastinal nodal disease was only 25% (14).

The routine use of a preoperative EBUS-TBNA or cervical mediastinoscopy for systematic mediastinal nodal sampling in clinical stage IA NSCLC has a poor sensitivity to detect mediastinal nodal disease, and does not greatly increase the NPV of a PET-CT. Whether or not invasive preoperative mediastinal staging is pursued, a thorough mediastinal and hilar lymphadenectomy at the time of lung cancer resection is essential. Instead of a preoperative mediastinal nodal sampling technique (EBUS-TBNA or mediastinoscopy), a video-assisted mediastinoscopic lymphadenectomy (VAMLA) could be offered at the time of lung cancer resection. VAMLA is a mediastinal lymphadenectomy technique performed through the cervical incision and video mediastinoscope used for mediastinoscopy. A prospective single center experience reported a sensitivity of VAMLA of 88% to detect mediastinal nodal disease in 97 patients with clinical N0 disease by PET-CT and occult mediastinal nodal disease rate of 16.5% (8). The pN2 rate of 16.5% suggests that not only cStage-IA but also cStage-IB and cStage-IIA tumors were included.

What is the number needed to treat (NNT)?

With a presumed sensitivity of 50% for mediastinoscopy and a prevalence of 7% unsuspected mediastinal nodal disease in cT1a-bN0 NSCLC after PET-CT, one must perform 29 invasive staging procedures to find 1 positive patient. The reported 5-year survival of PET-CT staged patients with unsuspected N2 disease at the time of resection is 35–40% (4,15). Again, up to 80% of patients with unsuspected N2-disease have single station N2 disease (4). In comparison, the 5-year survival rate of neo-adjuvant therapy followed by surgical resection for single station N2 disease at baseline mediastinoscopy can reach a similar 35–40% (16,17).

Supposing that the survival benefit of invasive mediastinal staging followed by neo-adjuvant treatment instead of upfront surgery with adjuvant treatment is between 1% and 5% at 5 years, one would need to treat between 20 and 100 patients with neo-adjuvant treatment to save one life at 5 years. In combination with the 29 invasive staging procedures needed to detect one extra patient with mediastinal disease, the projected NNT of combined invasive mediastinal staging and multimodal treatment is between 580 and 2,900 patients. Based on this modeling, it is unlikely that a preoperative invasive systematic mediastinal nodal sampling for cStage-IA achieves high enough value. Instead, an intervention starting with a mediastinal lymph node dissection (e.g., VAMLA) at the time of resection is most valuable.

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Footnote

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

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