Endosonographic Staging for N1 Disease

To the Editor:
I congratulate Dooms et al1 on their important study recently published in CHEST (January 2015) that investigated the role of endosonography for mediastinal nodal staging in patients with operable and resectable lung cancer and suspicion of N1 involvement based on CT and PET imaging. To my surprise, the sensitivity of endosonography to detect N2 disease was only 38%, with a negative predictive value of 81%. First, the data show that the sensitivity of endosonography in subcentimeter fluorodeoxyglucose-PET nonavid nodes is inferior in comparison with the sensitivity of enlarged and/or fluorodeoxyglucose-PET avid nodes (94%). Second, of key interest are the 14 patients whose conditions were staged as false-negative. In only one of these patients, endobronchial ultrasound (EBUS) was followed by endoscopic ultrasound (EUS) or EUS performed with the EBUS scope (EUS-B). Importantly, in eight of the 14 patients, the missed metastases (located in stations 4L, 7, and 8) were located well within reach of EUS-B, and in two more patients, nodes in station 5 could have theoretically been reached.

For adequate EBUS-guided sampling of small nodes (in this study only 6.9 mm), thin and flexible 25G needles can be helpful. Furthermore, besides the actual endosonographic nodal detection, subcentimeter nodal sampling of stations 4L (paratracheal left) and 7 (subcarinal) often is far easier to perform by a transesophageal (EUS-B) approach compared with a transbronchial (EBUS) approach.1 This specifically applies to a setting using conscious sedation (94% in this study) where cough regularly compromises adequate nodal aspiration.

In the Assessment of Surgical Staging vs Endoscopic Ultrasound in Lung Cancer: a Randomized Clinical Trial (ASTER Study), the landmark trial comparing endosonography with surgical staging,1 combined EBUS + EUS staging (sensitivity of 85%) was performed instead of staging by EBUS only. In a meta-analysis, combined EBUS + EUS-B staging proved to be superior over staging by EBUS alone.5 I do not agree with the conclusion of Dooms et al1 that endosonography is an unsatisfactory test to detect mediastinal nodal metastases in cN1 lung cancer; in my opinion, EBUS alone is. My interpretation of the study findings is that in cN1 disease, especially in patients with an adenocarcinoma, EBUS should be followed routinely by EUS-B. This scenario should be investigated, as should the added value of a confirmatory mediastinoscopy in that specific setting.

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References

Response

To the Editor:
We thank Dr Annema for his thoughtful commentary on our recent article in CHEST1 on the Assessment of Surgical Mediastinal Staging Added to Endoscopic Ultrasound in cN1 Lung Cancer (ASTER2) study. In fact, it highlights an important reflection on the potential added role of transesophageal endoscopic ultrasound (EUS) in addition to endobronchial ultrasound (EBUS) in the staging process of patients with lung cancer. Should
invasive mediastinal nodal staging by EUS or EUS performed with the EBUS scope (EUS-B) be considered as "selected complementary to EBUS" or as "systematic combined with EBUS?"

A combined EBUS-EUS staging was proposed initially to adhere to a complete invasive mediastinal nodal mapping of stations 4R, 4L, and 7, at least. Several studies included in the meta-analysis by Zhang et al\(^2\) on combined endosonography considered the second endoscopic modality for mediastinal nodes that were inaccessible or difficult to access by the first endoscopic modality. In recent years, it has become clear that standard mediastinal nodal mapping (at least of stations 4R, 4L, and 7) is actually feasible with EBUS alone. As a consequence, an additional EUS or EUS-B is considered of added value in those patients with nodes inaccessible for EBUS. The argument of Dr Annema that EUS-B makes the sampling of 7 and 4L easier is acknowledged. However, there are no data showing that EUS-B is actually better than EBUS. An EBUS procedure is now the standard in most centers, and the systematic addition of EUS is not (yet) widely implemented.

Taking this into account, as well as the fact that for cN1 lung cancer a lobe-specific mediastinal examination is sufficient, the rationale for using EUS or EUS-B as a selected complementary test was clear when designing ASTER2. EBUS with transbronchial needle aspiration alone was performed in 75% of patients, whereas a combined procedure was carried out in 25%. We acknowledge the observation that in eight out of 14 patients with false-negative endosonography, the missed metastases were located in stations 4L, 7, or 8. These are reachable for EUS or EUS-B. However, in six of these (75%), the cytologic samples obtained by EBUS with transbronchial needle aspiration were representative for lymphoid tissue. That 25G needles, or a systematic EUS or EUS-B would have made the difference is possible (as discussed), but it remains to be shown for these particular cN1 patients.

Our conclusion, therefore, remains: Staging cN1 lung cancer with endosonography (either EBUS or EBUS with EUS-B in selected cases) has a low sensitivity. Whether EBUS with the systematic adding of EUS or EUS-B is effectively better in cN1 remains an open question.

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