ASTER – another flower in the diagnostic field of lung cancer?

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Mediastinal staging of patients with lung cancer is used to avoid futile thoracotomies. Endoscopic, oesophageal and bronchial ultrasound procedures are methods to identify involved lymph nodes. The ASTER study indicates that the sensitivity of these new techniques is high, reducing the number of futile thoracotomies and improving outcomes when combined with mediastinoscopy.

Lung cancer has a very high incidence and is the most lethal cancer type worldwide, accounting for 12.7% of the total cancers diagnosed.[1] Patients presenting with localised tumours that can be resected completely tend to achieve the best outcomes after treatment; therefore, staging of the mediastinum is of great importance. Cervical mediastinoscopy is the standard procedure to investigate the mediastinum. Under general anaesthesiology a small incision is made in the collar just above the manubrium. A videoscope is introduced and proceeds along the trachea. Lymph nodes in front or on both sides of the trachea can be visualised and sampled (paratracheal, ventral and subcarinal lymph nodes) for histological examination.

Annema et al.[2] compare the use of standard mediastinoscopy with a combination of endobronchial ultrasound (EBUS) and endoesophageal ultrasound (EUS) for mediastinal nodal staging of lung cancer; if no cancer was detected in the experimental arm, mediastinoscopy was performed. EUS and EBUS have a clear advantage over mediastinoscopy in that they provide improved coverage of the mediastinal lymph node stations (see figure).[3] Theoretically, the combination of EUS and EBUS should lead to better staging and reduction of the number of futile thoracotomies; the ASTER study examined this theory. A direct comparison of EUS and/or EBUS versus mediastinoscopy was not performed because the current guidelines indicate that mediastinoscopy is the standard of care.[4] Therefore, Annema et al.[2] included this analysis in the experimental arm to determine the additional value of the combination.

The results were as expected; the experimental arm produced better results than mediastinoscopy alone and outcomes were substantially improved when endosonography (EBUS and EUS) and mediastinoscopy were combined. With the exception of ipsilateral or contralateral disease detection, direct invasion of the tumour can be visualised more easily with endosonography than with CT or PET imaging or mediastinoscopy. Positive mediastinal lymph node samples were recorded in 41 of 118 patients in the

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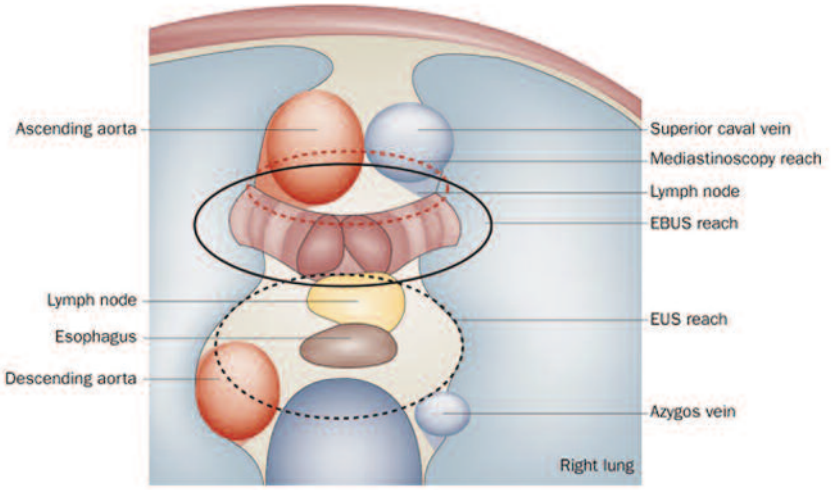
control arm and in 56 of 123 patients who underwent endosonography alone. The addition of mediastinoscopy to the experimental arm revealed an additional six lymph node metastases that had previously been missed by endosonography. The number of unnecessary thoracoscopies prevented was 21 (18%) in the experimental group compared with nine (7%) in the control arm.

The ASTER study is the first randomised trial that presents data on the sensitivity and negative predictive value of both arms. The study has many strong features; it is an investigator-initiated, multicentre, prospective study conducted in experienced centres and data are presented on an intent-to-treat basis. Features of this study have similarities to the implementation of the PET scan in the staging of lung cancer. The use of PET scanning has reduced the number of futile thoracotomies by 50%[5] and has become part of the accepted guidelines in the Western world.

Nonetheless, a number of criticisms can be made about the study by Annema et al.[2] Learning to use EBUS requires extensive training and keeping expertise at a high level requires a minimum number of cases per operator per year. Thus, identification of specific referral centres will be of importance. Coughing, patient distress and hypoxia can hamper the endobronchial procedure, leading to incomplete endobronchial or oesophageal examination. Proper patient selection for the use of midazolam or propofol anaesthesia can reduce these problems. One of the advantages of the endosonography procedure is that many institutes will use rapid on-site examination (ROSE), informing the bronchoscopist during the procedure whether or not more punctures are required. In the ASTER study, ROSE was used only in the experimental arm.[1] The limited amount of cytological material obtained by punctures is of concern when endosonography alone is performed in patients who present with positive mediastinal lymph nodes. Histology samples are preferred to test for molecular biomarkers such as *EGFR*-activating mutations, *EML4-ALK* translocations or *KRAS* mutations. This list of potential biomarkers is growing and requires a minimum amount of histological material. The cytological material obtained by punctures is, at the moment, insufficient and might increase the number of false-negative results.

The conclusion of this new approach is simple: endosonography using a combination of EBUS and EUS is here to stay and will allow a quick selection of patients suitable for major surgical interventions in lung cancer. Mortality is near zero, as is morbidity. Mediastinal bleedings are extremely infrequent and persistent hoarseness due to lesions of the recurrent laryngeal nerve has not been reported. Does this information mean that mediastinoscopy is now in its preterminal stage? Not yet. There will always be an indication for this procedure, such as the need for histological material, or in case of restaging after induction therapy when endosonography has failed to identify previously involved lymph nodes.[6,7] As applicable to surgical procedures, quality assurance, training and maintenance of expertise remain of great importance.



Transversal view of the chest at the level of the main carina. The red dotted line indicates the field approachable by mediastinoscopy; the black unbroken line for endobronchial ultrasound and the dotted black line for the endoesophageal ultrasound

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

The combination of endoesophageal ultrasound and endobronchial ultrasound offer the physician a new and less-invasive method to stage and restage the mediastinum. Its reach is superior to that of the mediastinoscopy and future developments in molecular genetics will allow the required analysis of specimens for molecular markers.

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