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Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer

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Journal club

Commentary on:

Decaluwé H, *et al*. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study. *Eur Respir J* 2017; 50: 1701493.

Lung cancer is the number one cause of death due to cancer worldwide. According to the World Health Organization, it accounted for 1.69 million new cases in 2015, whereas in Europe, 20.8% of all deaths due to cancer (>266000 cases) were attributable to lung cancer in 2011 [1, 2].

Accurate lung cancer staging is fundamental to plan optimum individualised therapy. Extensive mediastinal staging is recommended before surgical resection for patients with non-small cell lung cancer (NSCLC) and clinical/radiological stage I or II disease [3]. Previous guidelines published by European Society of Gastrointestinal Endoscopy in cooperation with the European Respiratory Society and the European Society of Thoracic Surgeons recommend that endosonography should be performed over surgical staging as the initial procedure for mediastinal nodal staging in patients with suspected or proven NSCLC and abnormal mediastinal and/or hilar nodes at computed tomography (CT) and/or fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT, (recommendation grade A) [4]. However, recent studies report relatively low sensitivity for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) to detect mediastinal disease in clinical N0 PET-CT, while others report a significant risk of mediastinal nodal involvement in patients classified as clinical N1 by PET-CT [5–10].

This article reports the findings of a prospective clinical trial by Decaluwé *et al*. [11]. Investigators attempted to evaluate preoperatively the sensitivity of video-assisted mediastinoscopy (VAM) or VAM–lymphadenectomy (VAM(LA)) in mediastinal staging of operable and resectable suspected NSCLC and clinical N1 disease (cN1).

Conventional mediastinoscopy has been considered the gold-standard method for preoperative mediastinal staging in NSCLC patients. Its sensitivity depends on the number of lymph nodes and the amount of lymph node tissue resected; this results in false-negative rates that have been reported to be as high as 10% [12]. VAM(LA) is a minimally invasive technique of systematic mediastinal lymph node dissection. Optic fibres

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are integrated to conventional mediastinoscopes, and further modifications are made in the mediastinoscope's working channel allowing bimanual surgery, optimum visualisation and access to lymph nodes. The technique was developed in an attempt to achieve maximum accuracy and radical lymph node excision in a minimally invasive manner, thus reducing the high false-positive rates of conventional mediastinoscopy. In VAM, lymph nodes of different stations are assessed and sampled, but not necessarily removed completely, as during VAM(LA) [13, 14].

Patients, methods, study design and end-points

For this prospective non-randomised multicentre clinical trial, inclusion criteria were age ≥18 years, operable suspected NSCLC and cN1 disease based on FDG-PET-CT. cN1 disease was defined as enlarged lymph nodes (⩾10 mm on the largest short axis on CT) or a FDG-PET-positive lymph node in an N1 position, as described in the International Association for the Study of Lung Cancer lymph node map [15]. FDG-PET-CT lymph node positivity was defined as FDG uptake higher than background uptake in the mediastinal blood pool. Conversely, patients with unresectable neoplasia, known medical history of cancer with previous treatment, cT3 or cT4 disease based on TNM classification or previous endobronchial ultrasound of mediastinal lymph nodes were excluded from the study.

Sensitivity in detecting mediastinal nodal involvement (N2 disease) by VAM(LA) was the primary end-point. Sensitivity was defined as the proportion of patients with positive mediastinal staging by VAM(LA) out of all patients with mediastinal nodal disease. Secondary endpoints were negative predictive value (NPV), accuracy, negative post-test probability and assessment of the prevalence of N2/3 disease.

Results

105 patients were enrolled and VAM(LA) was positive in 20 of these: 13 with single-level N2 disease, four with multilevel N2 and three with N3 disease. The median number of biopsied lymph node stations was four. The most frequently biopsied node stations were 4R, 7 and 4L: 98% (103 patients), 95% (100 patients) and 91% (96 patients), respectively. Adverse events related to VAM were reported in four (4%) patients: one case of bleeding, one case of uncomplicated wound infection and two cases of transient recurrent nerve paralysis.

Out of the 83 who ultimately underwent surgery, having no N2/N3 disease during preoperative VAM(LA), seven were found to have positive mediastinal lymph node disease at resection; two of them had multilevel N2 disease and five had single-level N2 disease.

The prevalence of mediastinal lymph node metastases was 0.26 (95% CI 0.18–0.35) overall, sensitivity of VAM(LA) was 0.73 (95% CI 0.54–0.86), its accuracy was 0.93 (95% CI 0.86–0.97), NPV was 0.92 (95% CI 0.83–0.97) and negative post-test probability was 0.08 (95% CI 0.03–0.17).

Discussion

The main findings of this prospective study on mediastinal staging in patients with cN1 disease were that approximately a quarter of patients with cN1 lung cancer proved to have N2 disease and that sensitivity of VAM(LA) to detect positive mediastinal nodes in these patients was 73%.

As mentioned, accurate staging is a key part of treatment planning for lung cancer patients and mediastinal staging is currently recommended before surgical resection of early-stage NSCLC. However, current guidelines leave open the choice between endosonographic and surgical preoperative mediastinal staging. This is the main question investigators of this study attempted to answer.

Endosonography's (EBUS-TBNA) sensitivity to detect nodal disease in the setting of operable cN1 NSCLC has been evaluated in previous studies and has been found to be moderate, with values ranging from 0.38 to 0.53 [9, 16, 17]. In a recent paper on lung cancer staging in the *European Respiratory Journal*, Rami-Porta *et al*. [10] suggest that in early-stage, operable NSCLC, EBUS-TBNA should not be of routine use and that mediastinoscopy may be the preferred method to preoperative mediastinal staging.

In this study by Decaluwé *et al*. [11], VAM(LA)'s sensitivity was estimated to be 73%, thus providing further evidence to support that this may represent the examination of choice for the pre-resection mediastinal nodal-staging.

The study's limitations include a smaller amount of enrolled patients (105 instead of the initial goal of 205) possibly because of increasing numbers of referrals for endosonography staging, which was an exclusion criterion. The smaller number of patients resulted in increased range of the 95% confidence intervals for the diagnostic indices. The investigators also stress that only in 31% (n=33) of patients, the mediastinoscopy was VAM(LA) and that in four patients, the false-negative station that was partially sampled during VAM would have been positive if the station had been removed completely. Moreover, the study was performed by institutions with well-established thoracic surgery departments that were willing to participate in a prospective study on surgical staging. Therefore, the results may be different than in daily clinical practice in institutions where endosonography is embedded in the diagnostic referral process and that may lack well established thoracic surgery departments. VAM(LA) in particular, a surgical procedure that performed excellently in this study, is only performed in certain thoracic centres with relevant expertise.

In conclusion, this study provides evidence that VAM(LA) has adequate sensitivity to be considered as the approach of choice for preoperative mediastinal staging in the subgroup of early-stage operable NSCLC patients. However, it is a special technique, performed only in tertiary thoracic surgery centres; therefore, future studies are needed to establish it widely in daily clinical practice.

Conflict of interest

None declared.

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