Factors predict the adequacy of cervical mediastinoscopy in nonsmall cell lung carcinoma lymph node staging and comparison computed tomography and integrated positron emission tomography

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Received: 28 May 2023
Revised: 29 July 2022
Accepted: 7 August 2023
Published: 6 October 2023

The Egyptian Journal of Surgery 2023, 42:610–617

Background
Standard cervical mediastinoscopy (SCM) has traditionally been considered the reference standard for grading mediastinal involvement in lung cancer. The objective of this research is to evaluate the impact of surgeon experience and patient-related restrictions on the adequacy of mediastinal lymph node (LN) sampling. Additionally, we aim to assess the effectiveness of PET/computed tomography (CT) in comparison to ECM (extended cervical mediastinoscopy), particularly in identifying metastases in the aortopulmonary window (APW) LN.
Methods
This prospective cohort study involved sixty individuals diagnosed with nonsmall cell lung cancer (NSCLC). The participants underwent fine needle transthoracic aspiration biopsy or bronchoscopy and subsequently had ECM performed. All participants underwent various diagnostic procedures, including thoracic CT, posteroanterior chest radiograph, pulmonary function tests, PET/CT, electrocardiography, cranial magnetic resonance imaging, and laboratory investigations.
Results
In terms of our outcomes, we evaluated the specificity, positive predictive value (PPV), sensitivity, negative predictive value (NPV), and accuracy of ECM. The results for ECM were as follows specificity of 100.0%, PPV of 100.0%, sensitivity of 78.3%, NPV of 88.1%, and accuracy of 91.7%. For PET/CT, the results were: a specificity of 90.5%, PPV of 75.0%, sensitivity of 57.1%, NPV of 80.9%, and accuracy of 78.3%.
Conclusion
The ECM procedure is highly beneficial in identifying APW LN metastasis in individuals diagnosed with nonsmall cell lung cancer. It exhibits a favorable NPV and efficiency. Moreover, it can be easily performed by a team with the necessary experience.

Keywords:
cervical mediastinoscopy, computed tomography, integrated positron emission tomography, nonsmall cell lung cancer, staging

Egyptian J Surgery 42:610–617

1110-1121

The actual work was done at King Fahad Armed Hospital, Jeddah.

Authors' Contributors: All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Introduction

Nonsmall cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all cases. Accurate grading of lymph node (LN) involvement plays a critical role in determining the prognosis and treatment strategy for patients with NSCLC [1]. Cervical mediastinoscopy has long been recognized as a reliable technique for obtaining mediastinal LN samples and assessing their involvement in cancer metastasis. However, the adequacy of LN sampling through cervical mediastinoscopy can be influenced by various factors, involving the surgeon's experience and patient-related restrictions [2].

Extended cervical mediastinoscopy (ECM) is a useful and safe technique that allows determining mediastinal

nodal disease or direct tumor involvement of the subaortic and para-aortic spaces with high accuracy and high negative predictive value, especially when it is performed selectively according to the results of computed tomography (CT) and PET. Although its main indication is the staging of bronchogenic carcinoma of the left lung, this procedure is also a good alternative for undiagnosed anterior mediastinal tumors or lymph nodes that have not been diagnosed by other minimally invasive methods [3].

Surgeon experience plays a pivotal role in performing cervical mediastinoscopy and obtaining accurate LN samples. Experienced surgeons are likely to possess advanced skills in identifying and sampling lymph nodes, resulting in a higher likelihood of adequate staging [2]. However, the influence of surgeon experience on LN sampling adequacy remains a subject of investigation, and understanding its impact is crucial for enhancing diagnostic accuracy [4].

In addition to surgeon experience, patient-related factors can also affect LN sampling adequacy during cervical mediastinoscopy. Various restrictions such as obesity, previous thoracic surgeries, and anatomical variations may pose challenges in obtaining representative LN samples. Assessing the impact of these patient-associated restrictions on LN staging adequacy can provide valuable insights into the limitations and potential areas of improvement for cervical mediastinoscopy.

Moreover, the effectiveness of PET/CT in identifying LN metastases, particularly in the APW region, is of significant interest. PET/CT has appeared as a noninvasive scanning method that combines functional and anatomical information, potentially enhancing LN grading accuracy [5]. Comparing PET/CT effectiveness with cervical mediastinoscopy can shed light on the diagnostic performance of these two modalities, particularly in detecting APW LN metastases [6].

Therefore, this study aimed to evaluate the mediastinal LN sampling adequacy by evaluating the surgeon's experience impact, and patient related restrictions (PRR) on the LN sampling adequacy. In addition, evaluate the effectiveness of PET/CT and ECM in identifying APW LN metastases.

Materials and methods

This prospective cohort study was conducted on 60 patients aged 18 years or older, of both sexes, diagnosed with NSCLC. The participants underwent transthoracic fine needle aspiration biopsy or bronchoscopy and were considered eligible for surgery based on the results of physical examinations. They were admitted for invasive mediastinal grading between January 2017 and January 2022.

Written consent was obtained from the patients or their families, and the research was conducted with the approval of the King Fahad Armed Hospital, Jeddah.

We included 60 patients who underwent ECM and met the following criteria: a centrally located tumor in the hemithorax adjacent to the mediastinal area, an APW lymph node larger than 1 cm in diameter (at the smallest measurement), and positive evaluation of APW and/or hilar lymph nodes by PET/CT.

All patients underwent a comprehensive evaluation that included the following: gathering detailed medical history, including age, sex, smoking history, and presence of comorbidities; conducting clinical examinations; performing thoracic CT scans; obtaining posteroanterior chest radiographs; conducting PET/CT scans; conducting electrocardiography (including stress testing and angiography, if necessary); conducting pulmonary function tests; conducting cranial MRI scans; and performing laboratory investigations as complete blood count (CBC).

Radiologic imaging and PET/CT evaluation

PET/CT scans were performed on all individuals using a high-resolution PET/CT scanner integrated with a multidetector CT at three different centers (Siemens Biograph LSO HI-REZ PET/CT scanner, Chicago, IL). Prior to the surgery, patients fasted for a minimum of 4 h and ensured proper hydration, with their blood glucose levels assessed. Once it was confirmed that the patient's blood glucose level was below 150 mg/dl, an intravenous injection of 370 to 555 MBq of 18F-fluorodeoxyglucose (FDG) was administered. Following a period of 1 to 1.5 h of relaxation in a comfortable environment, the patients underwent whole-body PET scanning. Mediastinal lymph nodes (LNs) with FDG uptake higher than the normal background activity of the mediastinal blood pool (approximately SUVmax 2–2.5) were considered suspicious for malignancy and documented according to their respective stations on the PET/CT images.

Surgical technique

ECM was performed on all patients using the same cervical incision that was used for standard cervical

mediastinoscopy (SCM) within a maximum of 30 days (mean duration: 19.0±4.0 days) after PET/CT scanning. During the procedure, SCM was utilized to access the peritracheal and paratracheal regions, enabling examination and removal of upper paratracheal lymph nodes (station 2), lower paratracheal lymph nodes (station 4), as well as investigation and harvesting of the carina and subcarinal lymph nodes. As explained by Ginsberg and colleagues [7], the procedure involved utilizing the standard cervical mediastinoscopy (SCM) incision. Index finger dissection was performed between the left carotid artery and the innominate artery over the aortic arch. The fascia was incised, creating a pathway beneath the innominate vein that traversed the aortic arch and led to the innominate triangle. Subsequently, the mediastinoscope was inserted through the same incision and directed towards the left sternoclavicular joint, utilizing the tunnel formed by the finger dissection.

Aortopulmonary window (APW) lymph nodes (LNs) were sampled and examined. Following the surgery, all patients underwent a posteroanterior chest radiograph. Assessment of any complications such as surgical wound infection, hoarseness, pneumothorax, or other complications arising from the mediastinoscopy procedure was done. Any observed issues were duly documented.

Surgical experience level

The surgical experience level was determined based on the number of cervical mediastinoscopies performed by each surgeon. During the study period, experienced surgeons were defined as those who had conducted a minimum of 25 mediastinoscopies.

Follow-up

One month of follow-up data was collected through direct outpatient visits or telephone interviews conducted with the patient and/or referring physician.

Sample size calculation

The sample size calculation was estimated by G*Power 3.1.9.2 (Universität Kiel, Germany) that the sample size was dependent on the following considerations: the sensitivity of PET/CT ranged from 53% to 88% [8,9], 95% confidence limit, 80% power of the study, and 8 cases were added to overcome dropout. Therefore, we included 60 patients in our study.

Statistical analysis

Statistical analysis was conducted using SPSS v26 (IBM Inc., Armonk, NY, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Quantitative variables were reported as mean and standard deviation (SD). Qualitative variables were presented as frequencies and percentages (%). Diagnostic performance was evaluated using measures such as specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV).

Results

The study included a total of 60 patients, with a mean age of 59.2±11.96 years. Out of these patients, 45 (75%) were males and 15 (25%) were females. The average BMI of the participants was 27.2±1.71 kg/m^2. Among the enrolled patients, 21 (35%) had hypertension, 17 (28.3%) had diabetes mellitus, and 20 (33.3%) were smokers Table 1.

Histopathologic tumor types were as follows: squamous cell carcinoma (SCC) in 23 (38.33%) patients, adenocarcinoma in 16 (26.67%) individuals, large cell carcinoma in 8 (13.33%) individuals, adenosquamous carcinoma in 7 (11.67%) individuals, and unclassified NSCLC in 6 (10%) individuals. The clinical N-status was N0-1 in 34 (56.67%) patients and N2 in 26 (43.33%) individuals. The tumor location was predominantly in the left upper lobe in 35 (58.33%) patients, while 25 (41.67%) patients had centrally located tumors Table 2.

The average number of samples per patient was 4.1 ±0.85. Patient-related restrictions were observed in a small number of cases, including adhesions in 3 (5%) patients, bleeding that impaired visibility in 1 (1.67%) patient, tumor growth into the mediastinum preventing access to all stations in 1 (1.67%) patient, and accurate biopsy of a highly suspicious node without further biopsies taken in 1 (1.67%) patient. The overall

Table 1 Patient characteristics and comorbidities of the studied patients

	N=60
Age (years)	59.2±11.96
Sex	
Male	45 (75%)
Female	15 (25%)
BMI (kg/m^2)	27.2±1.71
HTN	21 (35%)
DM	17 (28.3%)
Smoking	20 (33.3%)

Data are presented as mean±SD or frequency (%). BMI, Body mass index; DM, diabetes mellitus; HTN, hypertension.

adequacy of sampling, including both overall and patient-related restrictions, was 63.3% Table 3.

In 51.67% of patients who underwent thorax CT, pathologically enlarged aortopulmonary window (APW) lymph nodes were observed. Among these individuals, 19 had negative PET scan results for APW lymph nodes, while 12 had positive PET scan results for APW lymph nodes. In the remaining 29 (48.33%) individuals, no swollen APW lymph nodes were detected on CT. However, 6 (20.68%) of these individuals had positive PET scan results for APW lymph nodes.

PET/CT imaging indicated APW LN involvement in 16 (26.67%) patients, regardless of tumor size. Among the 16 individuals with APW LN involvement as diagnosed by PET/CT, 12 were confirmed to have metastatic disease through ECM or thoracotomy (true positive PET, *n*=12/16). ECM was performed in nine cases, while thoracotomy was performed in three patients, and both methods confirmed the presence of APW LN metastases.

Table 2 Preoperative data of the studied patients

	N=60
Histopathological tumor type	
Squamous cell carcinoma	23 (38.33%)
Adenocarcinoma	16 (26.67%)
Large cell carcinoma	8 (13.33%)
Adenosquamous carcinoma	7 (11.67%)
Unclassified NSCLC	6 (10%)
Clinical N-status	
N0-1	34 (56.67%)
N2	26 (43.33%)
Localization	
Left upper lobe	35 (58.33%)
Central	25 (41.67%)
Level of surgeon's experience	
Experienced	37 (61.67%)
Less experienced surgeon	23 (38.33%)

Data are presented as frequency (%). NSCLC, nonsmall cell lung carcinoma.

In four of the 16 patients who were reported by PET/CT to have APW LN involvement, ECM or thoracotomy did not reveal any APW LN metastases (false positive PET, *n*=4/16). PET/CT imaging showed that 44 (73.3% of patients) had negative APW LNs, regardless of LN size. Among the remaining 44 individuals, neither ECM nor thoracotomy detected APW LN metastases in 35 cases (PET true negative, *n*=35/44). However, ECM or thoracotomy identified APW LN metastasis in eight of these patients (PET false negative, *n*=8/44) Fig. 1.

ECT was able to detect all positive APW LN involvement in 20 (33.3%) individuals and could detect all negative cases, where 37 (61.7%) patients were true negative, and 5 (8.3%) patients were false negative Fig. 2.

Among the study participants, a total of 25 patients underwent thoracotomy due to the absence of mediastinal LN metastases. Among them, lobectomy was performed on 19 individuals, with 3 cases involving en bloc thoracic wall resection and 2 cases involving bronchial sleeve resection. Additionally, pneumonectomy was performed on 5 patients, including 2 cases with en bloc thoracic wall surgical resection and 1 case with intrapericardial vascular ligation. Furthermore, 6 individuals underwent exploratory thoracotomies. Among these 6 patients, 2 were deemed unresectable due to direct mediastinal infiltration that was inaccessible by ECM.

Regarding our outcomes, the specificity, PPV, sensitivity, NPV, and ECM accuracy were evaluated as 100.0%, 100.0%, 78.3%, 88.1%, and 91.7%, respectively. The specificity, PPV, sensitivity, NPV and PET/CT accuracy of were 90.5%, 75.0%, 57.1%, 80.9%, and 78.3%, respectively Table 4.

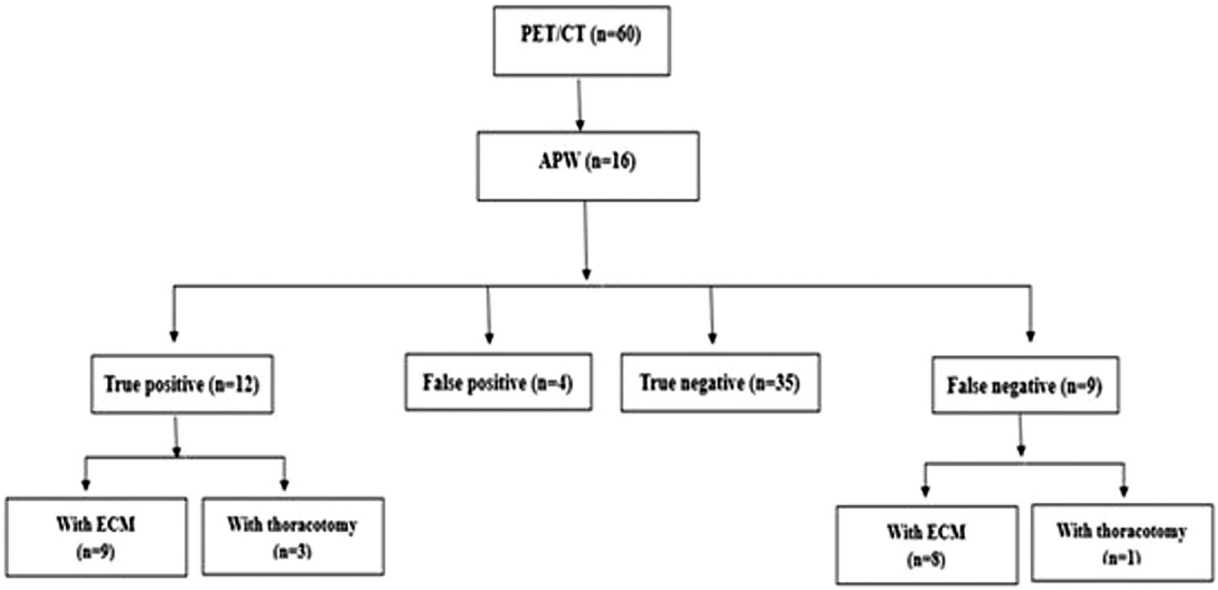
On univariate logistic regression analysis, experienced surgeon and PRR were significant predictors of lymph

Table 3 Intraoperative data of the studied patients

	N=60
Mean number of samples (per patient)	4.1±0.85
Patient-related restrictions	
Adhesions	3 (5%)
Bleeding, impairing sight	1 (1.67%)
Tumor growth into the mediastinum (inability to reach all stations)	1 (1.67%)
Adequate biopsy of very suspicious node (no further biopsies taken)	1 (1.67%)
Overall sample adequacy	38 (63.3%)
PRR sample adequacy	38 (63.3%)

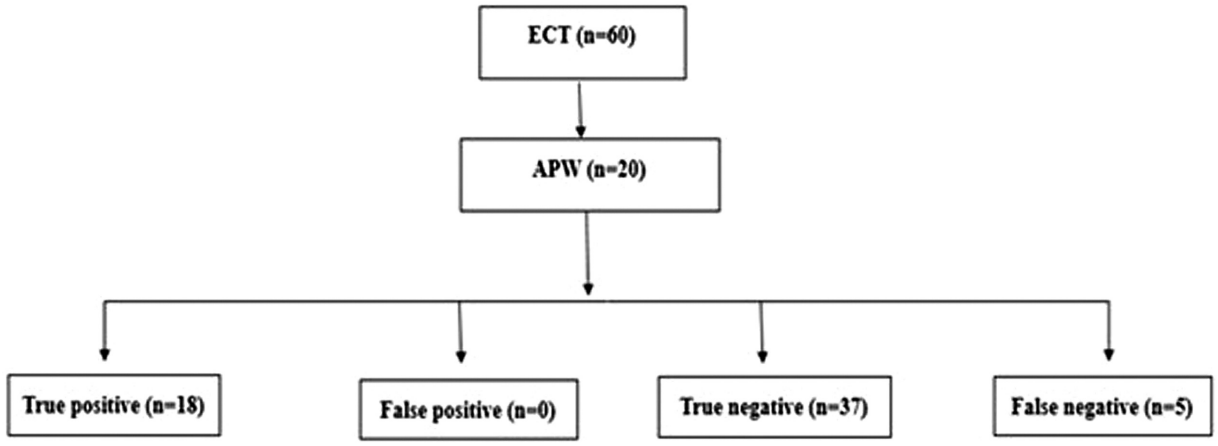
Data are presented as mean±SD or frequency (%). PRR, patient-related restrictions.

Figure 1



PET/CT results of the patients with or without lymph node metastasis accessed by ECM.

Figure 2



ECT results of the patients with or without lymph node metastasis.

node sampling adequacy (OR: 9.52, 95% CI: 2.78-32.61, $P < 0.001$, OR:0.150, 95% CI: 0.034-0.649, $P = 0.011$, respectively) whereas other variables age, female sex and SCC were insignificant predictors. Additionally, multivariate logistic regression analysis revealed that only level of surgeon's experience and PRR as significant predictors of lymph node sampling adequacy Table 5.

Table 4 Accuracy measures of extended cervical mediastinoscopy and positron emission tomography/computed tomography

	Sensitivity	Specificity	PPV	NPV	Accuracy
ECM (%)	78.3%	100.0%	100.0%	88.1%	91.7%
PET/CT (%)	57.1%	90.5%	75.0%	80.9%	78.3%

ECM, extended cervical mediastinoscopy; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value.

Discussion

This research reveals that both PRR and surgical experience are important and autonomous indicators of cervical mediastinoscopy appropriateness in NSCLC LN grading.

Our findings revealed that When performed by an experienced surgeon, appropriate LN sampling is more probable than when performed by a less experienced surgeon, and when PRR are absent, adequate LN sample is more likely than when PRR

Table 5 Univariate and multivariate logistic regression analysis for prediction of lymph node sampling adequacy

	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (years)	1.0219	0.98-1.07	0.348	—	—	—
Female sex	0.395	0.120-1.30	0.128	—	—	—
SCC	0.461	0.157-1.359	0.161	—	—	—
Experienced surgeon	9.52	2.78-32.61	<**0.001***	16.33	2.95-90.25	**0.014***
PRR	0.150	0.034-0.649	**0.011***	0.06	0.009- 0.442	**0.006***

CI, confidence interval; OR, odds ratio; PRR, patient related restrictions; SCC, Squamous cell carcinoma. *Statistically significant as *P* value less than 0.05.

are present. Previous research have also observed that mediastinoscopy yield heavily relies on LN position and operator skills [10–12].

Our study revealed that in multivariate analysis, PRR and surgical experience found to be independent NSCLC indicators.

In Klinkenberg and colleagues [2] study stated that experience level and PRR as autonomous determinants of adequate LN sampling. In this investigation, the most common PRR were adhesions, hemorrhage (impairing vision), and tumor development into the mediastinum (lack to reach all LN areas). Although there was no significant difference in PRR between less experienced and experienced surgeons, one could assume that a more experienced surgeon could overcome certain PRR more easily than a less experienced surgeon.

In two investigations, the utilization of an integrated FDG-PET/CT scan was described Steinert, Humbert and colleagues [13,14]. Due to the improved localization of localized FDG absorption in the mediastinum, the specificity rose dramatically to 93% and the false-negative rate reduced to 13% De Leyn and colleagues [15]. Early investigations shown that PET/CT is more accurate than CT and PET for noninvasive mediastinal grading. In spite of this, the usefulness of PET/CT in identifying mediastinal LN metastases in intrathoracic LN staging remains contradictory owing to the existence of varying outcomes Halpern and colleagues, Lee and colleagues [16,17].

According to one research involving 51 patients, individuals with negative PET/CT results for mediastinal LNs may have surgery without invasive mediastinal grading Boada and colleagues [18]. Despite the reduction in false-negative outcomes with advancements in PET technology, Lee and colleagues [17] demonstrated a considerable rise in false-positive findings, indicating that PET/CT should be used in conjunction with clinical grading and that surgical grading remains the gold standard in NSCLC.

To the best of our knowledge, there was a lack of studies that compare ECM with PET/CT for APW LNs assessment.

Although SCM, the most frequently utilized invasive diagnostic procedure for mediastinal grading, is still regarded as the gold standard for sampling superior mediastinal LNs, it is incapable of evaluating APW. Ginsberg and colleagues [7] suggested the assessment of APW by ECM in the late 1980s as an alternate approach for SCM combined with left anterior mediastinotomy (Chamberlain procedure) and for thoracoscopy. However, there are few studies investigating ECM Onat and colleagues, Leiro-Fernandez and Fernandez-Villar [19,20].

The sensitivity, specificity, PPV, NPV, and accuracy of ECM were determined to be 78.3%, 100%, 100%, 88.1%, and 91.7%, respectively, based on our findings. Nonetheless, the sensitivity measured in a series by Lopez and colleagues [21] and Freixinet and colleagues [22] was somewhat greater than those indicated by our research. This might be ascribed to the adoption of a modified ECM approach or CT evaluation of larger LNs in their chosen patient groups, allowing for easier LN identification using ECM.

Our results showed that sensitivity, specificity, PPV, NPV, and accuracy of PET/CT were 57.1%, 90.5%, 75.0%, 80.9%, and 78.3%, respectively.

In Metin, and colleagues [8] study, the sensitivity (53%), specificity (91 percent %), NPV (83%), PPV (70%), and accuracy (80%) of PET/CT were lower than those of ECM when evaluating APW LNs. The discovered PPV of PET/CT was compatible with the scientific literature Cerfolio and colleagues, Navani and colleagues [23,24]. In their investigation, total thoracic lymphadenectomy was conducted for both APW and

other mediastinal/hilar LNs, and the same pathologist conducted the histological evaluation on all individuals. Thereby, pN2 individuals with LNs that are too small to be detected by PET/CT could be defined. BilleÌ and colleagues [25] reported that station 5 was the second mediastinal LN station with the greatest PET/CT inaccuracy rate, and the sensitivity and NPV of PET/CT for APW LNs were predicted to be comparable with those in this research.

Conclusion

ECM is a valuable procedure that demonstrates high accuracy and NPV in identifying APW LN metastasis in individuals with NSCLC. It is a straightforward technique that can be easily performed by an experienced team. Considering the high incidence of APW LN metastases, ECM is recommended for individuals with upper lobe or central NSCLC and APW LNs larger than 1 cm, even in cases where PET/CT results are negative. PET/CT, on the other hand, showed limited sensitivity and NPV in detecting APW metastasis, and therefore, it does not reduce the need for invasive procedures targeting APW LNs.

Acknowledgements

There is none to be declared.

The manuscript has been read and approved by all the authors.

Declarations: Ethics approval and consent to participate: the study was approved by the institutional ethical committee. All participants included had signed a consent form.

Consent for publication: All authors give their consent for publication; they all have agreed to publish this work.

Availability for data and material: The data is available upon reasonable request from the authors.

Funding: None to be declared.

Financial support and sponsorship

Nil.

Conflicts of interest

Competing interests: The authors declare that they have no competing interests.

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