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Research Article

Mediastinal Diagnostics: Cervical Mediastinoscopy Vs. Transbronchial Needle Aspiration with Ultrasound Guidance. A Single Center Experience

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Abstract

Introduction: Cervical Mediastinoscopy (VMS) has long been considered the gold standard for mediastinal diagnostic work-up. Transbronchial needle aspiration with Ultrasound guidance (TBNA-EBUS) has proven a safe and efficient procedure for mediastinal neoplastic disease assessment.

Aim: Aim of this study was to define diagnostic accuracy and safety of these two fundamental techniques in a single-center experience.

Patients and Methods: In the period from January 2015 to October 2019, 135 procedures for diagnosis of enlarged mediastinal lymph-nodes were carried out: 61 VMS, 50 TBNA-EBUS, 13 anterior mediastinotomies and 11 biopsies in videothoracoscopy. We performed a retrospective analysis of patients undergoing VMS (62.29% males with mean age of 60.8 years, sd = 15.25 years) and TBNA-EBUS (60% males (with mean age of 66.32 years, sd = 9.28 years).

Results: VMS was performed under general anesthesia in all cases. Biopsies were taken in most cases in nodal station 4R (77.04%). TBNA-EBUS was carried out in 45 (90%) patients with laryngeal mask, in 4 (8%) cases with tracheal tube and in one patient (2%) in spontaneous breathing. The most frequently sampled mediastinal nodal station was the subcarinal (52%). No mortality was recorded in both groups. VMS and TBNA-EBUS were characterized by similar rates of complications (3.27% for VMS and 2% for TBNA-EBUS, $p = 0.70$), but the mean duration of TBNA-EBUS was significantly shorter (49.29 minutes for VMS and 30.44 minutes for TBNA-EBUS, $p < 0.001$). Diagnostic accuracy was similar for the two procedures: 96.72% for VMS and 94% for TBNA-EBUS ($p = 0.20$).

Conclusion: VMS and TBNA-EBUS presently stand as safe and efficient methods for mediastinal masses diagnosis. For lung cancer staging TBNA-EBUS represents the first choice, due to minor invasiveness correlated to the totally endoscopic conduction.

Keywords: *EBUS-TBNA; Cervical Mediastinoscopy; Diagnostic Accuracy; Safety*

Introduction

Cervical Mediastinoscopy (VMS) has long been considered the Gold Standard for mediastinal diagnostic work-up [1]. Transbronchial needle aspiration with Ultrasound guidance (TBNA-EBUS), introduced at the beginning of the XXI Century, has proven a safe and efficient procedure for mediastinal neoplastic disease, sarcoidosis and tuberculosis diagnosis [2-4]. Applied to lung cancer staging TBNA-EBUS is

as accurate as VMS, with a lower complication rate; for such reason various Scientific Societies indicate TBNA-EBUS as the first choice procedure in such setting [5-7].

Aim of the Study

Aim of this paper was to define diagnostic accuracy and safety of these two fundamental techniques for mediastinal diagnosis, in a single-center experience.

Patients and Methods

In the period from January 2015 to October 2019 at the Thoracic Surgery Unit of Santa Maria Hospital in Terni (Italy), 135 procedures for diagnosis of enlarged mediastinal lymph-nodes were carried out: 61 VMS, 50 TBNA-EBUS, 13 anterior mediastinotomies and 11 biopsies in videothoracoscopy. We performed a retrospective analysis of patients who underwent VMS and TBNA-EBUS. Preoperative work-up included clinical interview looking for symptoms suggestive for lymphomas like fever, sweating and fatigue and physical examination aimed at the identification of enlarged superficial lymph-nodes in the neck. All patients had undergone evaluation with CT scan or ^{18}FDG-PET/CT (Figure 1) and the mediastinal nodal stations involved were recorded. Mediastinal lymph-nodes were considered enlarged if the short axis was above 1 cm. VMS was performed under general anesthesia with tracheal tube. It was carried out according to the standard technique adopted by our group since the Nineties. Briefly, a 2 cm incision was made just above the sternal notch. The pretracheal fascia was opened to allow blunt digital dissection of the mediastinum. After the mediastinal vessels were identified the DCI® LERUT Storz Medical Mediastinoscope (Figure 2) was inserted and multiple biopsies of the lymph-nodes were performed, after checking the target by needle puncture-aspiration.

TBNA-EBUS was performed in all patients in the operating room. The procedure was conducted with a flexible ultrasound bronchoscope: Ecoendoscope Pentax® model EB-1979UK (Figure 3). A 22-Ga needle (EchoTip® Cook Medical) was used for TBNA. TBNA-EBUS

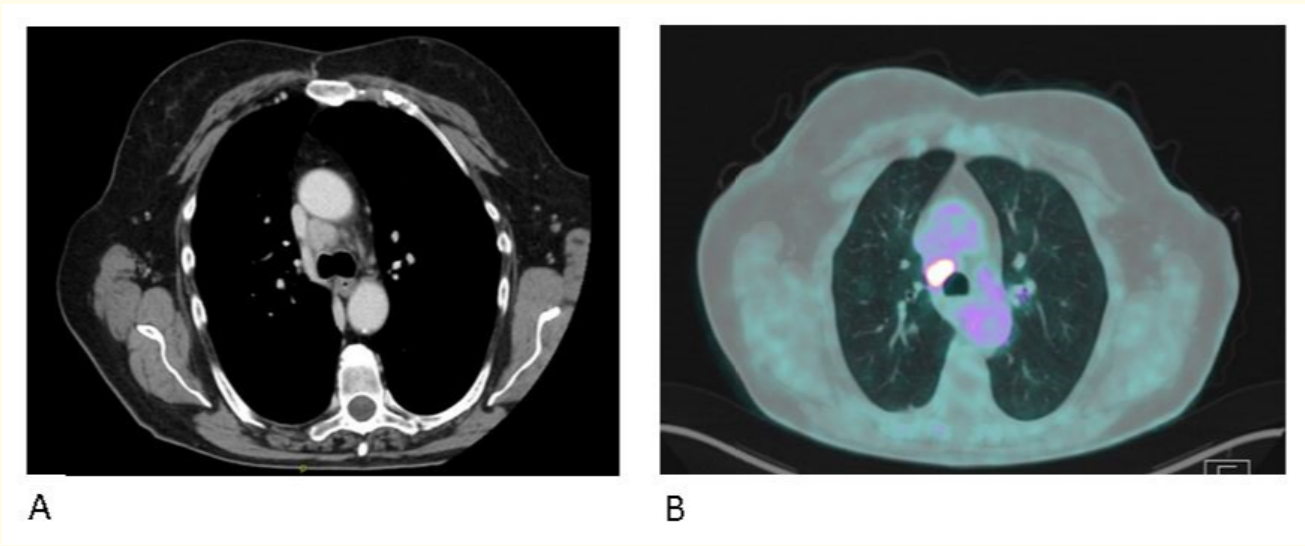

Figure 1: *Preoperative work out. A. CT scan showing lymph nodes with short axis larger than 1 cm in the right lower paratracheal station. B. PET/TC revealing ^{18}FDG avid lymph nodes in the right lower paratracheal station.*

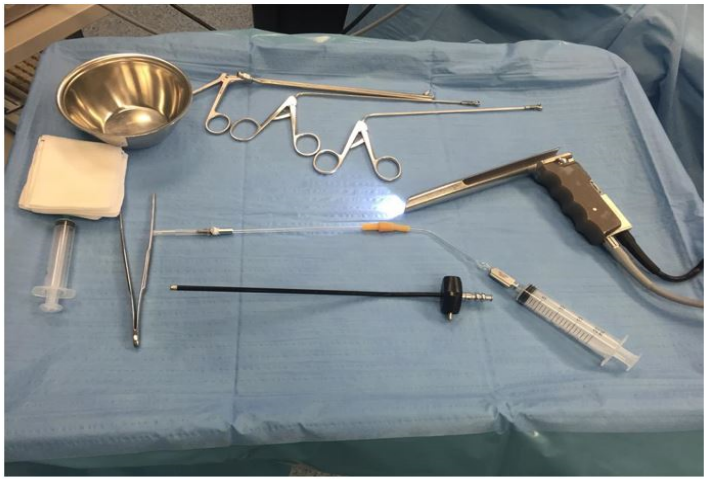

Figure 2: *Mediastinoscope tray: DCI® LERUT Storz Medical Mediastinoscope, biopsy forceps, electrified aspiration/dissection instrument and device for check-puncture.*

was performed according to a standardized protocol. Video-bronchoscopy was carried out in order to inspect the airway and remove secretions. Then the mediastinal nodal stations were examined with the echo-probe of the endoscope which is able to identify the airway and the vessels by means of B-mode ultrasonography and color-Doppler ultrasound (Figure 4). Since the ROSE (rapid-on-site-examination) is not available at our Institution, at least 3 biopsy sampling cycles per lymph-node were carried out.

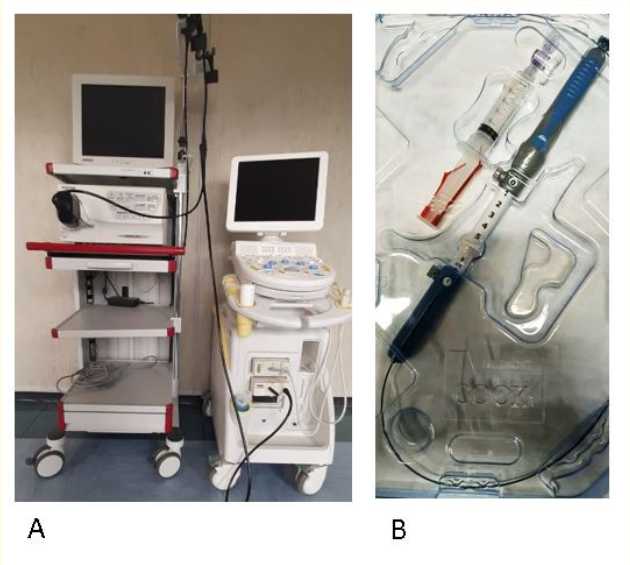

Figure 3: *TBNA-EBUS: Echoendoscope Pentax® model EB-1979UK (A) and 22-Ga needle EchoTip® Cook Medical (B).*

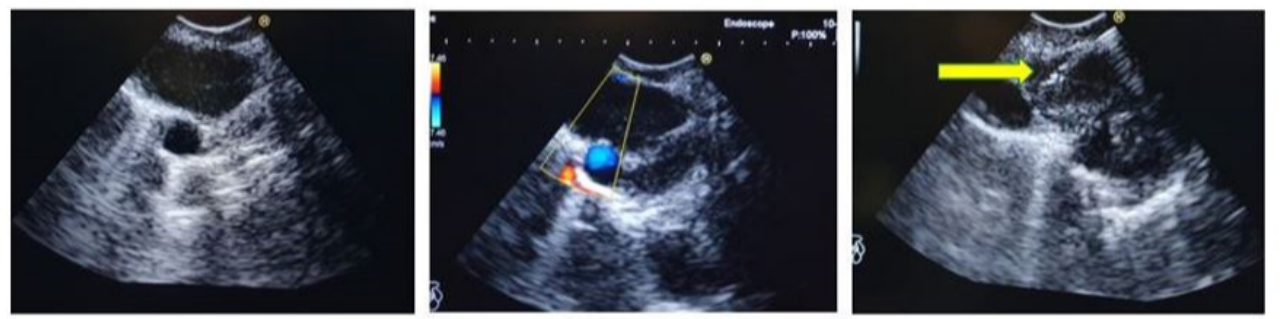

Figure 4: *TBNA-EBUS procedure. Ultrasound evaluation of Mediastinum (A), target identification and anatomical structure visualization by Color-Doppler (B), sampling with multiple needle passages (yellow arrow) (C).*

Statistical analysis

Descriptive statistics was performed using frequencies, percentages, frequency tables for categorical variables and mean ± standard deviation (SD) for quantitative variables. Non-parametric Mann-Whitney Test was performed to compare continuous variables. Categorical variables were evaluated by chi-square analysis or Fisher's exact test where appropriate. Data was analyzed with Stata 14 (Copyright 1996 - 2019 StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845 USA). P-values < 0.05 were considered significant. The present study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Each patient provided written consent and all patient information, including illustrations, was anonymized.

Results

The VMS group (61 patients) included 38 males (62.29%) and 23 females (37.7%) with mean age of 60.8 years (sd = 15.25 years). The TBNA-EBUS group (50 patients) consisted of 30 males (60%) and 20 females (40%) with mean age of 66.32 years (sd = 9.28 years). The two groups were homogenous for distribution of gender (p = 0.93) and perioperative risk according to the American Society of Anesthesiologists (ASA) classification system (p = 0.33) (Table 1). Patients undergoing VMS were significantly younger than those submitted to TBNA-EBUS (p = 0.01) probably because the first group included young patients with lymphoma. CT scan was performed in all patients, 18FDG-PET/CT in 35 (57.37%) and 32 (64%) patients of the VMS and TBNA-EBUS group, respectively. The two groups were also similar for the mediastinal nodal stations involved at CT scan (p = 0.08) and ^{18}FDG-PET/CT (p = 0.15). The nodal stations with enlarged lymph-nodes at CT scan and those ^{18}FDG-avid are shown in figure 5 and 6, respectively.

Characteristics of the two procedures, nodal stations sampled, duration, mortality and complications are reported in table 2. VMS was performed under general anesthesia in all cases. Biopsies were taken in most cases in nodal station 4R (77.04%), followed by station 2R (18.03%). The mean duration of the procedure was 49.29 minutes (sd = 5.86). No mortality. Perioperative complications were observed in 2 cases (3.27%): a pneumothorax treated with chest drainage and a delayed bleeding which required surgical exploration in a patient in anticoagulant therapy. TBNA-EBUS was carried out in 45 (90%) patients with laryngeal mask, in 4 (8%) cases with tracheal tube and in one patient (2%) in spontaneous breathing. The most sampled mediastinal nodal station was the subcarinal (52%). The mean duration of the procedure was30.44 minutes (sd = 5.65). No mortality. Bronchospasm was observed in one patient (2%) and subsided with medical therapy. VMS and TBNA-EBUS were characterized by similar rates of complications (p = 0.70), but the duration of TBNA-EBUS was significantly shorter (p < 0.001).

	VMS (n = 61)	EBUS (n = 50)	pvalue
Gender			
Males	38 (62.29%)	30 (60%)	0.93
Females	23 (37.7%)	20 (40%)	
Age (years)			
Mean (sd)	60.8 (15.25)	66.32 (9.28)	0.01
Perioperativerisk			
ASA 1	6 (9.83%)	3 (6%)	0.33
ASA 2	24 (39.34%)	16 (32%)	
ASA 3	24 (39.34%)	27 (54%)	
ASA 4	7 (11.47%)	4 (8%)	

Table 1: *Demographics and perioperative risk according to American Society of Anaesthesiologists classification system of patients undergone VMS and TBNA-EBUS.*
VMS: Videomediastinoscopy; EBUS: Endobronchial Ultrasound; ASA: American Society of Anaesthesiologists.

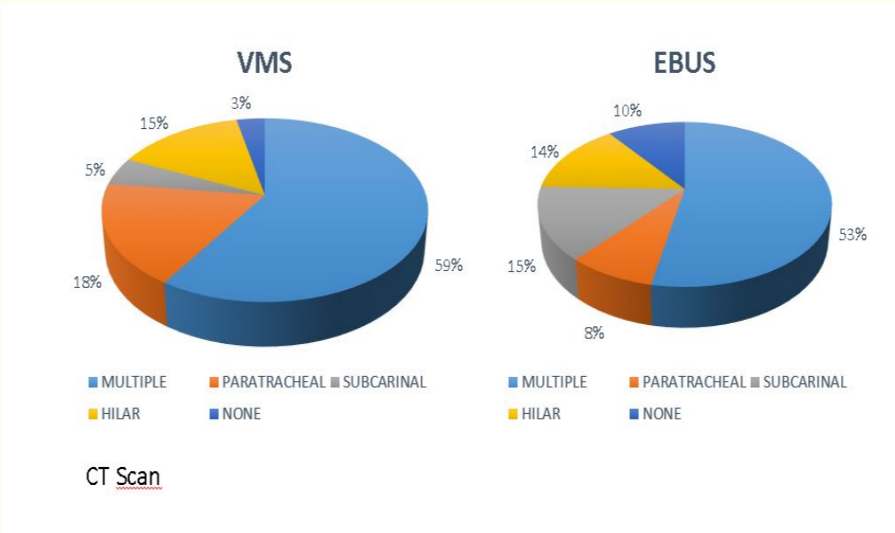

Figure 5: *Distribution of the mediastinal nodal stations involved at CT scan. The nodal stations with enlarged lymph-nodes were similar in the VMS and EBUS group (p = 0.08).*

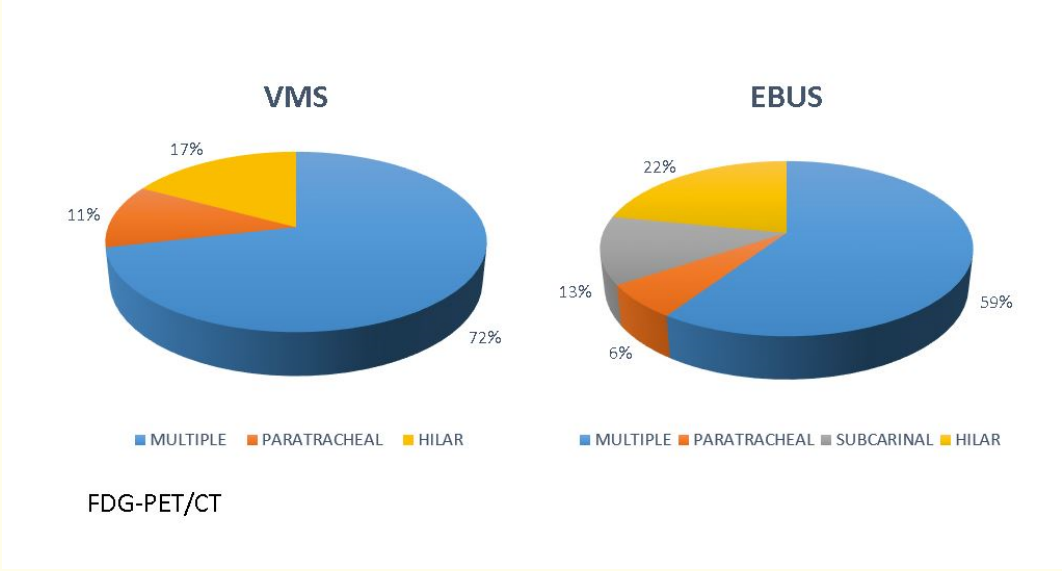

Figure 6: *Distribution of the mediastinal nodal stations involved at 18FDG-PET/CT. The nodal stations ^{18}FDG avid were similar in the VMS and EBUS group (p = 0.15).*

	VMS (n = 61)	EBUS (n = 50)	pvalue
Nodal stations sampled			
Upper paratracheal	11 (18.03%)	-	
Lower paratracheal	47 (77.04%)	11 (22%)	
Subcarinal	1 (1.63%)	26 (52%)	
Hilar	1 (1.63%)	11 (22%)	
Multiple	1 (1.63%)	2 (4%)	
Duration (minutes)			
Mean (sd)	49.29 (5.86)	30.44 (5.65)	< 0.001
Mortality	-	-	
Complications	2 (3.27%)	1 (2%)	0.70

Table 2: *Characteristics of the two procedures: nodal stations sampled, duration, mortality and complication rates.*

Out of 61 patients undergoing VMS, 21 (34.42%) had the diagnosis of sarcoidosis, 19 (31.14%) lung cancer (13 NSCLC and 6 SCLC), 13 (21.31%) reactive lymphadenitis and 6 (9.8%) lymphoma. In two cases (3.27%) VMS failed to achieve a diagnosis, but further procedures proved that those patients were affected by lung cancer and lymphoma, respectively. Regarding TBNA-EBUS, a second procedure was required in 9 patients (18%): in 2 adequate tissue sampling was not obtained, in 7 a confirmatory biopsy was indicated because these patients were observed in the first period, before completion of our learning curve. The further procedures confirmed the diagno-

sis achieved by means of TBNA-EBUS in 6 of the aforementioned cases. Overall, 22 patients (44%) were diagnosed with lung cancer (15 NSCLC and 7 SCLC), 14 (28%) reactive lymphadenitis, 8 (16%) metastases of solid tumors and 3(6%) with sarcoidosis. The diagnoses obtained with VMS and TBNA-EBUS are shown in figure 7.

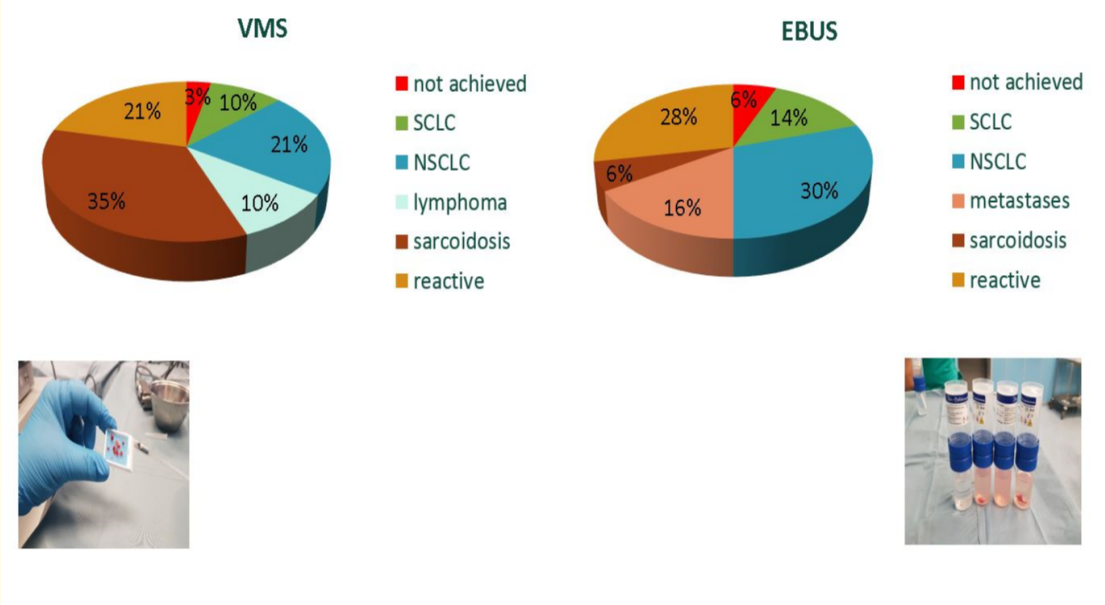

Figure 7: *Specimens (A) and distribution of the diagnosis (B) obtained with VMS and EBUS.*

Diagnostic accuracy was similar for the two procedures: 96.72% for VMS and 94% for TBNA-EBUS (p = 0.20).

Discussion

Cervical Mediastinoscopy (VMS) has played the principal role, for over fifty years, in the workup of mediastinal masses. Introduced by Carlens in 1959, the original procedure has undergone during the years several updatings in order to extend and refine its diagnostic range, with the aim of reaching farther lymph-nodes [1,8-11].

According to the original technique a minimal cervical incision in created in the neck, just above the sternal notch. The underlying planes are incised down to the pre-tracheal fascia, that must be opened. At this point digital exploration of the mediastinum is carried out, creating a tunnel along which the mediastinoscope is introduced. By blunt dissection the tissue planes are opened, and the target/s are visualized. Following a needle puncture of the target to ascertain that no vascular structures are involved, multiple biopsies are performed. The lymphatic stations amenable to biopsy are 2L/2R, 4L/4R, 7-anterior, 10L/10R. Stations 5 or 6 may be reached applying a modification of the original technique, the "Extended Cervical Mediastinoscopy", a very demanding procedure that entails digital dissection of the supra-aortic space, contoured by the Left Common Carotid Artery and the Innominate Artery [12]. Posterior station 7 and stations 8-9 R/L and 11/R/L are out of the scope of the described techniques [2]. VMS must be performed in the operating room, under general anesthesia. Reported complications occur at a rate of 2.5%, and include pneumothorax, bleeding from vascular lesions, an event that may be life-threatening, nerve or bronchial damage. Mortality in the Literature is 0.08%, mainly due to vascular lesions [13].

EndoBronchialUltraSound (EBUS) has played an ever-growing role in the diagnostic evaluation of mediastinal disease starting at the turn of the Century. The introduction of Echo-Video-Endoscopes by the major brands involved in Endoscopy Medicine ignited a very fast and wide spreading of new techniques and lead to the development of this new diagnostic approach to the Mediastinum, characterized by truly minimal invasiveness. EBUS examination can be carried out in a dedicated suite, even though in many Centers the procedure takes place in the operating room, with the patient under sedation, and application of a laryngeal mask. Stations 2L/2R, 4L/4R, 7, 10L/R, 8-9 R/L, 11/R/L can be reached and biopsied (8-9 passing in the esophagus) [14]. At times the exploration can be pushed to station 12 L/R. Stations 5-6 are out of the scope of such technique [15]. Complication rate is around 1.23%, sustained by blood loss, pneumothorax, and principally infections. Mortality is 0.02% [16].

As mentioned above, the interest in EBUS procedures has grown rapidly, along with the refinement of instrumentation and biopsy techniques, needles and on-the-spot evaluation. The issue was placed if EBUS can replace VMS, based on the low complication rate, the good diagnostic yield and the possibility of performing EBUS exams in a dedicated "Endoscopy Suite". Furthermore, EBUS has been carried out with a "multidisciplinary" physician approach, including Pneumologists and Endoscopy Physicians, whereas VMS can be performed only in the operating room, by an experienced surgeon.

High diagnostic yield, low complication rate, "Endoscopic" approach have all contributed to the widespread diffusion of EBUS. Yasufuku., *et al.* in a study carried out on 153 patients, reported Sensitivity, negative Predictive Value and Diagnostic Accuracy for EBUS and VMS of 81%/93%, 93%/79%, 90%/93%, respectively. Specificity and Positive Predictive Value were 100% for both techniques [17]. Similar results were reported also by Ernst [18]. In our population, diagnostic accuracy has been similar in the two groups (96.72% for VMS and 94% for TBNA-EBUS, p = 0.20). Similarly, in our experience, complications' rate was comparable in the two groups (3.27% for VMS and 2% for TBNA-EBUS, p = 0.70). At present we can affirm that both procedures afford comparable results in the diagnostic workup of lung cancer and inflammatory lung disease (sarcoidosis). Such statement is further confirmed by the recent recommendations by the American College of Chest Physicians (ACCP) and European Society of Thoracic Surgeons (ESTS) indicating EBUS (completed by Esophageal Ultrasonography - EUS – for stations 8,9) as the first-choice technique for N-staging of lung cancer, maintaining VMS for the cases lacking a conclusive diagnosis following the EBUS procedure [19,20]. Regarding the quantitative aspect of needle sampling by EBUS, enough material is collected in order to perform immunohistochemistry and genetic studies related to mutations in the pathologic tissue, necessary for planning of molecular targeted therapies [21,22].

A different scenario is observed when lymphoproliferative diseases are considered. In such setting, at present EBUS biopsy of mediastinal lymph-node targets is generally considered less effective than VMS in obtaining the necessary information for complete profiling of the disease. Even though some Authors consider TBNA-EBUS completely alternative to VMS for lymphoma workup [23], the general attitude is to prefer VMS as first choice technique in the present era. This is also our convincement, based on the available Literature and reported experience of experts. For the moment, in the cases where a serious suspicion of lymphoproliferative disease exists, we start directly with a mediastinoscopic exploration. There is little doubt, however, that in a future that appears to be not so far, EBUS sampling has the potential of paralleling VMS also in the field of lymphoma profiling.

Conclusion

In conclusion, VMS and TBNA-EBUS presently stand as safe and efficient methods for mediastinal masses diagnosis. For lung cancer staging TBNA-EBUS represents the first choice, due to minor invasiveness correlated to the totally endoscopic conduction. Furthermore, such aspect, added to the capability of reaching distant lymph-node stations, makes it the safest and definitely first-choice procedure when a "second mediastinal look" is necessary for restaging after induction chemotherapy. In the field of lymphoproliferative diseases, on the other hand, VMS maintains an edge due to the larger samples provided, enabling better profiling of the lymphocytic sub-populations.

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