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Usefulness of Endobronchial Ultrasound (EBUS) in the Diagnosis of Peripheral Pulmonary Lesions in a General Hospital

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Abstract. *Aim: To investigate the efficiency of guided bronchoscopy compared to blind techniques in the study of non-visible pulmonary lesions. Materials and Methods: A one-year, retrospective, study was conducted comparing two populations: Biopsies were either performed conventionally (FB-B) with the help of static images and the second where biopsies were performed after guidance (FB-EBUS). A 20-MHz radial-type ultrasound probe was used to obtain images. Sampling techniques, like bronchial brushing and transbronchial biopsies, were conducted in both populations by two separate bronchoscopists. If diagnosis was not achieved a surgical biopsy or observation followed. Results: Forty patients appeared with non-visible lesions and were included in this study. Twenty were examined with the use of FB-EBUS and in 20 cases FB-B was conducted. At the FB-EBUS population a pathologic lesion was visualized in 16 cases (80%) and in 15 cases (75%) a diagnosis was achieved. All lesions that weren't visualized had a diameter less than 30 mm. At the FB-B population a diagnosis was achieved in 11 cases (55%). In pulmonary lesions with a diameter more than 30 mm, the diagnostic yield was 87, 5% using guidance and 61, 5% using FB-B and in lesions less than 30 mm 66, 67% and 42, 85% respectively. Moreover, left lower lobe was the most promising to obtain a diagnosis. Conclusion: Our results suggest that in patients with a non- visible pulmonary lesion a diagnostic strategy involving the choice of EBUS-guided biopsy is a reasonable and effective choice.*

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Lung cancer is a major health problem in many parts of the world, including Greece. Recent reports have noted that the estimated number of new cases and deaths would be 228.190 and 164.480 respectively in the United States of America for 2013. Moreover 109.5200 men and 513.600 women have been diagnosed worldwide in the year 2008 and the estimated deaths were 951.000 men and 427.400 women for the same year (1, 2). Diagnosis is still a challenging task and obtaining an appropriate tissue sample as soon as possible with the least invasive technique is crucial. Under these circumstances, a chest physician is often called to evaluate possible lung lesions or solitary pulmonary nodules (SPNs) that are not visible in routine flexible fiberoptic bronchoscopy (FB). These cases are not only difficult to diagnose but are also most demanding for proper and precise histological diagnosis. In such cases the majority of the bronchoscopists still perform FBs with endobronchial biopsies (EB), transbronchial lung biopsies (TBB) and transbronchial needle aspirations (TBNA), mostly blindly, under the guidance of static images, or sometimes under fluoroscopy. Alterative use of percutaneous needle aspiration for biopsy or cytology samples with CT-guided techniques is also usual. Finally a large number of patients undergo surgical biopsy procedures such as video-assisted thoracic surgery (VATS) or even open lung surgery.

The ability to obtain images of the thorax beyond the visual horizon makes endobronchial ultrasound an extremely useful tool during FB. EBUS-guided transbronchial needle aspiration has already improved the N-staging yields for lung cancer. Furthermore this technology has been applied for a less invasive investigation of non-visual pulmonary lesion, including SPNs. Most of these studies originate from medical centers with significant experience in EBUS technology, and mostly reported the diagnostic yield of EBUS-guided biopsy techniques in the lung cancer population. In contrast we tried to compare two separate populations: the first one where biopsies were performed

blindly, under the guidance of static cross-sectional CT images, and the second group, with biopsies performed under the guidance of EBUS images.

Materials and Methods

This is a retrospective study. It took place between 1st June, 2010 and 31st May, 2011, at the bronchoscopic unit of the Hellenic Air Force General Hospital. Study time and the subsequent registry were divided into two separate periods: in the first six-month period, only conventional biopsies were performed and in the second, when EBUS technology was initialized at our department, EBUS guided biopsies took place. No fluoroscopy was used in any case. During that time, 124 patients with suspected lung cancer were examined by diagnostic bronchoscopy. Among them 40 presented with a possible non-visible pulmonary lung lesion (32.25% of all), 33 men, and 7 women, mean age 66.27 years, range 38-87 years old. These were included in the study. All had been previously evaluated with a contrast enhanced helical chest CT scan in order to provide information on the bronchoscopic plan, and the pathological lesions had been measured to their maximum diameter. Written informed consent was obtained and standard FB procedure was performed in all patients.

The procedure took place after the upper respiratory tract was locally anesthetized using 4% lidocaine solution and mild sedation was achieved using intravenously midazolam and/or pethidine hydrochloride solutions. The procedures were performed by two bronchoscopists using a flexible bronchoscope EB-1970K; Pentax, at the bronchoscopic unit of the Hellenic Air Force General Hospital, Athens, Greece. At the EBUS FB population, after the first inspection has ended, EBUS was performed of the suspicious segments. For this purpose, an endoscopic ultrasound system with a 20 MHz mechanical radial-type probe UM-BS 20-26R; Olympus was used. The probe was initially inserted into the instrument channel of the bronchoscope and manipulated up to the suspicious segment as peripherally as possible. Multiple segments were examined if needed. Ultrasound images were obtained and when the abnormal lesion had been indentified, the probe was removed and biopsy instruments, for bronchial brushing cytology and transbronchial biopsy samples, were inserted through the bronchoscope working channel to the specific lung segment. At least three samples were obtained with each biopsy method. When no pathological lesion was visually detected, biopsy samples were collected blindly with the help of static CT images. This was the same procedure which has been performed for the FB-B population as well. In these cases after the initial inspection, at least three, blind biopsy samples (separate bronchial brushing cytology and transbronchial biopsies) were collected from the suspicious lung segments. Our aim was not only to visualize but also to teach a pathological diagnosis. All patients in EBUS-FB population without diagnosis finally underwent surgical intervention. On the contrary at FB- B population surgically diagnosis or follow-up was followed.

Results

A total of 40 patients were examined, 20 of whom with the use of EBUS (EBUS-FB population) (Figure 1). The mean diameter of the pulmonary lesions in this population was 30.2 mm and eight (40%) were more than 30 mm in diameter. In 16 patients

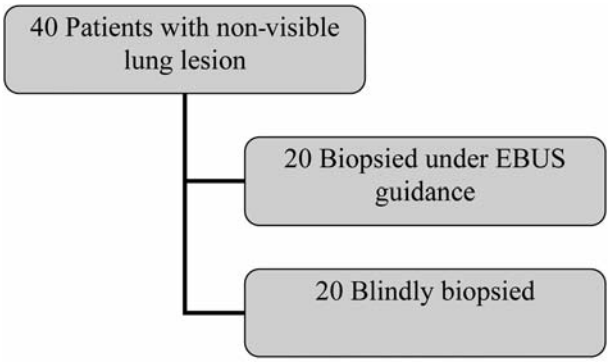

Figure 1. *Flow chart of the study.*

(80%), EBUS detected the pathological lesion. All of the non detected lesions were less than 30 mm. A definite pathological diagnosis was established in 15 patients (75%). When the mean diameter was more than 30 mm, the diagnostic yield was 87.5% (7/8 patients) and when 30 mm or less it was only 66.67% (8/12 patients).

Most of the suspicious lesions were localized in the lower left lobe (6/20, 30%), almost all were visualized and a pathological diagnosis was achieved in all cases (5/6, 83.33% and 6/6, 100% respectively). Although only two lesions were localized in the middle right lobe, they were both visualized and a diagnosis was set. Lobe distribution of the visible lesions and those with positive pathological diagnosis using EBUS are shown in Table I. In the remaining undiagnosed patients (5, 20%), surgical intervention followed. Finally pathological diagnosis was lung malignancy in 17 cases (85%), most commonly adenocarcinoma, metastatic malignancy (kidney cancer) in one case (5%) and in two cases Wegener's granulomatosis (one possible).

The other 20 patients (FB-B population) were examined with the use of conventional techniques. The mean diameter of the pathological lesions was 35.2 mm and 13 (65%) were more than 30 mm in diameter. The majority of them were localized in the upper right lobe (13/20, 65%). Only in 11 patients (55%) a pathological diagnosis was achieved. When the lesions were more than 30 mm in diameter the diagnostic yield was 61.5% (8/13 patients) but it was only 42.85% (3/7 patients) if they were 30 mm or less. Finally, the most common diagnosis was lung malignancy in 14 cases (70%), metastatic malignancy (colon and liver cancer) in two (10%) and no diagnosis was obtained in four cases (20%) and the patients were put in an observation program. The overall diagnostic yield in both populations is showed in Table II. Three cases of pneumothorax occurred, one in the EBUS-FB population, and in two patients a thoracic tube was needed and successfully inserted (Figures 2-4).

Table I. *Diagnostic yields of visible and diagnostic lesions according to specific lobes in EBUS- FB population.*

LOBE	EBUS-FB	
	Visible lesions	Positive diagnosis
Upper right	3/4	3/4
Middle right	2/2	2/2
Lower right	3/4	2/4
Upper left	3/4	2/4
Lower left	5/6	6/6

Table II. *Diagnostic yield of both populations (EBUS- FB and FB-B) of the study according to lesion's size.*

Lesion size	Diagnostic yield	
	EBUS-FB	FB-B
>30 mm	7/8, 87.5%	8/13, 61.5%
≤30 mm	8/12, 66.67%	3/7, 42.85%

Discussion

The evaluation of possible lung lesions and solitary pulmonary nodules that are not visible in routine FB remains a challenging task and more than 90% of the bronchoscopists until now perform FB with EB, TBB and TBNA. These techniques have indeed proven their use for many years, but diagnostic yields range widely according to the location inside the parenchyma, the lesion size (estimating approximately 11%-42% for peripheral lung nodules ≤2 cm) and the use of fluoroscopic devices (estimated to approximately 14%-71% in cases when fluoroscopy is involved) (3, 4). Moreover there is always the possibility that the lesion can't be visualized and the biopsy will finally be a blind one. (5) Alterative use of percutaneous needle aspiration for biopsy or cytology samples with CT-guided techniques present high diagnostic accuracy, approximately 76%-97%, but also significant risk such as pneumothorax, especially in lesions deep within the lung parenchyma. This risk is greater in patients with poor pulmonary function (6, 7). Finally a number of patients undergo surgical biopsy procedures such as (VATS), or even open lung surgery, with all the potential risks of such invasive procedures. Moreover these procedures are undesirable for older patients or for those with poor pulmonary function. In such cases a less invasive approach using radial EBUS seems a reasonable choice.

We examined the ability of EBUS-guided biopsy techniques, such as bronchial brushing cytology and transbronchial biopsy, to provide a definite pathological diagnosis of non-visible, peripheral pulmonary lesions, including SPNs. For this purpose, we compared two separate populations: the first one underwent EBUS-guided biopsies, and the second, conventional biopsies collected from the suspicious segments with the help only of static chest CT images. The study is important for us as it refers to a turning point for our bronchoscopic unit: the initiation of the use of EBUS technology in daily practice at a general hospital.

Our data underline the fact that the overall diagnostic yield for the peripheral pulmonary lesions for EBUS guidance is 75% and that for conventional biopsies is 55%. This difference is still obvious for lesions of more than 30 mm in diameter, 87.5% and 61.5% respectively, and for those 30 mm or less, 66.67% and 42.85% respectively. Finally the lower left lobe presented the highest diagnostic yield.

Other groups have also tried to estimate the diagnostic yield of EBUS-guided biopsy techniques. Shirakawa and colleagues conducted a study where they performed transbronchial lung biopsy combined with radial EBUS and fluoroscopic guidance on 50 patients and they compared the results to those of 42 controls assessed with only fluoroscopy. The accuracy of EBUS-guided FB to distinguish between lung cancer and benign disease was 84% and reached 100% when the probe was inserted inside the lesion. On the other hand although the authors claimed that the sensitivity of transbronchial diagnosis seemed superior when EBUS was performed this was not established it statistically (8). Another study conducted, by Kikuchi and colleagues, examined the impact of EBUS-guided TBB in the diagnosis of small peripheral lung lesions (<30 mm) combined with fluoroscopy. They reported that the overall diagnostic yield was 58.3%. Moreover, even in lesions with a diameter less than 20 mm, the diagnostic sensitivity remained 53.3% (9). More recent studies examined the use of EBUS without fluoroscopy. Kurimoto and colleagues, in a study performed with the use of combined EBUS and fluoroscopy in lesions >30 mm, they reported the maximum diagnostic yield to date, which was 92%. Moreover, it was 73% in lesions <20 mm and 77% in lesions in between. (10) Herth and colleagues performed a study in 54 patients with SPNs not visualized in fluoroscopy and with a mean diameter of 22 mm, where EBUS-guided biopsy was performed. In 48 patients, the lesion was localized (89%) and a definite diagnosis established in 38 (70%). (11) On a recent study performed by this same team dedicated to EBUS the conclusion was that even in small lesion approximately 22 mm in diameter, the achievable diagnostic yield was 70% (12). On the other hand, in a study performed by Yoshikawa and colleagues examining 123 peripheral pulmonary lesions

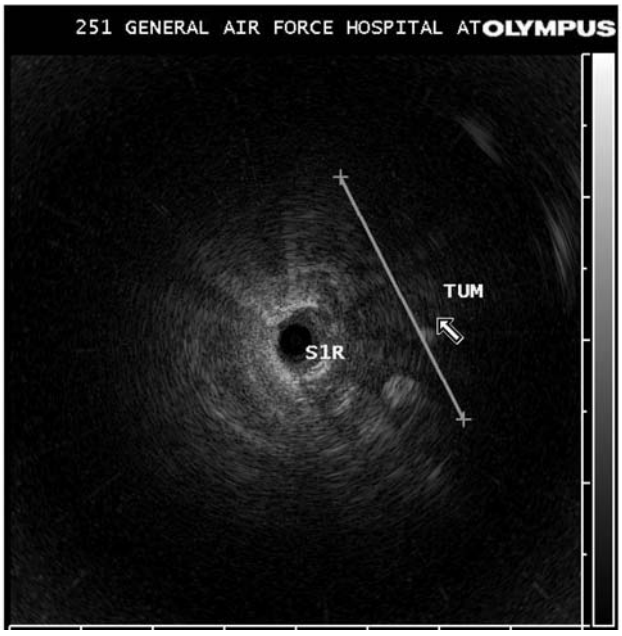

Figure 2. *Ultrasonographic image using a 20-MHz radial probe of peripheral parenchymal lesion. Adenocarcinoma at S1R (Arrow: abnormal lesion, TUM: tumor).*

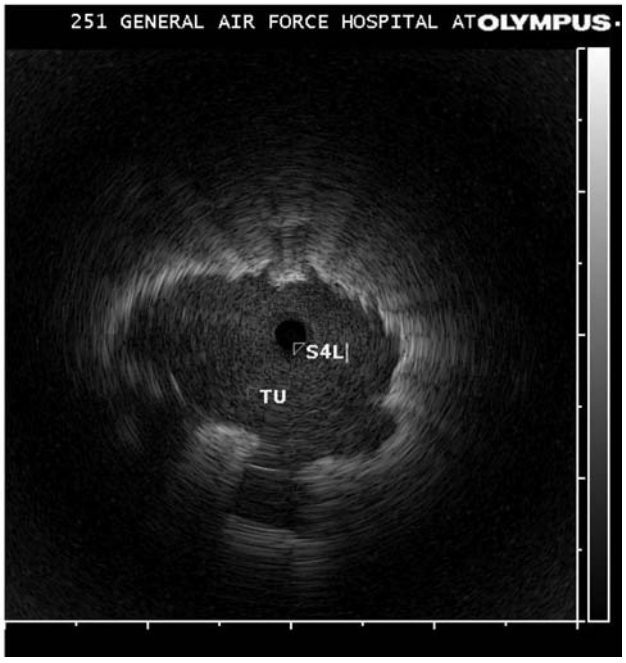

Figure 3. *Ultrasonographic image using a 20-MHz radial probe of adenocarcinoma at S4L. TU: Tumor.*

with EBUS, without fluoroscopy, but with the use of biopsy and/or bronchial brushing, the 75.6% diagnostic yield for lesion ≥20 mm this became only 29.7% for lesions ≤20 mm, which seems a rather disappointing result. Moreover, they reported that regarding lesion location the diagnostic yields were higher in the middle right lobe and the lingula segment; on the contrary it was lower for pulmonary lesions located in upper right lobe and lower lobes (13). Two previous groups are also pointed that lower diagnostic yield is presented in right upper lobe (8, 11).

A rather interesting, prospective, randomized, blinded study was performed by Paone and colleagues on 799 patients with peripheral lung lesions, with complete follow-up in 209 patients of them. For 87 of them EBUS-TBB was performed and there was a control group of 119 patients where only TBB was performed. Sensitivity for patients with lung cancer diagnosis was 83% in the EBUS-TBB subgroup and 77% in TBB subgroup when the lesion diameter was >30 mm. For diameters <30 mm, the sensitivity on EBUS-TBB subgroup was 75% and that in TBB subgroup only 31%; when the diameter was ≤20 mm the sensitivity was 71% and 23% respectively. (14) Other research groups have also underlined the efficiency of EBUS in the study of peripheral pulmonary lesions (15-24).

Recently two separate teams conducted meta-analyses on the usefulness of radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer. Steinfort and colleagues and Wang Memoli and colleagues reported almost similar results (sensitivity 73% and 70% respectively). The rate of pneumothorax was also low in both studies (1% and 1.5% respectively) (25-26).

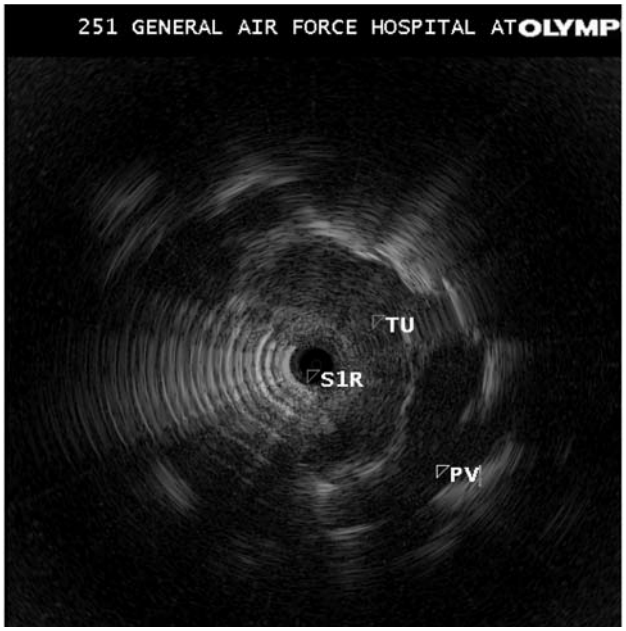

Figure 4. *Ultrasonographic image using a 20-MHz radial probe of peripheral parenchymal lesion. Adenocarcinoma at S1R. TU: Tumor, PV: pulmonary vein.*

Our study had some limitations. It was a retrospective, one-center study, with a relatively low number of patients. The difference in mean diameter of the examined lesions in these populations possibly reflects two different aspects: Firstly it was strongly established in the pulmonary community that lesions of small diameter must be referred to a thoracic surgeon or an interventional radiologist. Secondly, we believe that in the future EBUS will be the first choice in the diagnosis of any intrapulmonary lesion.

Despite the above, the findings of this study seem to be in accordance with the results of other groups. Some points on the other hand must be underlined: most of these studies are from specific US, German and Japanese medical centers with significant experience in EBUS technology, reflecting the lack of infiltration of EBUS technology into the pulmonary community and the impossibility of equal comparison of the reported studies due to the great variability in the expertise and experience of the operators. Combining data is almost impossible as well, because of variations in imaging and sampling techniques (with the use or not of fluoroscopy, guide sheaths and various biopsy methods such as forceps biopsy, brushing, washing, needle aspiration or their combination) (25).

Furthermore, it is well known that under fluoroscopic guidance, lesions less than 30 mm frequently cannot be visualized. EBUS is an adequate tool to visualize peripheral pulmonary lesions safely even without the use of fluoroscopic guidance, or even replaces fluoroscopy, thus sparing radiation exposure to patients and medical staff. On the other hand even with the use of EBUS, lesions ≤15 mm are also hard to be defined. The overall yields using a radial probe are depended on the lesion size. When this is ≥30 mm, the diagnostic yield ranges approximately from 60% to 92% and varies from 58.3% to almost 80% when it is ≥20 mm. Contrary to this optimum when the lesion is <20 mm, it is estimated from almost 30% to 70%. Moreover in cases when the probe is been positioned within the lesion on the ultrasound image a higher diagnostic yield can be achieved than if it is adjacent to the target. Finally a negative sample cannot exclude a final positive pathological result and a more invasive method should follow to verify the diagnosis (27).

In conclusion our study provides evidence that radial EBUS can visualize and provide significant help in the diagnosis of peripheral, non-visual, pulmonary lesions compared to routine bronchoscopic techniques, even in a general hospital setting, with adequate accuracy and safety. As a result a diagnostic strategy including radial EBUS before a more invasive intervention seems reasonable enough in order to achieve a pathological diagnosis of any suspicious intrapulmonary lesions.

Conflicts of Interest

All Authors declare they have no conflict of interest in regard to this study.

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