IMPLEMENTING EBUS TBNA: FIRST EXPERIENCE AND REVIEW OF LITERATURE

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(Abstract): Lung cancer has a very dismal prognosis and careful diagnosis and staging is of utmost importance. EBUS has become a cornerstone investigation for diagnosis and staging and current guidelines stress that there is a steep learning curve when introducing this technique in practice (only 30 procedures are considered necessary). Over a period of 10 months a total of 21 patients have been addressed to our unit for an EBUS TBNA procedure. Only three were referred for staging purposes (for lung, digestive and cervix cancers) the others being primary diagnostic approaches where simpler procedures had previously failed. Procedures were initially performed under local anesthesia (3 cases) then under general anesthesia and jet ventilation using a laryngeal mask approach. Mediastinal lymph node group 7 was the most frequent target (9 cases) followed by group 4R (8 cases) and peribronchial tumoral processes (7 cases); one case did not require any needle-aspiration. On average each examination resulted in the sampling of 1.4 targets. There were no significant procedure related severe adverse events. Although 21 G cytology needles were used, adequate histological samples were obtained for 11 cases and cytology was the examination of choice for 9 cases. The pathology/cytology results were retrospectively assessed as satisfactory for 15 cases (confirmed neoplastic or other disease) and inconclusive for 5 cases. Non neoplastic disorders were represented by sarcoidosis, tuberculosis and bronchogenic cyst (3 cases). The procedure can be considered fast and safe; trained pathology personnel play an extremely important role; presently referrals are rare for staging purposes. Keywords: LUNG CANCER, DIAGNOSIS, STAGING, EBUS TBNA, ENDOSCOPIC ULTRASOUND.

Lung cancer has a very dismal prognosis and careful diagnosis and staging are of utmost importance in choosing the optimum therapeutic approach - surgery, chemotherapy, radiotherapy or combinations. Assessing the N2 nodes status in non small cell lung cancer patients has become essential as multimodal therapeutic approaches became available. Despite significant advances in mediastinum imaging, careful clinical lymph node staging is preferable in guiding therapy as frequently radiologic criteria may prove unreliable. Overall sensitivities of 75% and 84% and
specificities of 82% and 89% were cited for CT and PET/CT respectively (1, 2). Therefore invasive (i.e. histological proven) mediastinal staging should be the norm if N2 or N3 disease is suspected (3).

Since the 1954 initial report mediastinoscopy quickly became the gold standard for invasive mediastinal assessment with a sensitivity of 81% and a negative predictive value of 91% (1, 4). It has been partially superseded by minimal invasive approaches as endoscopic ultrasound (EUS) and endobronchial ultrasound (EBUS). These became cornerstone investigations for diagnosis and staging as results are comparable to mediastinoscopy with a much lower adverse event rate and cost. A pooled specificity of 1.00 (95% CI 0.92 to 1.00) and sensitivity of 0.88 (95% CI 0.79 to 0.94) has been reported for EBUS TBNA as far as mediastinal lymph node staging is concerned (5).

Similar values have been reported for endoscopic ultrasound (EUS) approaches for non-small cell cancer staging (6). A combination of both techniques have been proved to be superior compared with mediastinoscopy with a combined sensitivity of 94 % vs. 79 % (7).

A recent meta analysis (8) reported a negative likelihood ratio of around 15 % a value suggesting that there is still a role for more invasive approaches in selected cases.

However EBUS/EUS is considered as the first intent approach - considering the fast patient recovery since only minimal anesthesia is required and no significant surgical trauma is involved. Most mediastinal lymph nodes groups can be sampled (with the exception of groups 5 and 6 (9, 10) which can be usually reached by VATS). Its role is clearly expanding as more potential targets are considered – such as left adrenal, left liver lobe or thyroid gland (11). Apart from versatility, ultrasound imaging may contribute with additional data to CT appearance to assess node involvement. Indeed, apart a small diameter over 10 mm and a round shape (features usually assessed on CT) heterogeneous echogenity and absence of central hilar structure were recently mentioned as predictors for malignant involvement (12). Furthermore EBUS TBNA can be readily repeated if inadequate samples are obtained or for the purpose of disease progression monitoring as no significant sequelae are expected. There were some concerns when comparing EBUS to mediastinoscopy as far as yield was concerned. Recent data suggests that a usual approach entailing at least 3 passes per target will return an acceptable sample for pathology and molecular examinations. This will ensure high (over 95%) sensitivity and accuracy values for mediastinal staging (13).

Current guidelines stress that there is a steep learning curve when introducing this technique in practice – on a yearly basis significant improvement is seen after 25 procedures and diminishing returns are encountered after 50 procedures (14).

Since the introduction of EBUS TBNA in our unit some particular issues and pitfalls became apparent and we report on our initial experience.

**MATERIAL AND METHOD**

A total of 21 patients have been assessed using an EBUS TBNA approach over a year starting with June 2013; this was performed using an OLYMPUS EU-ME1 on an OLYMPUS EVIS EXERA III infrastructure.

Only three patients were referred for staging purposes (for lung, digestive and cervix cancers). The rest of the procedures were primary diagnostic approaches where simpler less invasive procedures had previ-
ously failed or were judged to be potentially useless (mainly bronchoscopy and trans-thoracic approaches).

**METHODOLOGY**

Standard preprocedure requirements included – complete medical history, signed informed consent, coagulation assessment, EKG, chest CT, per month for 12 hours.

Main contraindications considered were: significant arrhythmias or cardiac conditions, high bleeding risk (thrombocytopenia, anticoagulant / antiplatelet agents, renal failure), acute respiratory failure. There were no absolute contraindication; two procedures were postponed until antiplatelet agents effects wore off (seven days). No antibiotic prophylaxis was routinely considered although seven cases received postprocedure antibiotherapy.

Initially potentiated local anesthesia was used (three cases) then a switch was made to general anesthesia under high frequency jet ventilation administered on laryngeal mask (this approach ensured good working conditions and patient comfort). Median working time was 60 minutes (anesthesia time included).

EBUS examination was preceded by standard bronchoscopy to exclude evident bronchial lesions as the EBUS scope has a lower resolution image and a narrow 30 degree angled field of view. Once the EBUS scope was passed into trachea the convex ultrasound probe was brought in contact with the lateral tracheal wall (an inflatable balloon was used to improve contact). Main lymph nodes groups were identified (hypo echoic and Doppler negative) and assessed (shape and size) using the following approaches/landmarks using a N3 to N1 approach:

- 2R, trachea, superior vena cava, brachioccephalic veins
- 2L, trachea, above the aortic arch
- 4R, trachea, superior vena cava, below the azygos vein (Fig. 1)
- 4L, trachea, aortic arch, pulmonary artery
- 7, right or left main bronchus
- 10R, right main bronchus, interlobar pulmonary artery branch (Fig. 2)
- 10L, left main bronchus, left pulmonary artery
- 11R, intermediary trunk, interlobar pulmonary artery branch
- 11L, distal left main bronchus, interlobar pulmonary artery branch

![Fig. 1. Groups 10R and 4R lymph nodes – CT section](image1.png)

![Fig. 2. Group 10 R lymph node – echographic view](image2.png)
Abnormal nodes were identified on CT. Identified lymph on the endoechochographic images were punctured under ultrasound control using 21 G Olympus needles; at least three passes were done per target as recommended. Rapid on site cytology assessment although available was not considered necessary (16). Aspirated specimens were discharged in 90 degrees alcohol – this approach while convenient as it provided immediate feedback caused some difficulties for pathology personnel as instantly formed large blood clots obscured aspirated fragments. Therefore it was later changed to saline followed fixing by addition of the same volume of 97% alcohol. Cytoblocks were obtained after centrifugation and inclusion in a support matrix and then processed as regular biopsies for Paraffin embedding.

RESULTS
Mediastinal lymph node group 7 was the most frequent target (9 cases) followed by group 4R (8 cases) and peribronchial processes (7 cases). Targets also included groups 4L, 10 and 11 on both sides. Each examination involved an average of 1.4 targets to a total of 29.

There were no procedure associated adverse events in our group except for two cases. In first case the procedure was prematurely stopped due to anesthesia issues. The second was a foreign body situation - distal latex balloon disengaged; it was promptly recovered using a biopsy forceps and a video bronchoscope. Minor procedural bleeding was not considered a significant adverse event and did not require any specific intervention. Recovery was fast; all patients were returned to the ward by next day and usually discharged soon after.

Estimated expenditure was around 350 euro per procedure - mainly due to disposable equipment and standard short hospitalization costs.

Although 21 G cytology needles were used adequate histological samples, albeit small were obtained for 11 cases and cytology results were available for 9 cases.

For one case no invasive approach was needed as ultrasound examination revealed a small diameter adenopathy (suspicious on anterior CT scan).

The pathology/cytology results were retrospectively assessed as satisfactory for 15 cases (confirmed neoplastic or other disease) and inconclusive for 5 cases (non specific aspects except lymphoid tissue).

These were referred for more invasive approaches if there was a high index of suspicion.

Non neoplastic disorders were represented by sarcoidosis, tuberculosis and bronchogenic cyst (3 cases).

DISCUSSION
While the optimum number of stations to be assessed during an EBUS examination is still open to debate it is generally considered that sampling more than two may improve staging accuracy (17). Still as for our case series the average was 1.4 stations per procedure – a figure which must be interpreted taking account of the diagnostic purpose of the approach. More often than not the patient had an imaginistically assessed stage IV disease which precluded or made inadequate invasive approaches such as thoracotomy and also made unnecessary N staging.

Group 7 was the most frequent target in our group and could have probably been reached by conventional TBNA – still EBUS was preferred as it allowed multiple
target assessment and cost was roughly similar. Furthermore recent data suggests conventional TBNA skill improvement after implementing EBUS training (18).

While peripheral lung nodules may not always be assessed by EBUS this approach proved useful in selected cases (seven for our group) as have been reported before; all seven peripheral pulmonary nodules/masses were positively diagnosed (19).

EBUS-TBNA complications were previously reported – agitation, post-procedural cough, hypoxia, laryngeal injury, fever, bacteremia/infection, pneumothorax, mediastinal abscess, laryngospasm/laryngeal edema, bronchospasm; their frequency was estimated around 1.4%. The main risk factor was considered the presence of a concurrent transbronchial lung biopsy (20). There were no procedure related complications in our group. This may partly be explained by the general anesthesia/high frequency jet ventilation approach we used which circumvented upper airways reactions and total refrain from transbronchial lung biopsies. Post procedure antibiotic therapy was prescribed if purulent bronchial secretions had been found.

Fast recovery – due to either low anesthesia requirements or low surgical trauma involved may imply a special role for EBUS TBNA for frail patients for whom a more invasive approach may associate a significant vital risk. This is also suggested by the fact that no patient was refused once addressed as their concurrent conditions were not considered to be absolute contraindications. There was one case for which active watch was preferred as available clinical data was suggestive for reactive inflammatory adenopathy; chest CT repeated after three months showed complete resolution (21).

As far as results were concerned 15 procedures returned positive diagnosis – five were considered inconclusive. Given the low negative likelihood ratio (8) and the high suspicion threshold we decided to refer the patients for subsequent more aggressive approaches. Still we consider 15 positive diagnoses to be encouraging given the fact that histological samples were available in only 11 cases. This was probably possible because EBUS samples proved to be generally suitable to immunohistochemistry assays either as core biopsies or as cell blocks (22, 23).

There were some non neoplastic conditions in our group. While tubercular lymph node involvement and bronchogenic cysts are not usually explored by TBNA (mainly because late complications such as fistulae may develop) these were incidental findings while suspecting malignancy. On the other hand sarcoidosis node involvement was suspected and confirmed for one patient; EBUS TBNA was preferred as there were no significant endobronchial lesions and no infiltrates on chest CT. Because of group 4R involvement which is particularly difficult to assess on an unguided approach; current practice strongly encourages the use of EBUS TBNA over TBNA for these cases (24).

More while transbronchial lung biopsies seem to have the highest diagnostic yield as a standalone procedure adding EBUS TBNA may improve the figure to over 80% and is probably superior to conventional TBNA (25) as recent data suggests a particular appearance for sarcoid lymph nodes – distinct margins and granular appearance (26).

**CONCLUSIONS**

EBUS TBNA may be used for diagnos-
tic and staging purposes in broncho-pulmonary carcinoma patients as it can reliable reach mediastinal node stations (excepting groups 5, 6, 8, 9) and peri-bronchial masses.

It can be considered a reasonably fast procedure with an excellent safety profile, acceptable cost as compared to mediastinoscopy and a particularly fast post procedure recovery.

General anesthesia under jet ventilation greatly improves comfort for both the patient and the medical team but the procedure may be performed reasonably well under local anesthesia.

Trained pathology personnel play an extremely important role and sample management protocol should be adequate for immunohistochemistry assays.

Although diagnostic yield is encouraging for both neoplastic and non neoplastic conditions more invasive approaches may still be necessary as negative predictive power is low.

The procedure is little known to other health professionals and thus referrals are rare for staging purposes – more publicity would probably be useful.

REFERENCES


