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The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis

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ABSTRACT

A clinicoradiological presentation of thoracic sarcoidosis requires histopathology to establish the diagnosis. Flexible bronchoscopy (FBX) has a reasonable diagnostic yield and is the procedure of first choice for diagnosis. Endoscopic ultrasound (EUS-FNA/EBUS-TBNA) can help to diagnose sarcoidosis. We examined prospectively in 15 clinics an implementation strategy of endoscopic ultrasound for the diagnosis of sarcoidosis after a negative FBX.

We included 137 patients (92 men, median 43 yr) and found sarcoidosis in 115 (84%). Alternative diagnoses were tuberculosis, lymphangitis carcinomatosa, pneumoconiosis and alveolitis. All patients were send for FBX, which was performed in 121 (88%) resulting in a definite diagnosis in 57 (42%). 80 patients were send for endoscopic ultrasound which could be done in 72 (90%) yielding a definite diagnosis in 47 (59%). Endoscopic ultrasound after negative FBX avoided a surgical procedure in 47/80 pts. The sensitivity of FBX for sarcoidosis was 45% (95%CI 35-54), but 62% (95%CI 50-72) if biopsies were taken. The sensitivity of endoscopic ultrasound after negative FBX was 71% (95%CI 58-82). With this strategy, 97/115 or 84% (95%CI 76-90) of proven sarcoidosis was diagnosed with endoscopy.

This large prospective implementation study shows that endoscopic ultrasound is valuable to diagnose sarcoidosis after a negative FBX. (NCT00888212).

INTRODUCTION

Sarcoidosis is a disease of unknown etiology and affects 5-40/100,000 persons making it the most prevalent interstitial lung disease in the western world [1]. There is no single diagnostic test. The diagnosis is based on a compatible clinical and/or radiological picture, supported by pathologic evidence of noncaseating epitheloid cell granulomas in the absence of organisms or particles [1]. The diagnosis of sarcoidosis is reasonably certain without biopsy only in patients with Löfgren's syndrome. Otherwise, a biopsy specimen should be obtained from an involved organ that is most easily accessed. Since pulmonary sarcoidosis is the most frequent form, a bronchoscopy with tissue sampling is advised as the first step to obtain a tissue based diagnosis and to exclude possible alternative diagnoses. Flexible bronchoscopy is cheap and has a reasonable diagnostic yield; especially if transbronchial biopsies (TBB) are taken [2]. However, clinicians are frequently confronted with a non-diagnostic result after bronchoscopy needing to decide if a surgical biopsy should be taken. Cervical mediastinoscopy, and in some cases video-assisted thoracoscopic surgery (VATS) procedures are regarded as the next diagnostic step after a non-diagnostic bronchoscopy. Although surgery has a high yield [3, 4], it requires general anaesthesia, is costly, is associated with a certain morbidity [5] and results invariably in scars.

Recent reports show that with either curvilinear transoesophageal endoscopic ultrasound with fine-needle aspirations (EUS-FNA) and endobronchial ultrasound with transbronchial needle aspirations (EBUS-TBNA), non-caseating granulomas can be demonstrated upon sampling of the intrathoracic nodes and that as such, these techniques can contribute to diagnose sarcoidosis [6-10]. Although these reports indicate the feasibility, they did never assess the value of these techniques in routine daily practice where a bronchoscopy is still the first diagnostic step [1]. In addition, these reports originate invariably from tertiary care institutes where endoscopic ultrasound was performed by experts in the field, possibly resulting in an overestimation of the yield.

We here report on the largest prospective implementation trial where patients with suspected thoracic sarcoidosis in 15 hospitals were first send for a conventional bronchoscopy. Only if no definite diagnosis was obtained, the patient was offered endoscopic ultrasound (either EUS-FNA or EBUS-TBNA). We hypothesised that the addition of endoscopic ultrasound after a preceding non-diagnostic bronchoscopy, would result in an increase in diagnostic yield and that by this strategy, the need for a surgical biopsy could be reduced in a significant number of patients.

METHODS

Study Design and Patients

The study was performed in 15 participating hospitals where consecutive patients with a clinicoradiological suspicion for thoracic sarcoidosis were included between June 2008 and May 2009. The study was approved by the central ethics committee of the Ghent University Hospital (UZG2008069) and all 14 local committees. The protocol was registered (NCT00888212) under the acronym MITOSIS (Minimally Invasive Techniques Or Surgery In Sarcoidosis). The study was designed as a prospective implementation study. The 15 participating chest physicians (median age 40 years, range 32-61) were all experienced with routine bronchoscopy procedures while 80% is involved in respiratory training programs (including bronchoscopy). Eleven performed E(B)US independently so 4 referred their patients to one of the participating colleagues in case this was needed. The median number of E(B)US per year was 120 (range 30-250). The median years in practice was 7 (range 2-31). Written informed consent was obtained from all patients. Consecutive patients with suspected sarcoidosis in whom tissue confirmation is considered necessary were recruited. Patients with other than lung involvement where a simple diagnostic biopsy could be performed to obtain the diagnosis were excluded. Accordingly, patients with Löfgren's syndrome, patients unfit to undergo an endoscopy or a surgical intervention and patients unable to provide a written informed consent were excluded from participation in the trial.

The participating chest physicians were instructed to follow a diagnostic algorithm developed to measure the yield of bronchoscopy and endoscopic ultrasound in case bronchoscopy did not result in a definite diagnosis. If no definite diagnosis was obtained after endoscopic ultrasound with fine needle aspiration, a surgical biopsy was proposed. Samples were analysed according to the institutional practices. Rapid on site analysis was not available. The presence of naked granulomas in lung biopsies or non-caseating granulomas and giant cells on the fine needle aspirates or biopsies of the lymph nodes was considered sufficient for making the diagnosis of sarcoidosis in this population. If the samples were not representative or if they showed normal tissue, the result was categorized as non-diagnostic.

Bronchoscopy

A flexible bronchoscopy was the first step in this diagnostic algorithm. The procedure was performed according to the institutional practice. Because data have shown the benefit of routinely adding endobronchial biopsy and transbronchial needle aspiration to traditional transbronchial biopsy specimens, the endoscopists were stimulated to apply these procedures during the bronchoscopy [2]. Bronchoalveolar washing was routinely performed for microbiological analysis while performing a bronchoalveolar lavage was left at the discretion of the local endoscopist. All procedural details were recorded, as were complications.

Endoscopic Ultrasound

EBUS-TNBA and/or EUS-FNA were performed in the participating centers. The choice to perform either technique depended on the investigators' preference and on the availability of the technique. EBUS-TBNA and EUS-FNA were performed as out-patient procedures using a curvi-linear scanning ultrasound bronchoscope (Olympus, BF UC160F OL8) connected to an ultrasound unit (EU-C60 Olympus Ltd; or ALOKA α5-10) and a curvi-linear scanning oesophagoscope (Olympus, GF-UCT160-OL5) connected to the ultrasound unit (ALOKA). The procedures were performed under local anaesthesia and moderate sedation or general anaesthesia according to investigators' preference. EBUS-TBNA was performed using a 22-gauge needle (NA-2015X-4022 Olympus Ltd) while EUS-FNA was performed using a 22-gauge needle (NA-200H-8022 Olympus Ltd). Patients were observed for 2 hours post-procedure. Cell smears of aspirates were stained with a quick staining method (Diff-Quick®) while cell suspensions were collected in CytoRich® medium (BD Benelux – Erembodegem - Belgium) for making a Papanicolaou staining and paraffin cell blocks.

Surgical procedures

Only if a preceding bronchoscopy and endoscopic ultrasound procedure did not result in a definite diagnosis, the patient was referred for a surgical biopsy. The type of intervention was guided by the clinicoradiological presentation. Primarily, a mediastinoscopy was advised in case of unexplained mediastinal or hilar lymphadenopathies although a video-assisted thoracoscopic surgery (VATS) procedure with parenchymal biopsy was allowed if thought necessary.

Sample size and data analysis

Standardized evaluation forms recording demographic characteristics, technical investigations and procedural characteristics were available for all investigators. All data were transferred into an electronic database (SPSS 17.0). The co-primary endpoints of the study were the sensitivity of bronchoscopy and endoscopic ultrasound after a negative bronchoscopy to diagnose sarcoidosis. To demonstrate a gain of 15% diagnostic yield by endoscopic ultrasound after a negative bronchoscopy, the latter having a yield of 60%, we calculated that with a type 1 error of 5% and a power of 90%, a sample size for one proportion of 104 patients with sarcoidosis would be needed. Taking into account that 80% of all patients would indeed end up with sarcoidosis, we aimed to collect data of 130 patients. Data were analysed according to the "intention to diagnose" principle unless explicitly indicated (per protocol analysis). Secondary endpoints were technical characteristics, complication rates, protocol adherence and multivariate analysis to find determining factors. Diagnostic yields were compared with the Fishers' exact test (two-sided).

RESULTS

Patient characteristics

In table 1, the main demographic characteristics of the 137 Caucasian patients are summarized. There were twice as many males as females and about two thirds were never-smokers. On the X-ray of the chest, about 60% was classified as stage 0-I, while 40% was thought to have stage II-IV. All patients underwent computed tomography, and the majority had enlarged (≥10mm largest short axis) lymph nodes while parenchymal abnormalities were found in 52%.

Procedures and diagnoses

The procedures performed are summarized in a flow chart (figure 1). Bronchoscopy was performed in 121 patients (88%) and resulted in a definite diagnosis in 57 (42%) patients. In 16 patients (12%), a bronchoscopy was cancelled. Eighty (58%) patients had no definite diagnosis after a bronchoscopy was offered, and were therefore scheduled for an endoscopic ultrasound procedure. Either EUS-FNA or EBUS-TBNA was performed in 72 patients (90%) resulting in a definite diagnosis in 47 (59%). The cancellation of a planned bronchoscopy or endoscopic ultrasound in respectively 16 and 8 patients was related to a variety of reasons including refusals upon second thoughts, technical failures and endoscopists judging a bronchoscopy or an endoscopic ultrasound to have a very unfavourable risk benefit ratio in particular cases. As a result 33 (24%) patients were left without a definite diagnosis after bronchoscopy and endoscopic ultrasound. Twenty-two underwent a surgical procedure that resulted in a definite diagnosis. In 11 patients, a surgical intervention was refused by the patient or was thought to have no added value above a follow up strategy.

With the current implementation strategy, we obtained a definite histopathological diagnosis in 126 patients (92%) of the study population. The final diagnoses are summarized in table 2. There were 115 patients with sarcoidosis (84%) while in 5, acid fast bacilli were found. In 6 other patients, we found pneumoconiosis, alveolitis, lymphangitis carcinomatosa and aspecific lymphadenitis.

As summarized in table 3, bronchoscopy was performed mainly under local anaesthesia although mild sedation was added in one quarter. TBNA was applied in 21% while EBB was performed in 63% as was TBB. In 21 patients, the endoscopist decided not to take a tissue sample except a washing for microbiological and cytological analysis. A definite bronchoscopic diagnosis was made in 57 patients, in whom TBB did significantly better than EBB (72% versus 26%; p=0.0003), even though both procedures were equally performed (63%). The relative yield for all diagnoses per biopsy modus was highest for TBB (41 diagnoses in 76 TBB procedures, or 54%), followed by TBNA (42%) and EBB (20%). Minor complications were encountered with bronchoscopy: minor bleeding, intolerance and one pneumothorax; the latter treated with a simple manual aspiration.

Table 4 shows the procedural characteristics of EUS-FNA and EBUS-TBNA. The majority was performed under local anaesthesia with mild sedation, while general anaesthesia was applied in 10%. EBUS-TBNA was 3 times more done as was EUS-FNA. Mediastinal lymph nodes were sampled in 95% while hilar lymph nodes alone were approached in only 4 patients. The yield of EUS-FNA was 94% as compared to 56% for EBUS-TBNA (p=0.03). No complications were noted in the patients investigated with endoscopic ultrasound.

The surgical interventions performed in 22 patients were cervical mediastinoscopy in 19 (86%), a VATS in 2 (9%) and an open lung biopsy in 1 patient (5%). All surgical procedures resulted in a definite diagnosis. One patient developed mediastinitis and was treated with antibiotics with a favourable course.

Test characteristics to diagnose sarcoidosis

When proposing bronchoscopy as a first diagnostic step, we identified 52 (45%) of the 115 patients who finally had sarcoidosis. This diagnostic yield increased to 52% and 62%, respectively, when a bronchoscopy was effectively performed and when at least one biopsy was taken (table 5). We found that the sensitivity to find sarcoidosis with a bronchoscopy was 70% among females, but only 44% in males (p=0.03). Not surprisingly, taking a biopsy strongly determined the procedure to be successful (p<0.0001).
With endoscopic ultrasound proposed to the 63 remaining patients with sarcoidosis; the diagnosis was found in 45 (71%). This diagnostic yield increased to 77% if the procedure was effectively performed. The diagnostic yield for sarcoidosis was comparable for EUS-FNA and

EBUS-TBNA (p=0.08). In the 20 patients with sarcoidosis investigated first with a blind TBNA followed by E(B)US if necessary; the former yielded the diagnosis in 8 (40%) while addition of the latter increased the yield to 70%. For endoscopic ultrasound, we found none of the measured factors as predictive.

The overall diagnostic yield for sarcoidosis with the proposed endoscopic strategy of bronchoscopy plus endoscopic ultrasound in case the former is not conclusive, is 84%. The incremental yield by adding endoscopic ultrasound on to bronchoscopy is therefore 39%. This means that, by adding endoscopic ultrasound to a prior non-diagnostic bronchoscopy, 3 patients should be investigated in order to avoid one surgical diagnostic procedure.

DISCUSSION

The most important finding done in the current largest implementation trial ever on sarcoidosis is that in patients with thoracic sarcoidosis, the proposed algorithm of bronchoscopy followed by endoscopic ultrasound only in those cases where no definite diagnosis was obtained, yields a histological proof of the disease in 84%. Although 45% of the sarcoidosis patients were diagnosed with bronchoscopy, endoscopic ultrasound provided the diagnosis in additional 39% of the cases.

According to the available guidelines of ERS, ATS and World Association of Sarcoidosis and Other Granulomatous Disorders; a bronchoscopy should be the first step in the diagnostic course [11]. Flexible bronchoscopy is readily available, safe and a well tolerated procedure allowing several modalities of tissue sampling from different anatomic sites [2, 12]. TBB has been suggested to be the method of preference with yields ranging from 40-90% in case series [13-15]. EBB have an added value, even without apparent endobronchial abnormalities [16]. The same holds for blind TBNA, especially when added to TBB [17-19]. Besides these procedures, bronchial washing is recommended for microbiological analysis while a bronchoalveolar lavage with CD4/CD8 counting is variable and less sensitive [20].

With this study, we found that when bronchoscopy is offered as a first line tool in a study population with a suspicion to have thoracic sarcoidosis, the overall diagnostic yield is 42% while the sensitivity for sarcoidosis is 45%. This is at the lower end of what has been reported before [2] and illustrates the erosion of diagnostic yield once a technique is widely implemented. A possible reason for that is all aforementioned studies were done in expert centres where specialized endoscopists investigated very selected patients. This largely differs with implementation studies where a variable degree of expertise is present and where some of the procedures even did not or only partially took place because of a variety of patient, endoscopist or technical related reasons. In addition, it requires a large expertise to perform all biopsy modalities during a single bronchoscopy session. It is also remarkable to note that only 76 patients had TBB, the same amount had EBB and 19 had TBNA. This shows that endoscopists not always feel comfortable to perform some of the biopsy procedures. Nevertheless, when we analysed per-protocol the yield of TBB in the current study, we found that in 72% of the procedures a definite diagnosis was obtained. For sarcoidosis only, the sensitivity of TBB was 62%. This is a value comparable to what has been published before

[12] [15]. As reported recently bys, we also did not find a relationship of TBB yield and the stage of sarcoidosis on chest X-ray [15]. The safety figures of bronchoscopy appeared very acceptable with only one case of pneumothorax cured with manual aspiration.

When a bronchoscopy does not result in a definite diagnosis, and when no other accessible sites for biopsy are identified, the guidelines suggest that a surgical biopsy may be indicated if there are readily identified abnormalities by radiology [11]. The finding of mediastinal adenopathies should therefore prompt biopsy by mediastinoscopy before video-assisted thoracoscopy or even open lung biopsy [21]. Although these procedures have a superior yield, they are costly and have a comorbidity that cannot be denied. Given the above data obtained with bronchoscopy, it is clear that in daily practice, new tools that could provide a definite diagnosis in a minimally invasive way are very welcomed.

EUS-FNA and EBUS-TBNA are minimally invasive out-patient techniques that have shown good test characteristics in lung cancer staging [22, 23] and have been recommended in the guidelines [24, 25]. By consequence, these techniques are also getting implemented in non-academic hospitals. Up to now, few series have shown that EUS-FNA and EBUS-TBNA can be used to demonstrate sarcoidosis [6-10] in up to 80-90% of highly selected cases. However what remains unknown is their value after a non-diagnostic bronchoscopy procedure.

We found that endoscopic ultrasound performed after a negative bronchoscopy provided a definite diagnosis in 59% of the patients in whom otherwise a surgical procedure would have been considered. The sensitivity to diagnose sarcoidosis was 71%. These figures are lower than what has been reported in the series where EUS-FNA or EBUS-TBNA were evaluated mainly as a first line tool to diagnose sarcoidosis [6-10]. The reasons for that are probably comparable to the reasons discussed for the yield of bronchoscopy in an implementation setting. Our calculation also takes into account that not all patients effectively had endoscopic ultrasound because of a variety of reasons such as refusal for a second endoscopy. When applying the per-protocol analysis, a sensitivity of endoscopic ultrasound to diagnose sarcoidosis after a negative bronchoscopy of 77% is found. Recently, it was shown that EBUS-TBNA had a 30% higher yield to find sarcoidosis as compared to blind TBNA [26]. Although calculated in a subgroup, we found that EBUS-TBNA after a false negative blind TBNA also increases the yield with 30%. This indicates that a preceding negative blind TBNA is not a reason to skip E(B)US in patients with presumed sarcoidosis.

The overall strategy, where patients with sarcoidosis are investigated first with bronchoscopy and E(B)US only if the former did not yield the diagnosis, results in an overall sensitivity of 84% representing an absolute increase of 39% above the yield of bronchoscopy. In the current study, the majority of the endoscopic ultrasound procedures were performed under mild sedation allowing the patient to leave the hospital after a short observation. Although the safety of endoscopic ultrasound has been described mainly in lung cancer populations, we also noted in this series no serious complications. We therefore conclude that the algorithm used here is valuable, safe and useful for daily practice.

Some notes can be considered upon these data. First, we pursued final histopathological diagnosis in all our patients, although we ended up with 11 patients (8%) in whom this was not achieved. On the other hand, this figure is probably very reasonable taking into account the study population (mainly patients with benign diseases) and the fact this is an implementation trial. Nevertheless, it could be there were patients with sarcoidosis that were left undetected. Second, it should be noted that the presence of non-caseating epitheloid granulomas without necrosis is not per se diagnostic for sarcoidosis. The diagnosis can only be made by an integration of the clinicoradiological picture, the histological data and an exclusion of other identifiable causes of granulomatous diseases [1, 11]. For example, sarcoid like inflammation in lymph nodes nearby lymphomas or carcinomas [27], or in the context of histoplasmosis or tuberculosis can be misdiagnosed as sarcoidosis. On the other hand; histoplasmosis is virtually non existent in Northern Europe, and the currently applied methods showed to be sensitive to diagnose mycobacterial disease making the chance of misdiagnosis probably very low. Finally, the current data do not formally answer the question: should we continue to do a bronchoscopy or should we better do or refer for immediate endoscopic ultrasound when thoracic sarcoidosis is suspected? The only way to find out is to perform a randomized controlled trial with a direct comparison between these. When thinking about this, one should however always remind that bronchoscopy is cheap and readily available because it is routinely taught to all chest physicians, which is not the case for endoscopic ultrasound.

In conclusion, we propose a high yield and safe diagnostic algorithm for patients with thoracic sarcoidosis requiring tissue confirmation, stating that they are first investigated with a bronchoscopy followed by endoscopic ultrasound only in those cases where no definite diagnosis was obtained.

Figure 1 – Procedures performed in the study population

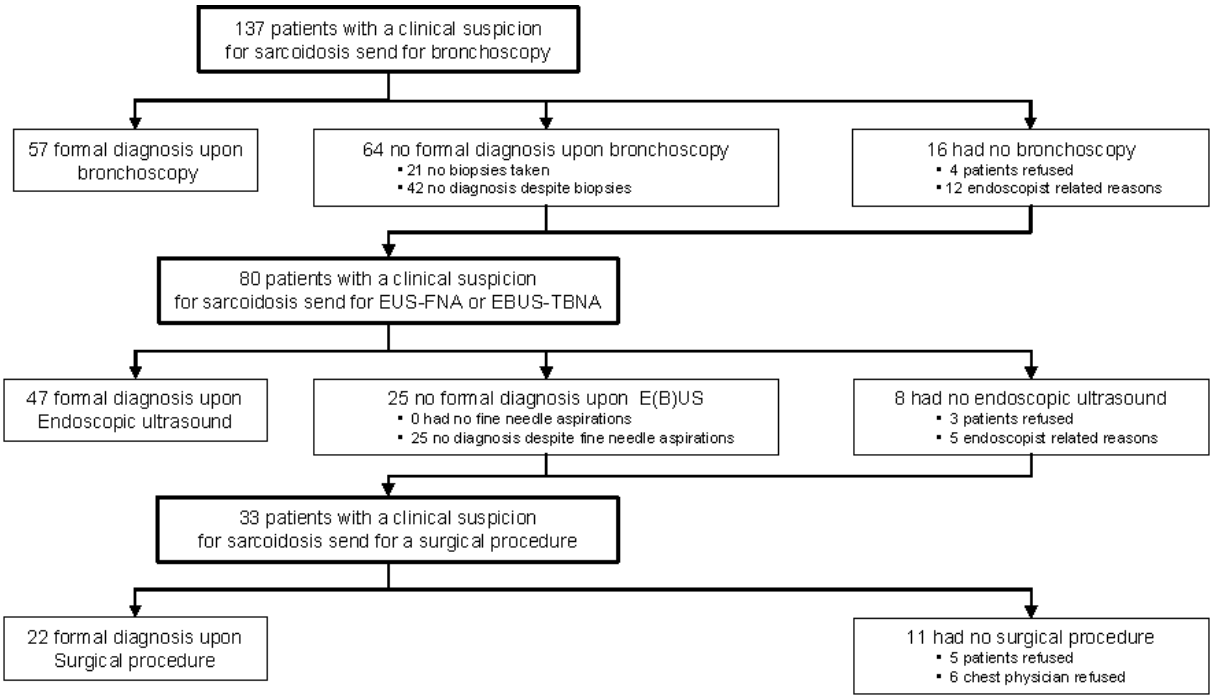

Table 1 - Demographic characteristics of the study population

Number of patients, n	137
Median age, y	43
Gender, n (%)	
Male	92 (67)
Female	45 (33)
Smoking History, n (%)	
Never	88 (65%)
Current	21 (15%)
Ex-smoker	27 (20%)
Pulmonary function test, body box (mean % predicted; 95%CI)	
TLC	94 (91-96)
VC	94 (91-97)
FEV_1/VC (%; 95%CI)	78 (76-80)
FEV_1	90 (87/93)
DLCO	81 (78-84)
RX stage, n (%)	
0	7 (5%)
I	75 (55%)
II	32 (23%)
III	22 (16%)
IV	1 (1%)
CT characteristics, n	
Enlarged LN (N/Y)	7 / 130
ILD (N/Y)	66 / 71

Table 2 - Final pathology diagnosis of the mediastinal lymph nodes in the study population

Diagnosis	n (%)
Sarcoidosis	115 (84%)
Tuberculosis	5 (4%)
Other diseases	6 (4%)
No definite pathological diagnosis	11 (8%)

Other diseases include extrinsic allergic alveolitis (n=2); lymphangitis carcinomatosa (n=1); pneumoconiosis (n=1) and aspecific lymphadenitis shown with surgical biopsies (n=2). No definite pathological diagnosis when bronchoscopy or E(B)US did not yield a diagnosis different from "unrepresentative or benign lymphadenitis" and which was not confirmed by a surgical biopsy.

Table 3 - Procedural details of bronchoscopy

Bronchoscopy (n=121)	
- Anaesthesia	
□ Local	91 (75%)
□ Local + Sedation	30 (25%)
□ General	0 (0%)
- Biopsy modus	
□ TBNA	26 (21%)
□ EBB	76 (63%)
□ TBB	76 (63%)
□ No biopsies taken	21 (17%)
- Diagnosis obtained by*	
□ TBNA	8 (14%)
□ EBB	15 (26%)
□ TBB	41 (72%)
□ Wash and microbiology	2 (4%)
- Complications	
□ Bleeding (minor)	5 (4%)
□ Intolerance & Stop	3 (2%)
□ Pneumothorax	1 (1%)
□ Other	3 (2%)

* There was a definite diagnosis (this includes sarcoidosis and other diagnoses) obtained by bronchoscopy in 57 patients; this was by means of a unique method in 49 patients while in 8; a diagnosis was obtained by a combination of methods.

Table 4 - Procedural details of endoscopic ultrasound

Endoscopic Ultrasound (n=72)	
- Anaesthesia	
□ Local	2 (3%)
□ Local + Sedation	63 (88%)
□ General	7 (10%)
- Type of endoscopic ultrasound	
□ EUS-FNA	18 (25%)
□ EBUS-TBNA	54 (75%)
- Biopsy zone	
□ Mediastinal LN	59 (82%)
□ Hilar LN	4 (6%)
□ Mediastinal + Hilar LN	9 (13%)
- Diagnosis obtained by*	
□ EUS-FNA	17/18 (94%)
□ EBUS-TBNA	30/54 (56%)
- Complications	
□ None	72 (100%)

***** The chance to obtain a definite diagnosis (this includes sarcoidosis and other diagnoses) was significantly higher with EUS-FNA as compared to EBUS-TBNA (Fisher's Exact Test; p=0.03).

Table 5 – Test characteristics of bronchoscopy and endoscopic ultrasound for making the diagnosis of sarcoidosis

Yield of bronchoscopy	# diagnosed	% (95% CI)
□ Intention to diagnose	52/115	45 (35-94)
□ Per-protocol (1)	52/100	52 (41-62)
□ Per-protocol (2)	52/84	62 (50-72)
Yield of endoscopic ultrasound [E(B)US]		
□ Intention to diagnose	45/63	71 (58-82)
□ Per-protocol overall (3)	45/58	77 (64-87)
□ Per-protocol EUS (4)	16/17	94 (91-99)
□ Per-protocol EBUS (5)	29/41	71 (54-83)
□ Per-protocol after negative bronchoscopy (6)	33/43	77 (61-88)
Yield of bronchoscopy plus E(B)US		
□ Intention to diagnose	97/115	84 (76-90)

(1) For the sarcoidosis patients who effectively did undergo a bronchoscopy.
(2) For the sarcoidosis patients in whom during bronchoscopy minimally one biopsy was taken (either EBB or TBB or TBNA or any combination). The relative sensitivities to diagnose sarcoidosis were 62% (95%CI: 48-74) for TBB; 24% (95%CI: 14-36) for EBB and 35% (95%CI: 16-57) for blind TBNA.
(3) For the sarcoidosis patients who effectively did undergo endoscopic ultrasound.
(4) For the sarcoidosis patients undergoing EUS-FNA.
(5) For the sarcoidosis patients undergoing EBUS-TBNA.
(6) For the sarcoidosis patients who effectively underwent a bronchoscopy and endoscopic ultrasound.

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