Respiratory Medicine (2012) **106**, 883–892

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: A systematic review and meta-analysis

Ritesh Agarwal, Arjun Srinivasan, Ashutosh N. Aggarwal, Dheeraj Gupta*

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Received 13 January 2012; accepted 22 February 2012
Available online 13 March 2012

KEYWORDS
Sarcoidosis;
Endobronchial ultrasound;
EBUS;
Transbronchial needle aspiration;
TBNA;
Meta-analysis

Summary
Background and aim: Real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive technique for diagnosis of mediastinal lymphadenopathy. Although most studies have reported the utility of EBUS-TBNA in malignancy, its use has been extended to benign conditions including sarcoidosis. Herein, we perform a systematic review and meta-analysis of studies reporting the diagnostic yield and safety of EBUS-TBNA in sarcoidosis.
Methods: We searched the PubMed and EmBase databases for relevant studies published from 2004 to 2011, and included studies that have reported the diagnostic yield of EBUS-TBNA in sarcoidosis. The quality of studies was assessed using the QualSyst tool. We calculated the proportions with 95% confidence interval (CI) to assess the diagnostic yield of EBUS-TBNA in individual studies and then pooled the results using a random effects model. Heterogeneity was assessed using the I^2 and Cochran-Q tests while publication bias was assessed using both graphical and statistical methods.
Results: Our search yielded 15 studies (553 patients of sarcoidosis). The diagnostic yield of EBUS-TBNA ranged from 54 to 93% with the pooled diagnostic accuracy being 79% (95% CI, 71–86%) by the random effects model. The yield was not statistically different in studies employing on-site cytological evaluation (80.1%) vs. those without (81.3%). However, the diagnostic yield was significantly higher in prospective studies (83.9%) vs. the retrospective studies (74.3%). Only five minor complications were reported in 553 patients. There was evidence of heterogeneity and publication bias.
Conclusions: EBUS-TBNA is a safe and efficacious procedure in the diagnosis of sarcoidosis, and should be routinely employed wherever available.

* Corresponding author. Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh 160012, India. Tel.: +91 172 2756823; fax: +91 172 2748215.
E-mail address: dheeraj1910@gmail.com (D. Gupta).

0954-6111/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2012.02.014

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that commonly presents with bilateral hilar adenopathy, pulmonary infiltrates, ocular and skin lesions. The diagnosis is established in presence of compatible clinicoradiographic findings and histologic evidence of noncaseating epithelioid cell granulomas after exclusion of other known causes for granulomatous inflammation.[1] As the lung and mediastinal lymph nodes are most often affected in sarcoidosis, bronchoscopic techniques are often employed for demonstration of noncaseating granulomas. Bronchoscopic lung biopsy (BLB), endobronchial biopsy (EBB) and transbronchial needle aspiration (TBNA) are currently the most commonly used methods for demonstration of granuloma in sarcoidosis. Endobronchial ultrasound-guided TBNA (EBUS-TBNA) is a minimally invasive technique for sampling the hilar/mediastinal lymph nodes, and can improve the diagnostic yield by direct visualization of lymph node beyond the tracheobronchial wall thereby allowing real-time sampling of the lymph nodes.[2]

Krasnik et al. first reported the utility of convex probe EBUS-TBNA in sampling mediastinal nodes in 2003.[3] With time, the diagnostic yield of EBUS-TBNA has been further enhanced by rapid on-site cytological evaluation (ROSE), increasing the number of lymph nodes sampled, increase in the number of aspirates taken per node, and use of a larger bore 21G needle. Although EBUS-TBNA was primarily intended for minimally invasive staging of bronchogenic carcinoma, its use has been extended in diagnosis of lymphoma and benign conditions like tuberculosis and sarcoidosis.[4–6] Several systematic reviews and meta-analyses have reported the diagnostic performance of EBUS-TBNA but most of these reviews have primarily focused on patients with malignancy.[7–11]

Sarcoidosis is a common pulmonary disorder worldwide. Demonstration of noncaseating granulomas and exclusion of other causes of granulomatous inflammation is essential particularly in countries with high prevalence of tuberculosis. We had previously reported the diagnostic yield of BLB and the additive yield of EBB in patients with sarcoidosis.[12] We have also recently reported the diagnostic yield of TBNA in patients with mediastinal lymphadenopathy of diverse etiologies including sarcoidosis.[13] In this study, we perform a systematic review and meta-analysis to define the diagnostic efficacy and safety of convex probe EBUS-TBNA in patients with sarcoidosis.

Material and methods

Search strategy

We first searched the literature for available systematic review that had reported the diagnostic efficacy of EBUS-TBNA in sarcoidosis. No systematic reviews were found. All the authors independently searched two computer databases PubMed and EmBase for relevant studies published from 2004 to 2011 describing the diagnostic value of EBUS-TBNA in patients with sarcoidosis using the following search terms: ("ebus" OR "ebus tbna" OR "tbna" OR "endobronchial ultrasound" OR "endobronchial ultrasonography" OR "endobronchial ultrasound-guided" OR "endoscopic ultrasound" OR "transbronchial needle aspiration") AND sarcoidosis; and, ("ebus" OR "endobronchial ultrasound" OR "endobronchial ultrasonography" OR "endobronchial ultrasound-guided" OR "endoscopic ultrasound") AND ("tbna" OR "transbronchial needle aspiration"). We reviewed the reference lists of primary studies, reviews, and editorials. In addition, we reviewed our personal files. We excluded the following studies: (a) abstracts, editorials, reviews and case reports; (b) studies describing diagnostic accuracy of TBNA or endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or radial probe EBUS-TBNA in sarcoidosis; (c) studies describing EBUS-TBNA in $\leq$10 patients with sarcoidosis; (d) studies in which the denominator number i.e. number of patients with final diagnosis of sarcoidosis (granulomas on EBUS-TBNA or demonstration of granulomas from any site by any methodology AND a clinical picture deemed by the investigator to be compatible with sarcoidosis) was not reported. The criteria for conclusive diagnosis by EBUS-TBNA in sarcoidosis was lymph node aspirates showing epithelioid, noncaseating granulomas without necrosis OR epithelioid and giant cells AND absence of identifiable malignancy, lymphoma, or infection (i.e. tuberculosis or fungal disease).

Initial review of studies

The initial database created from the electronic searches was compiled and all duplicate citations were eliminated. Two reviewers (RA and AS) screened these citations, without blinding, by title and abstract review to capture the relevant studies. Any disagreement was resolved by discussion between the authors. This database was then screened again to include only primary articles, and the full text of each citation was obtained and reviewed. Studies were eligible for inclusion if they reported the diagnostic yield of convex probe EBUS-TBNA in patients with clinical suspicion of sarcoidosis.

Data abstraction

Data was recorded on a standard data extraction form. The following items were extracted: (a) publication details (title; authors; and other citation details) including the geographic location of the study; (b) type of study (prospective or retrospective); (c) stage of sarcoidosis and lymph node size on CT chest; (d) type of sedation used, diameter of EBUS-TBNA needle, stations sampled, size of lymph node on EBUS, number of lymph node aspirated and/or passes made through EBUS, availability of on-site cytology; (e) diagnostic yield of EBUS-TBNA in sarcoidosis wherein the numerator was the diagnosis of sarcoidosis with EBUS-TBNA, and the denominator was number of patients with confirmed sarcoidosis; and, (f) complications associated with the procedure.

Assessment of study quality

The quality and validity of each article included in this meta-analysis was assessed using the QualSyst tool for qualitative studies.[14] This tool consists of 10 questions with

score from 0 to 2 with the maximum total score being 20. Each study was independently evaluated by two authors (RA, AS) for the stated criteria. Weighted Cohen's kappa (κ) co-efficient was used to determine the inter-observer agreement for selection of studies.

Statistical analysis

The statistical software package (StatsDirect, version 2.7.8 for MS Windows; StatsDirect Ltd; Cheshire, UK [http://www.statsdirect.com]) was used to perform all the statistical analysis.

Determination of the pooled effect

We calculated the diagnostic yield of EBUS-TBNA by calculating proportion with 95% confidence intervals (CI) for each study and then pooled the data to derive a pooled proportion with 95% CI. For the purpose of proportion meta-analysis, the proportions were first turned into a quantity (the Freeman-Tukey variant of the arcsine square root transformed proportion) suitable for the random effects summary.[15,16] The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using DerSimonian weights for the random effects model[17] in the presence of significant heterogeneity.

Assessment of heterogeneity

The impact of heterogeneity on the pooled estimates of the outcome was assessed using the Cochran Q statistic and I^2 test (measures the extent of inconsistency among the results of the studies). An I^2 value $\geq$50% indicates significant heterogeneity.[18] As the Cochran Q test has a low sensitivity for detecting heterogeneity, a p value <0.1 was considered to be significant for the presence of statistical heterogeneity.[19]

Sensitivity/subgroup analysis

We planned sensitivity analysis a priori by using subgroup analysis of prospective vs. retrospective studies due to the limitations associated with retrospective studies, and the occurrence of errors associated with the retrieval of information retrospectively from databases. A subgroup analysis was also planned by partitioning the studies based on the utilization of ROSE for histological diagnosis.

Assessment of publication bias

The presence of publication bias was evaluated using the Begg's funnel plot,[20] which is a measure of the proportion (in the *X*-axis) against the standard error of the proportion (in the *Y*-axis). Each open circle represents an individual study in the meta-analysis. The line in the center indicates the pooled proportion and the other two lines indicate the 95% CI. The proportion estimates from smaller studies are expected to be scattered above and below the summary estimate, producing a triangular or funnel shape, if there is no publication bias.

Publication bias was also investigated using three statistical tests: (a.) Egger test: detects asymmetry of the funnel plot[21]; (b.) Harbord's test: similar to Egger's test but uses a modified linear regression method[22]; and, (c.) Begg and Mazumdar's test: tests the interdependence of variance and effect size using a rank correlation method.[23]

An Institutional review board clearance was not required for this study as this was a meta-analysis of published studies.

Results

Our initial database search retrieved a total of 504 citations (Fig. 1) of which 15 studies finally met our inclusion criteria.[24–38] Of these, nine studies were prospective[24–26,29,31–34,37] and six were retrospective (Table 1). These 15 studies were published from across the globe and included 553 confirmed patients of sarcoidosis. Eight studies included stage I and II patients of sarcoidosis,[25,26,28–31,37,38] two studies[24,33] included all stages of sarcoidosis while the stage was not reported in five studies (Table 1). The procedure was performed under conscious sedation without any artificial airway in 12 studies (Table 2). Two studies used conscious sedation with either endotracheal tube or laryngeal mask[25,38] while one study used general anesthesia with laryngeal mask.[30] Majority of the studies had sampled the paratracheal, subcarinal, hilar and interlobar nodes, and all the studies had used the 22G dedicated EBUS-TBNA needle. The lymph node size on CT and EBUS, the number of lymph nodes aspirated and the number of aspirates per patient is shown in Table 2. Five studies employed additional rapid on-site cytology,[24,26,28,36,38] and two studies employed liquid-based cytological technique for diagnosis.[30,35] The quality of studies was generally good (Table 3) with the median (IQR) score being 18 (18–19). The inter-observer agreement for scoring the quality of studies was good. (Cohen's $\kappa = 0.78$).

The diagnostic yield of EBUS-TBNA in sarcoidosis ranged from 54 to 93% with the pooled accuracy being 79% (95% CI, 71–86%) by the random effects model (Fig. 2). The yield was not statistically different ($p = 0.66$) in studies employing on-site cytological evaluation (165/206; 80.1%) vs. those without (282/347; 81.3%). The diagnostic yield was higher in prospective studies (314/374; 83.9%) compared to retrospective studies (133/179; 74.3%), and this difference was statistically significant ($p = 0.006$). Only five minor complications (minimal pneumothorax, minor bleeding, airway edema/hypoxemia [$n = 2$], prolonged cough) were reported in 532 patients.[24,34,36,37]

There was clinical heterogeneity reflected in the nature of the study (prospective vs. retrospective), inclusion of patients with various stages, variation in the number of passes or lymph nodes sampled, utilization of on-site cytology and use of different cytological techniques (Tables 1and 2). There was also significant statistical heterogeneity (I^2 79.7; [95% CI, 65.9–86.3%]; Cochran Q statistic 69.03, $p < 0.0001$). There was evidence of publication bias on visual examination of the funnel plot (Fig. 3). There was also evidence of publication bias on some (Egger: bias $= -3.22$, $p < 0.0008$) but not all statistical tests (Begg-Mazumdar: Kendall's tau $= -0.371$, $p = 0.05$; Harbord-Egger: bias $= -2.89$, $p = 0.19$).

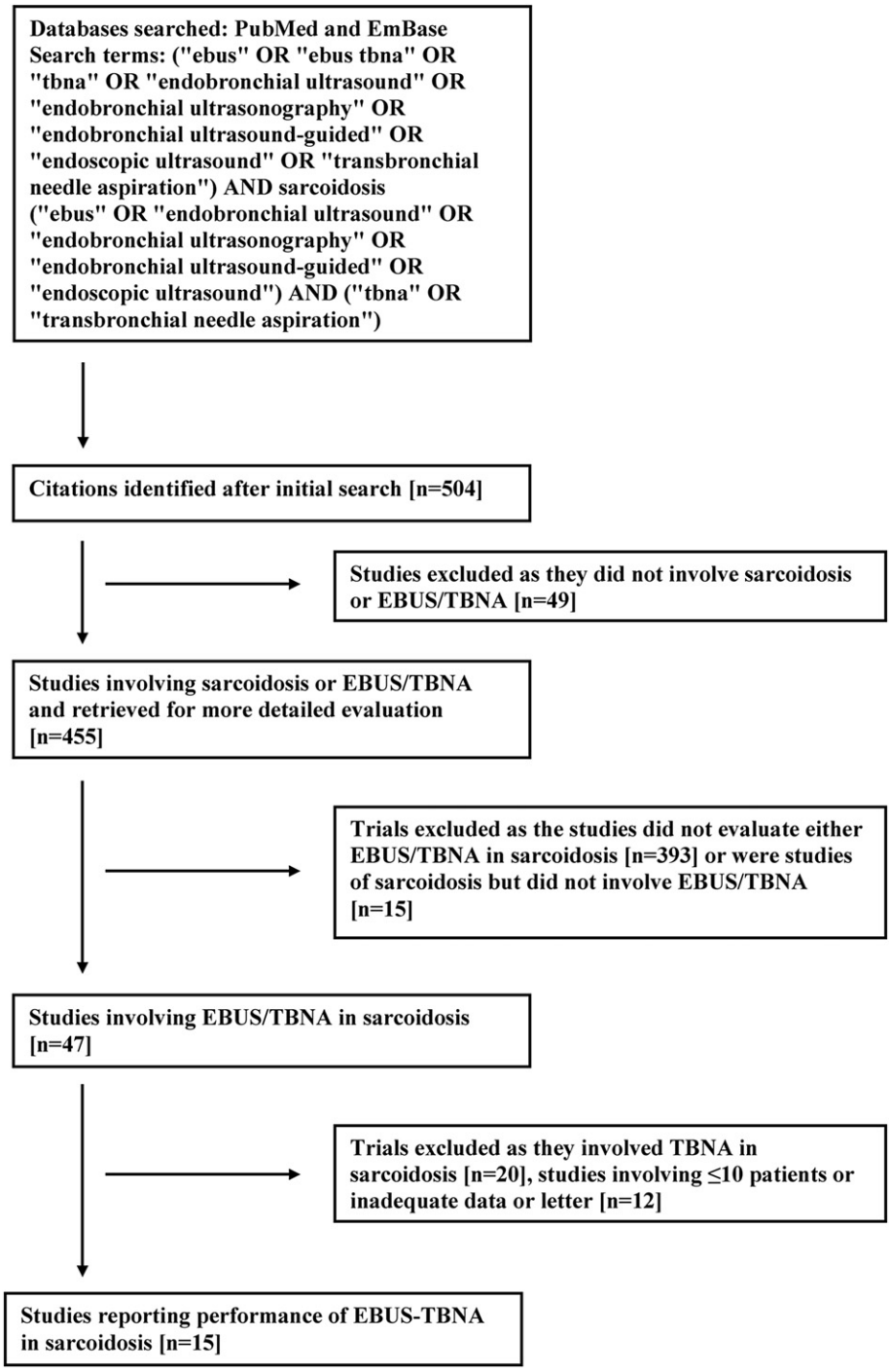

Figure 1 Citation selection process for the systematic review.

Sensitivity analysis

A subgroup analysis was performed and only prospective studies were included after which there was no significant change in heterogeneity (I^2 84%; Cochran Q statistic 50.1 [$p < 0.0001$]) or publication bias (Egger: bias $= -3.01$, $p < 0.02$; Begg-Mazumdar: Kendall's tau $= -0.33$, $p = 0.18$; Harbord-Egger: bias $= -2.81$, $p = 0.38$). Similarly there was no change in heterogeneity (I^2 79.4%; Cochran Q statistic 19.4 [$p = 0.0007$]) and publication bias (Egger: bias $= -5.46$, $p = 0.01$; Begg-Mazumdar: Kendall's tau $= -1$, $p < 0.0001$; Harbord-Egger: bias $= -13.56$, $p = 0.03$) after inclusion of studies employing ROSE.

Discussion

The result of this meta-analysis suggests an excellent overall diagnostic yield (79%) of EBUS-TBNA in sarcoidosis suggesting that this technique should be routinely

Table 1 Demographic characteristics of patients in studies reporting the performance of EBUS-TBNA in sarcoidosis.

Author (year)	Geographic locale	Type of study	Age (in years)	Patients included	Stage of sarcoidosis
Garwood (2007)[24]	USA	Prospective	19–79 (range)	48	0–4
Oki (2007)[25]	Japan	Prospective	27–73 (range)	14	1,2
Wong (2007)[26]	Germany, Japan	Prospective	45 (mean)	61	1,2
Szlubowski (2008)[27]	Poland	Retrospective	NA	21	NA
Nakajima (2009)[28]	Japan	Retrospective	48.2 (median)	32	1,2
Tremblay (2009)[29]	Canada	Prospective	39.5 (mean)	24	1,2
Eckardt (2010)[30]	Denmark	Retrospective	53 (median)	43	1,2
Kim (2010)[31]	Korea	Prospective	45.1 (mean)	25	1,2
Tian (2010)[32]	China	Prospective	52.3 (mean, all patients)[a]	16	NA
Tournoy (2010)[33]	Belgium	Prospective	43 (median, all patients)[a]	54	0–4
Cetinkaya (2011)[34]	Turkey	Prospective	50.2 (mean, all patients)[a]	105	NA
Delattre (2011)[35]	France	Retrospective	21–79 (range)	18	NA
Jernlas (2011)[36]	Sweden	Retrospective	63 (mean, all patients)[a]	28	NA
Navani (2011)[37]	United kingdom	Prospective	19–68 (range)	27	1,2
Plit (2011)[38]	Australia	Retrospective	42 (mean)	37	1,2

NA – not available.
[a] All patients of mediastinal lymphadenopathy including the subgroup of patients with sarcoidosis.

employed in diagnosis of sarcoidosis wherever available. The analysis includes good quality studies involving more than 550 confirmed predominantly stage I and II patients of sarcoidosis. The lower paratracheal and subcarinal lymph nodes (stations 4 and 7) were the most frequently accessed with a very low rate of complications.

The diagnosis of sarcoidosis is incomplete without the demonstration of noncaseating granuloma.[1] Serum angiotensin converting enzyme levels are often elevated in sarcoidosis, but are non-specific as several common conditions like tuberculosis and diabetes mellitus also show similar elevation.[39,40] Gallium-67 scan findings of panda or

Table 2 Details of the EBUS-TBNA procedure in various studies reporting the performance of EBUS-TBNA in sarcoidosis.

Author (year)	Node size on CT (mm)	Sedation	Stations examined	Node size on EBUS (mm)	Number of lymph nodes	Number of passes	ROSE
Garwood (2007)[24]	>10 mm	Conscious sedation	4,7,10,11	4–40 (median 16)	NA	4 (majority)	Yes
Oki (2007)[25]	>10 mm	Conscious sedation via endotracheal tube	4,7,10,11	11–38	23 in 14 patients	NA	No
Wong (2007)[26]	>10 mm	Conscious sedation	2,4,7,10,11	7–37	77 in 64 patients	NA	Yes
Szlubowski (2008)[27]	>10 mm	Conscious sedation	2,3,4,7,10,11	7-42 (total)	30 in 21 patients	NA	No
Nakajima (2009)[28]	>10 mm	Conscious sedation	4,7,10	7.3–30	51 in 38	3 passes per node	Yes
Tremblay (2009)[29]	>10 mm	Conscious sedation	As appropriate	NA	4 (mean)	10.1 (mean per patient)	No
Eckardt (2010)[30]	NA	GA via LMA	2,3,4,7,10,11	NA	NA	2 per node	No
Kim (2010)[31]	NA	Conscious sedation	4,7,10,11	5–40	50 in 25	2 per node	No
Tian (2010)[32]	NA	Conscious sedation	2,3,4,7,10,11	NA	NA	2 per node	No
Tournoy (2010)[33]	>10 mm	Conscious sedation	4,7,10,11	NA	NA	NA	No
Cetinkaya (2011)[34]	>10 mm	Conscious sedation	2,4,7,10	NA	1–13 (mean 4.6)	2.6 per node	No
Delattre (2011)[35]	NA	Conscious sedation	As appropriate	NA	NA	3 per node	No
Jernlas (2011)[36]	>10 mm	Conscious sedation	As appropriate	NA	NA	NA	Yes
Navani (2011)[37]	>10 mm	Conscious sedation	4,7,10	10–45 (mean 24)	NA	4 per node	No
Plit (2011)[38]	NA	Conscious sedation via LMA	4,7	8–36 (median 16)	61 in 40 patients	1–3 per node	Yes

CT – computed tomography.
GA – general anesthesia.
LMA – laryngeal mask airway.
NA – not available.

Table 3 QualSyst tool for quality assessment of the included studies.

	Garwood (2007)	Oki (2007)	Wong (2007)	Szlubowski (2008)	Nakajima (2009)	Tremblay (2009)	Eckardt (2010)	Kim (2010)	Tian (2010)	Tournoy (2010)	Cetinkaya (2011)	Delattre (2011)	Jernas (2011)	Navani (2011)	Plit (2011)
Question/objective sufficiently described?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Study design evident and appropriate?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Context for the study clear?	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2
Connection to a wider body of knowledge?	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2
Sampling strategy described, relevant and justified?	2	2	2	1	1	2	1	2	2	1	2	2	1	2	2
Data collection methods clearly described?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Data analysis clearly described?	2	2	2	2	1	1	2	2	1	2	2	2	1	1	2
Use of verification procedure(s) to establish credibility?	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Conclusions supported by the results?	2	2	2	1	2	2	2	1	1	2	2	1	2	2	1
Reflexivity of the account?	1	2	1	2	2	2	1	1	1	1	1	1	2	1	1
Total score	18	19	19	18	18	19	18	18	16	18	19	18	18	18	18

lambda sign can support the diagnosis but are seen only in limited patients and cannot replace histology.[41,42] Over the last two decades, bronchoscopic techniques are most often used to confirm the diagnosis of sarcoidosis. The bronchoalveolar lavage fluid lymphocyte marker specifically the CD4/CD8 ratio (>3.5) has been used as an adjunct to support the diagnosis of sarcoidosis. Although a high CD4/CD8 ratio supports the diagnosis of sarcoidosis, its distribution is variable and is not a substitute for histology.[43] BLB is the most commonly performed procedure in establishing a diagnosis of sarcoidosis.[1] However, the yield of BLB depends not only on the experience of operator but also on the stage of sarcoidosis (higher in stage II than I),[44] and the number of biopsies obtained (optimal at 8–10).[45,46] The diagnostic yield of BLB ranges between 40 and 90%,[45,47] and carries a risk of pneumothorax (2%) and hemoptysis (5%).[48] EBB can add to the diagnostic yield of BLB especially if the mucosa appears abnormal, although 30% of normal appearing mucosa can also show evidence of granuloma on histology.[12,49] Conventional TBNA alone has a variable success ranging from 42 to 76%, with a higher yield in stage I disease.[48,50,51] However, the steep learning curve and variable yield has lured few pulmonologists to adopt TBNA as a routine procedure.[52,53] Combination of modalities such as conventional TBNA, EBB and TBLB can increase the yield to 70–90%,[13,48,54] but is often associated with increase in duration of procedure and complications. EUS-FNA has shown promise in diagnosis of sarcoidosis with studies reporting sensitivity of 89–100% and specificity of 94–96%.[55–57] The limitations of EUS-FNA include inability to perform additional procedures like BLB or EBB at the same time and difficulty in accessing paratracheal, hilar and interlobar (stations 2, 4, 10, 11) especially on the right side given the fact that these are the nodes that are usually enlarged in sarcoidosis.

Mediastinoscopy is currently the 'gold' standard for sampling mediastinal lymph nodes.[58] However, the procedure is not routinely available at all centers, and is associated with major morbidity/mortality ranging from 1.4 to 2.3% depending on the experience of the operator.[59] The diagnostic yield ranges between 82 and 97% for undiagnosed mediastinal adenopathy,[60–62] with the major caveat being that not all mediastinal nodes can be accessed with this technique. Mediastinoscopy however is the final resort if all other techniques fail. There is scarce evidence regarding computed tomography (CT)-guided transthoracic needle aspiration (TTNA) and/or biopsy of the mediastinal nodes for diagnosis of sarcoidosis. Moreover, there is a high risk of complications especially pneumothorax with CT-guided TTNA. Klein et al. recently reported their 10 year single center experience in 41 patients of sarcoidosis. The diagnostic yield was 78% with cytology and 96% with core biopsy, however they also reported pneumothorax in 22% of patients.[63]

Most studies included in this meta-analysis have reported a diagnostic yield around 80% for EBUS-TBNA in sarcoidosis.[24–27,29,31,34,35,37,38] According to the results of this study, the diagnostic yield of EBUS-TBNA surpasses every other bronchoscopic investigation in isolation. Moreover, combining EBUS-TBNA with BLB and EBB would significantly add to the diagnostic yield, and would be able to achieve a diagnosis in majority of the cases. Of the

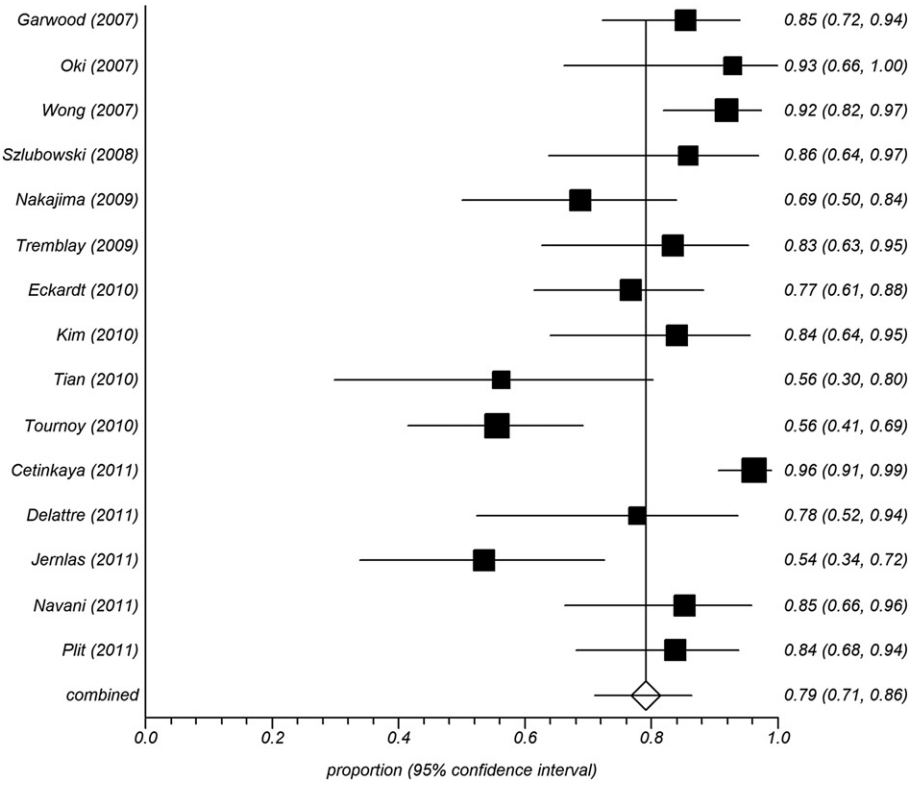

Figure 2 Diagnostic yield of EBUS-TBNA in patients with sarcoidosis (random effects model). The yield in individual studies is represented by a square (percentage) through which runs a horizontal line (95% confidence interval). The diamond at the bottom represents the pooled prevalence from the studies (79% [95% CI, 71—86%]).

studies reporting a lower yield, Jernlas et al. and Tian et al. have attributed their results to learning curve, diversity of diagnosis and referral bias.[32,36] Eckardt et al. and Tournoy et al. included only patients who remained undiagnosed despite usual bronchoscopic interventions and thus a subset of patients where the granuloma load was likely to have been less than usual.[30,33] Nakajima et al. reported a diagnostic yield on 91.4% however they had used the presence of epithelioid cells alone as criteria for diagnosis of sarcoid in 10 of the 32 cases thereby decreasing their actual yield to 69%.[28]

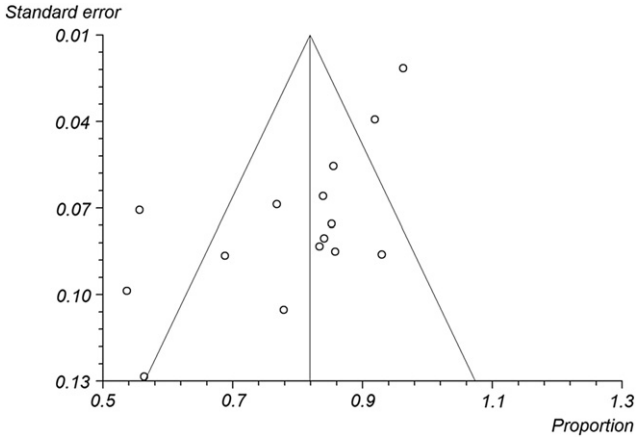

Figure 3 Funnel plot comparing proportion vs. the standard error of proportion. Open circles represent trials included in the meta-analysis. The line in the center indicates the summary proportion. The other lines represent the 95% confidence intervals. Asymmetry about the pooled line is consistent with the presence of publication bias.

Finally, the meta-analysis has certain limitations. There was presence of significant clinical and statistical heterogeneity in the studies evaluated although we used the random effects model for minimizing the effects of heterogeneity.[18] We also performed a sensitivity analyses to investigate the cause of heterogeneity by including only studies of prospective nature and those employing ROSE. The sensitivity analysis did not explain the statistical heterogeneity suggesting that other factors contributed to heterogeneity. The meta-analysis included studies from various centers with operators having differing levels of expertise in performing EBUS-TBNA which we believe is the prime contributor of heterogeneity in this analysis. Heterogeneity is the presence of variability among studies included in a systematic review and can be broadly classified as *clinical heterogeneity* (variability in the participants, interventions, and outcomes) or *methodological heterogeneity* (variations in trial design and quality) or *statistical heterogeneity* (variability in the treatment effects being evaluated in different trials). In fact, one can argue that in a meta-analysis heterogeneity is inevitable whether or not statistical tests detect them or not. The strength of this meta-analysis is the sample size (almost 550 patients with sarcoidosis), detailed extraction of data from

individual studies and the robust statistical methods applied in the analysis. Future studies on EBUS-TBNA in sarcoidosis should employ a uniform methodology with regards to the number of lymph nodes aspirated (at least two lymph node stations), the number of passes per lymph node (at least two passes per lymph node) and the use of consistent liquid-based cytology protocol.

Conclusions

In conclusion, the result of this study suggests a high diagnostic yield and safety of EBUS-TBNA in sarcoidosis, indicating that EBUS-TBNA should be routinely employed in the diagnosis of sarcoidosis wherever available.

Author contributions

RA — systematic review, meta-analysis, drafted and revised the manuscript

AS — systematic review, drafted and revised the manuscript

ANA — systematic review, drafted and revised the manuscript

DG — conceived the article, systematic review, drafted and revised the manuscript

DG — guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article

Conflict of interest statement

All authors do not have any conflict of interest.

Financial disclosure

None.

References

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *American Journal of Respiratory and Critical Care medicine* 1999;**160**:736—55.
2. Chin Jr R, McCain TW, Lucia MA, Cappellari JO, Adair NE, Lovato JF, et al. Transbronchial needle aspiration in diagnosing and staging lung cancer: how many aspirates are needed? *American Journal of Respiratory and Critical Care Medicine* 2002;**166**:377—81.
3. Krasnik M, Vilmann P, Larsen SS, Jacobsen GK. Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. *Thorax* 2003;**58**:1083—6.
4. Navani N, Molyneaux PL, Breen RA, Connell DW, Jepson A, Nankivell M, et al. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. *Thorax* 2011;**66**:889—93.
5. Ko HM, da Cunha Santos G, Darling G, Pierre A, Yasufuku K, Boerner SL, et al. Diagnosis and subclassification of lymphomas and non-neoplastic lesions involving mediastinal lymph nodes using endobronchial ultrasound-guided transbronchial needle aspiration. *Diagnostic Cytopathology* 2011.
6. Kennedy MP, Jimenez CA, Bruzzi JF, Mhatre AD, Lei X, Giles FJ, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. *Thorax* 2008;**63**: 360—5.
7. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *The Journal of Thoracic and Cardiovascular Surgery* 2011;**142**(6):1393—400 e1.
8. Yasufuku K, Nakajima T, Motoori K, Sekine Y, Shibuya K, Hiroshima K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006;**130**:710—8.
9. Holty JE, Kuschner WG, Gould MK. Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis. *Thorax* 2005;**60**:949—55.
10. Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *European Journal of Cancer (Oxford, England: 1990)* 2009;**45**:1389—96.
11. Varela-Lema L, Fernandez-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology* 2009;**33**:1156—64.
12. Gupta D, Mahendran C, Aggarwal AN, Joshi K, Jindal SK. Endobronchial vis a vis transbronchial involvement on fiberoptic bronchoscopy in sarcoidosis. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases: Official Journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders* 2001;**18**:91—2.
13. Khan A, Agarwal R, Aggarwal AN, Gupta N, Bal A, Singh N, et al. Blind transbronchial needle aspiration without an on-site cytopathologist: experience of 473 procedures. *The National Medical Journal of India* 2011;**24**:136—9.
14. Kmet LM, Lee RC, Cook LS. *Standard quality assessment criteria for evaluating primary research papers from a variety of fields*. Edmonton: AHFMR, www.ahfmr.ab.ca; 2004.
15. Freeman MF, Tukey JW. Transformations Related to the Angular and the square root. *The Annals of Mathematical Statistics* 1950;**21**:607—11.
16. Miller JJ. The Inverse of the Freeman-Tukey double arcsine transformation. *American Statistician* 1978;**32**:138.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177—88.
18. Deeks JJ, Higgins JPT, Altman DG. Analysing and presenting results [updated March 2004]. In: Alderson P, Green S, Higgins JPT, editors. *Cochrane reviewers' handbook*, vol. 422. Chichester, UK: John Wiley & Sons, Ltd; 2004. p. 68—139.
19. Fleiss JL. Analysis of data from multiclinic trials. *Controlled Clinical Trials* 1986;**7**:267—75.
20. Dear K, Begg C. An approach to assessing publication bias prior to performing a meta-analysis. *Statistical Science* 1992;**7**:237—45.
21. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 1997;**315**:629—34.
22. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**:3443—57.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**: 1088—101.

24. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. *Chest* 2007;**132**:1298—304.
25. Oki M, Saka H, Kitagawa C, Tanaka S, Shimokata T, Kawata Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. *Respirology (Carlton, Vic)* 2007;**12**:863—8.
26. Wong M, Yasufuku K, Nakajima T, Herth FJ, Sekine Y, Shibuya K, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology* 2007;**29**:1182—6.
27. Szlubowski A, Kuzdzal J, Pankowski J, Obrochta A, Soja J, Hauer J, et al. *Ultrasound guided transbronchial needle aspiration as a diagnostic tool for lung cancer and sarcoidosis]. Pneumonologia i alergologia polska: organ Polskiego Towarzystwa Ftyzjopneumonologicznego*, vol. 76. Polskiego Towarzystwa Alergologicznego, i Instytutu Gruzlicy i Chorob Pluc; 2008. p. 229—36.
28. Nakajima T, Yasufuku K, Kurosu K, Takiguchi Y, Fujiwara T, Chiyo M, et al. The role of EBUS-TBNA for the diagnosis of sarcoidosis — comparisons with other bronchoscopic diagnostic modalities. *Respiratory Medicine* 2009;**103**:1796—800.
29. Tremblay A, Stather DR, Maceachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. *Chest* 2009;**136**:340—6.
30. Eckardt J, Olsen KE, Jorgensen OD, Licht RB. Minimally invasive diagnosis of sarcoidosis by EBUS when conventional diagnostics fail. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases: Official Journal of WASOG/World Association of Sarcoidosis and Other Granulomatous Disorders* 2010;**27**:43—8.
31. Kim WY, Chang YJ, Lyu JW, Park YS, Jang SJ, Song JW, et al. Pulmonary sarcoidosis diagnosed by endobronchial ultrasound fine needle aspiration. [Korean]. *Tuberculosis Respiratory Diseases* 2010;**68**:267—72.
32. Tian Q, Chen LA, Wang HS, Zhu BH, Tian L, Yang Z, et al. Endobronchial ultrasound-guided transbronchial needle aspiration of undiagnosed mediastinal lymphadenopathy. *Chinese Medical Journal* 2010;**123**:2211—4.
33. Tournoy KG, Bolly A, Aerts JG, Pierard P, De Pauw R, Leduc D, et al. The value of endoscopic ultrasound after bronchoscopy to diagnose thoracic sarcoidosis. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology* 2010;**35**:1329—35.
34. Cetinkaya E, Gunluoglu G, Ozgul A, Gunluoglu MZ, Ozgul G, Seyhan EC, et al. Value of real-time endobronchial ultrasound-guided transbronchial needle aspiration. *Annals of Thoracic Medicine* 2011;**6**:77—81.
35. Delattre C, Fournier C, Bouchindhomme B, Renaud F, Escande F, Ramon P, et al. Endoscopic ultrasound guided transbronchial fine needle aspiration: a French Department of Pathology's 4-year experience. *Journal of Clinical Pathology* 2011.
36. Jernlas B, Nyberger H, Ek L, Ohman R, Jonsson P, Nozohoor S. Diagnostic yield and efficacy of endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal lymphadenopathy. *The Clinical Respiratory Journal* 2011.
37. Navani N, Booth HL, Kocjan G, Falzon M, Capitanio A, Brown JM, et al. Combination of endobronchial ultrasound-guided transbronchial needle aspiration with standard bronchoscopic techniques for the diagnosis of stage I and stage II pulmonary sarcoidosis. *Respirology (Carlton, Vic)* 2011;**16**:467—72.
38. Plit M, Pearson R, Da Costa J, Glanville AR. The diagnostic utility of endobronchial ultrasound-guided transbronchial needle aspiration compared to transbronchial and endobronchial biopsy for suspected sarcoidosis. *Internal Medicine Journal* 2011.
39. Lieberman J. Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. *The American Journal of Medicine* 1975;**59**:365—72.
40. Allen RK. A review of angiotensin converting enzyme in health and disease. *Sarcoidosis* 1991;**8**:95—100.
41. Israel HL, Albertine KH, Park CH, Patrick H. Whole-body gallium 67 scans. Role in diagnosis of sarcoidosis. *The American Review of Respiratory Disease* 1991;**144**:1182—6.
42. Sulavik SB, Spencer RP, Weed DA, Shapiro HR, Shiue ST, Castriotta RJ. Recognition of distinctive patterns of gallium-67 distribution in sarcoidosis. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine* 1990;**31**:1909—14.
43. Nagai S, Izumi T. Bronchoalveolar lavage. Still useful in diagnosing sarcoidosis? *Clinics in Chest Medicine* 1997;**18**:787—97.
44. British thoracic society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001;**56**(Suppl. 1):i1—21.
45. Gilman MJ, Wang KP. Transbronchial lung biopsy in sarcoidosis. An approach to determine the optimal number of biopsies. *The American Review of Respiratory Disease* 1980;**122**:721—4.
46. Roethe RA, Fuller PB, Byrd RB, Hafermann DR. Transbronchoscopic lung biopsy in sarcoidosis. Optimal number and sites for diagnosis. *Chest* 1980;**77**:400—2.
47. Koonitz CH, Joyner LR, Nelson RA. Transbronchial lung biopsy via the fiberoptic bronchoscope in sarcoidosis. *Annals of Internal Medicine* 1976;**85**:64—6.
48. Bilaceroglu S, Perim K, Gunel O, Cagirici U, Buyuksirin M. *Combining transbronchial aspiration with endobronchial and transbronchial biopsy in sarcoidosis*. In: *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace/Fondazione clinica del lavoro*, vol. 54. IRCCS [and] Istituto di clinica tisiologica e malattie apparato respiratorio, Universita di Napoli, Secondo ateneo; 1999. p. 217—23.
49. Shorr AF, Torrington KG, Hnatiuk OW. Endobronchial biopsy for sarcoidosis: a prospective study. *Chest* 2001;**120**:109—14.
50. Trisolini R, Lazzari Agli L, Cancellieri A, Poletti V, Tinelli C, Baruzzi G, et al. The value of flexible transbronchial needle aspiration in the diagnosis of stage I sarcoidosis. *Chest* 2003;**124**:2126—30.
51. Cetinkaya E, Yildiz P, Altin S, Yilmaz V. Diagnostic value of transbronchial needle aspiration by Wang 22-gauge cytology needle in intrathoracic lymphadenopathy. *Chest* 2004;**125**:527—31.
52. Haponik EF, Shure D. Underutilization of transbronchial needle aspiration: experiences of current pulmonary fellows. *Chest* 1997;**112**:251—3.
53. Dasgupta A, Mehta AC. Transbronchial needle aspiration. An underused diagnostic technique. *Clinics in Chest Medicine* 1999;**20**:39—51.
54. Trisolini R, Lazzari Agli L, Cancellieri A, Poletti V, Candoli P, Paioli D, et al. Transbronchial needle aspiration improves the diagnostic yield of bronchoscopy in sarcoidosis. *Sarcoidosis, Vasculitis, and Diffuse Lung Diseases: Official Journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders* 2004;**21**:147—51.
55. Annema JT, Veselic M, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. *The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology* 2005;**25**:405—9.
56. Wildi SM, Judson MA, Fraig M, Fickling WE, Schmulewitz N, Varadarajulu S, et al. Is endosonography guided fine needle aspiration (EUS-FNA) for sarcoidosis as good as we think? *Thorax* 2004;**59**:794—9.
57. Fritscher-Ravens A, Sriram PV, Topalidis T, Hauber HP, Meyer A, Soehendra N, et al. Diagnosing sarcoidosis using endosonography-guided fine-needle aspiration. *Chest* 2000;**118**:928—35.

58. Lerut T, De Leyn P, Coosemans W, Decaluwe H, Decker G, Nafteux P, et al. Cervical videomediastinoscopy. *Thoracic Surgery Clinics* 2010;**20**:195—206.
59. Reich JM, Brouns MC, O'Connor EA, Edwards MJ. Mediastinoscopy in patients with presumptive stage I sarcoidosis: a risk/benefit, cost/benefit analysis. *Chest* 1998;**113**: 147—53.
60. Gossot D, Toledo L, Fritsch S, Celerier M. Mediastinoscopy vs thoracoscopy for mediastinal biopsy. Results of a prospective nonrandomized study. *Chest* 1996;**110**:1328—31.
61. Porte H, Roumilhac D, Eraldi L, Cordonnier C, Puech P, Wurtz A. The role of mediastinoscopy in the diagnosis of mediastinal lymphadenopathy. *European Journal of Cardio-thoracic Surgery: Official Journal of the European Association for Cardio-thoracic Surgery* 1998;**13**:196—9.
62. Mikhail JR, Shepherd M, Mitchell DN. Mediastinal lymph node biopsy in sarcoidosis. *Endoscopy* 1979;**11**:5—8.
63. Klein JS, Johnson A, Watson E, Mount S. CT-guided transthoracic needle biopsy in the diagnosis of sarcoidosis. *Journal of Thoracic Imaging* 2009;**24**:23—30.