Endosonography vs Conventional Bronchoscopy for the Diagnosis of Sarcoidosis

The GRANULOMA Randomized Clinical Trial

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Importance Tissue verification of noncaseating granulomas is recommended for the diagnosis of sarcoidosis. Bronchoscopy with transbronchial lung biopsies, the current diagnostic standard, has moderate sensitivity in assessing granulomas. Endosonography with intrathoracic nodal aspiration appears to be a promising diagnostic technique.

Objective To evaluate the diagnostic yield of bronchoscopy vs endosonography in the diagnosis of stage I/II sarcoidosis.

Design, Setting, and Patients Randomized clinical multicenter trial (14 centers in 6 countries) between March 2009 and November 2011 of 304 consecutive patients with suspected pulmonary sarcoidosis (stage I/II) in whom tissue confirmation of noncaseating granulomas was indicated.

Interventions Either bronchoscopy with transbronchial and endobronchial lung biopsies or endosonography (esophageal or endobronchial ultrasonography) with aspiration of intrathoracic lymph nodes. All patients also underwent bronchoalveolar lavage.

Main Outcomes and Measures The primary outcome was the diagnostic yield for detecting noncaseating granulomas in patients with a final diagnosis of sarcoidosis. The diagnosis was based on final clinical judgment by the treating physician, according to all available information (including findings from initial bronchoscopy or endosonography). Secondary outcomes were the complication rate in both groups and sensitivity and specificity of bronchoalveolar lavage in the diagnosis of sarcoidosis.

Results A total of 149 patients were randomized to bronchoscopy and 155 to endosonography. Significantly more granulomas were detected at endosonography vs bronchoscopy (114 vs 72 patients; 74% vs 48%; $P < .001$). Diagnostic yield to detect granulomas for endosonography was 80% (95% CI, 73%-86%); for bronchoscopy, 53% (95% CI, 45%-61%) ($P < .001$). Two serious adverse events occurred in the bronchoscopy group and 1 in the endosonography group; all patients recovered completely. Sensitivity of the bronchoalveolar lavage for sarcoidosis based on CD4/CD8 ratio was 54% (95% CI, 46%-62%) for flow cytometry and 24% (95% CI, 16%-34%) for cytospin analysis.

Conclusion and Relevance Among patients with suspected stage I/II pulmonary sarcoidosis undergoing tissue confirmation, the use of endosonographic nodal aspiration compared with bronchoscopic biopsy resulted in greater diagnostic yield.

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Sarcoidosis is a multisystem granulomatous disease of unclear etiology, with an estimated lifetime risk of 1% to 2%.[1] The incidence of sarcoidosis in the United States is high, with up to 40 cases per 100 000, and sarcoidosis-related mortality is increasing.[2,3] The disease is characterized by tissue accumulation of noncaseating granulomas and affects the lungs and intrathoracic lymph nodes in almost all patients.[4]

A diagnosis of sarcoidosis is based on clinical and radiologic suspicion, tissue confirmation of noncaseating granulomas, and exclusion of similar presenting diseases such as tuberculosis, lymphoma, and lung cancer.[5,6] In the absence of easily accessible biopsy sites (skin or superficial lymph nodes), flexible bronchoscopy with transbronchial lung biopsies (TBLBs) is recommended.[5] TBLB, however, has moderate sensitivity (60%) to detect granulomas even when combined with endobronchial biopsies.[7-9] Additionally,

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TBLB is associated with hemorrhage and pneumothorax in up to 6% of patients.[10]

Tissue confirmation of noncaseating granulomas can alternatively be obtained by sampling intrathoracic lymph nodes under ultrasonographic guidance from the airways (endobronchial ultrasonography[EBUS]-guided transbronchial needle aspiration [TBNA]) or the esophagus (transesophageal ultrasonography[EUS]-guided fine-needle aspiration). The detection rate of noncaseating granulomas for endosonography is approximately 80%.[11-14]

We performed a randomized controlled trial comparing conventional bronchoscopy (including transbronchial and endobronchial mucosal biopsies) with endosonography (EUS or endobronchial ultrasonography–guided nodal aspiration) for the detection of noncaseating granulomas in patients with suspected pulmonary sarcoidosis. Additionally, we performed bronchoalveolar lavage (BAL) in all patients to assess its utility in diagnosing sarcoidosis.

METHODS

Patients

Patients older than 18 years, with a clinical and radiologic suspicion of sarcoidosis stage I (mediastinal or hilar lymphadenopathy) or II (lymphadenopathy and intraparenchymal abnormalities), and with an indication for tissue verification of noncaseating granulomas were eligible for inclusion. The decision to obtain tissue for diagnostic purposes vs a clinical and radiologic follow-up was made in dialogue between the treating physician and the patient. Previous diagnostic evaluation consisted of a conventional evaluation (medical history, physical examination, and laboratory tests) with radiograph and computed tomography of the chest. Exclusion criteria were obvious organ involvement of sarcoidosis with the possibility to confirm granulomas with a minimally invasive diagnostic procedure (eg, biopsy of skin lesions or superficial lymph nodes), Lofgren syndrome, inability to undergo endoscopy, pregnancy, or inability to consent.

Candidates for study participation were identified in 14 university and regional hospitals in the Netherlands, Belgium, Germany, Denmark, Poland, and the United Kingdom between March 2009 and November 2011 (Leiden University Medical Center; Radboud University Hospital Nijmegen; Medical Center Haaglanden; Catharina Hospital Eindhoven; St. Franciscus Hospital Rotterdam; Rijnstate Hospital Arnhem; Erasmus University Medical Center Rotterdam; Thoraxclinic Heidelberg; Hospital Grosshansdorf; John Paul II Hospital Krakow; Pulmonary Hospital Zakopane; Gentofte Hospital Copenhagen; Royal Brompton Hospital London; Gent University Hospital). This investigator-initiated trial, registered under the acronym GRANULOMA, was approved by the human research ethics committee at each center, and written informed consent was obtained from every participant before randomization.

Study Design

This was an investigator-initiated, unblinded, randomized trial. Block randomization was performed, stratified by center, with variable block sizes (randomly chosen between 4 and 8 blocks). Randomization software determined the random allocation (drawn from a uniform distribution). For all patients, the random-sequence allocation remained concealed until consent. Patients were assigned 1:1 to either conventional bronchoscopy with TBLB and endobronchial mucosal biopsy (bronchoscopy group) or to endosonography (esophageal or endobronchial) ultrasonography-guided mediastinal or hilar lymph node aspiration (endosonography group). For all patients, bronchoscopy with BAL was performed. Patients were enrolled at each site by the local study coordinator.

Nodal aspirates and histologic lung and mucosal biopsies were sent to the local pathologist for pathologic assessment. In addition, tissue samples were routinely sent in for Auramine/Ziehl-Neelsen staining, as well as culture and polymerase chain reaction (where available) for mycobacterium tuberculosis testing.

For patients without a conclusive diagnosis after endoscopy (ie, biopsies/aspirates without granulomas or an alternative diagnosis), it was optional to perform additional tissue sampling techniques to obtain a classifying diagnosis (for instance, to perform TBLB after a nondiagnostic endosonography result). The diagnosis of sarcoidosis was made by the treating physician according to all available information (including the findings from initial bronchoscopy or endosonography), using the European Respiratory Society/American Thoracic Society/World Association of Sarcoidosis and Other Granulomatous Disorders consensus statement (clinical and radiologic compatibility, presence of noncaseating granulomas, and the exclusion of similar presenting diseases).[5] Clinical and radiologic follow-up was performed 6 months after randomization to reassess the diagnosis. The diagnosis after 6 months was considered the reference standard.

After completion of the study, all bronchoscopy-obtained biopsies and endosonography-obtained fine-needle aspirates were blindly reevaluated by a reference pathologist (T.M.) and cytologist (F.D.B.), respectively.

Definition of End Points

The primary end point was the detection of granulomas or clusters of epithelioid cells concordant with a granulomatous inflammation. False-positive cases were defined as patients receiving a diagnosis of sarcoidosis after bronchoscopy or endosonography but for whom during follow-up another diagnosis was made. Diagnostic yield of granuloma detection was defined as the number of patients with detected granulomas or clusters of epithelioid cells obtained by the initial diagnostic procedure divided by the number of patients with a final diagnosis of sarcoidosis.

The rate of (serious) adverse events related to the diagnostic procedures was a secondary end point. Sensitivity and

specificity of the BAL were also secondary end points. The sensitivity of the BAL (for flow cytometry or cytospin analysis) was calculated as the proportion of patients with CD4/CD8 ratio ≥3.5 among patients receiving a diagnosis of sarcoidosis. The specificity was calculated as the proportion of patients with CD4/CD8 ratio <3.5 among patients with a diagnosis other than sarcoidosis.

Diagnostic Procedures

In the bronchoscopy group, conventional bronchoscopy was performed, including a complete endobronchial inspection followed by BAL. Bronchoalveolar lavage was performed preferably in the middle lobe or lingula with 150 to 200 mL of saline, according to the guidelines of the European Respiratory Society.[15] Lymphocyte percentage within inflammatory cells counted and CD4/CD8 ratio were assessed with either cytospin or flow cytometry analysis. Subsequently, at least 4 TBLB and 4 endobronchial mucosal biopsy samples were obtained.

In the endosonography group, EUS or endobronchial ultrasonography-guided TBNA was performed with linear echo-endoscopes, using 22-gauge needles, as previously described.[16,17] The decision to perform an esophageal or endobronchial procedure was left to the local investigator and could depend on equipment availability, computed tomography findings, or preference of either physician or patient. During endosonography, a systematic evaluation of the intrathoracic nodes was made and samples were to be taken from easily accessible nodes, often the subcarinal area. On-site cytologic evaluation was optional. In absence of on-site evaluation, a minimum of 4 nodal aspirates were to be obtained and processed for cytologic smearing and preferably cell block analysis. Flexible bronchoscopy with BAL, as described above, was performed immediately after EUS fine-needle aspiration or before endobronchial ultrasonography-guided TBNA.

Sedation was performed according to institutional practice. Vital signs were monitored and the duration of the procedure was recorded. Immediate procedure-related adverse events were documented and generally patients were observed for at least 1.5 hours after endoscopy. Patients were instructed to report symptoms (eg, persistent cough, fever, chest pains) occurring in the days and weeks after the procedure. Adverse events occurring immediately up to 1 week after the study procedure were assessed routinely. Later complications were evaluated in the event patients reported symptoms. Data were entered with web-based case report forms at randomization, 2 weeks after the endoscopy, and after 6-month follow-up.

Statistical Analysis

We hypothesized that the diagnostic yield for granuloma detection would be 70% for bronchoscopy[7-9] and 85% for endosonography.[11-14] With this assumption, we estimated that 300 patients would provide a power of 80% with a 2-sided α level of .05, assuming an 80% estimated prevalence of sarcoidosis and compensating for a 5% dropout rate. The primary analysis was intention to treat based on randomization. A single patient who was lost to follow-up after randomization but before scheduled endoscopy was excluded from analysis. The interobserver agreement between the initial pathology assessment and the reference pathology outcome was determined by κ measurement of interobserver agreement. χ^2 and Fisher exact tests were used for the analysis of categorical data and to compare the sensitivity of both endosonography and bronchoscopy. Independent *t* tests were used to compare groups of continuous, normally distributed variables. CIs of binominal distributions were calculated with the Clopper-Pearson method.

Analyses were performed with SPSS version 20.0. $P<.05$ was considered statistically significant.

RESULTS

Between March 2009 and November 2011, 366 consecutive patients with suspected sarcoidosis were assessed for study eligibility. A total of 62 patients were excluded and 304 were randomized: 149 to conventional bronchoscopy and 155 to endosonography (FIGURE 1). One patient randomized to the endosonography group did not attend any procedure or follow-up and was excluded from analysis. One patient randomized to bronchoscopy insisted later on undergoing endosonography and another patient randomized to endosonography inadvertently underwent bronchoscopy. These 2 patients were analyzed in accordance with the groups to which they were randomized (ie, with the intention to diagnose). Thus, 301 patients underwent endoscopy according to the protocol.

At baseline, patients in both groups were well balanced for major characteristics (TABLE 1). Patients were predominantly men (62% [bronchoscopy group] vs 58% [endosonography group]), with a mean age of 41 vs 45 years. Fatigue (63%; 95% CI, 58%-96%) and cough (55%; 95% CI, 50%-61%) were the most prevalent symptoms, and 31% of patients (95% CI, 26%-37%) reported nocturnal sweating (20%; 95% CI, 16%-25%), weight loss (22%; 95% CI, 17%-27%), or both (9%; 95% CI, 6%-12%). The onset of symptoms before randomization was 4 months in both groups. Fifty-three percent of bronchoscopy patients (95% CI, 44%-61%) and 44% of endosonography patients (95% CI, 36%-52%) had pulmonary opacities on chest radiography.

Mean duration of the procedure was 20 minutes for bronchoscopy (range, 7-37) vs 29 minutes for endosonography (range, 7-60). The majority of procedures were performed under conscious sedation, usually with midazolam (bronchoscopy, 66%; endosonography, 79%), and general anesthesia was used in 14% of the bronchoscopy group and 15% of the endosonography group. Transbronchial lung biopsies were performed under fluoroscopic guidance in 55 of 142 patients (39%). Bronchoalveolar lavage was performed in all patients and processed for analysis in 285 of 303 patients (94%) by flow cytometry (175/285 patients; 61%) and cytospin

(110/285 patients; 39%). Further procedural endoscopy details are provided in TABLE 2.

Final Diagnoses

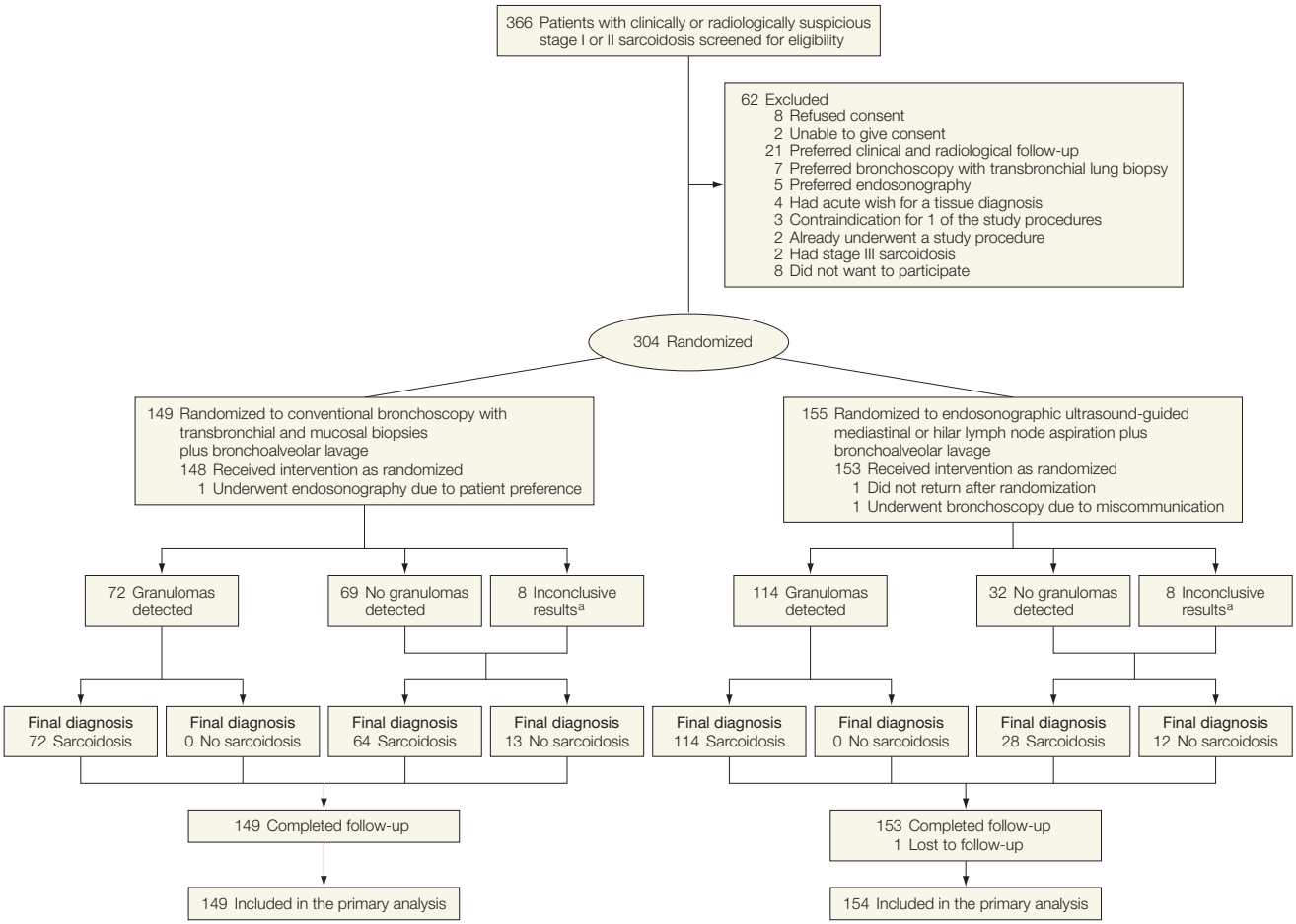
The final diagnosis determined at 6 months after randomization was sarcoidosis in 278 of 303 patients (92%; 95% CI, 88%-95%) (bronchoscopy, 91%, 95% CI, 86%-95%; endosonography, 92%, 95% CI, 87%-96%), which was based on tissue-proven granulomas in 250 of 278 patients (90%; 95% CI, 86%-93%) and in 28 of 278 patients (10%; 95% CI, 7%-14%) on clinical and radiologic follow-up (TABLE 3). Of the 75 patients in the bronchoscopy group for whom no diagnosis was available after bronchoscopy, 64 of 75 (85%; 95% CI, 75%-92%) underwent additional (endoscopy) procedures, resulting in a disease-classifying tissue diagnosis in 47 of 64 (73%; 95% CI, 61%-84%). Of the 36 patients undergoing endosonography without a diagnosis after endosonography, 25 underwent additional investigations, in which granulomas were found in 16 of 25 (64%; 95% CI, 43%-82%). Auramine/Ziehl-Neelsen staining, culture, and polymerase chain reaction for *Mycobacterium tuberculosis* were performed in 295 of 303 patients (97%), 297 of 303 patients (98%), and 200 of 303 patients (66%), respectively. Six-month follow-up was completed for 302 of 303 patients (99%); 1 patient did not attend follow-up visits. There were no false-positive diagnoses of sarcoidosis.

Detection of Granulomas

Granulomas or epithelioid clusters compatible with a sarcoidlike granulomatous inflammation were found significantly more often at endosonography than bronchoscopy (114/154 [74%; 95% CI, 66%-81%] vs 72/149 [48%; 95% CI, 40%-59%], $P < .001$) (Table 3).

The diagnostic yield to detect granulomas for endosonography vs bronchoscopy was 80% (95% CI, 73%-86%) vs 53% (95% CI, 45%-61%) ($P < .001$) (FIGURE 2).

Figure 1. Study Flowchart



Enrollment, randomization, and outcome of study participants. Granulomas were defined as granulomas or clusters of epithelioid cells, as can be observed in patients with sarcoidosis. The box "no granulomas" contains all other outcomes.
[a]No representative biopsy material was present.

For stage I sarcoidosis, the diagnostic yield of bronchoscopy was 38% (95% CI, 26%-51%) compared with 66% (95% CI, 54%-77%) for stage II ($P<.001$). For endosonography, diagnostic yield for stage I was 84% (95% CI, 74%-92%) compared with 77% (95% CI, 64%-86%) for stage II ($P=.24$). Endosonography had a significantly higher diagnostic yield for stage I sarcoidosis than bronchoscopy ($P<.001$); for stage II sarcoidosis, the difference was not statistically significant ($P=.18$). Transesophageal ultrasonography–guided fine-needle aspiration performed better in comparison with endobronchial ultrasonography–guided TBNA, with a diagnostic yield of 88% (95% CI, 80%-93%) vs 66% (95% CI, 53%-77%) ($P<.01$).

In the bronchoscopy group, biopsies demonstrated eosinophilic and granulomatous vasculitis in one patient and metastasized thyroid cancer in another. In the endosonography group, noncaseating granulomas without necrosis were found in 2 patients, of whom one received a diagnosis of tuberculosis; the other, of metastasized non–small cell lung carcinoma. In 2 more patients, a non–small cell lung carcinoma and colon carcinoma nodal metastasis were found.

Reference pathology was obtained for 95% of patients (288/303). The interobserver agreement for granuloma detection of the TBLB/endobronchial biopsy and the endosonography-obtained aspirates between the initial pathologist in each hospital and the reference pathologist was $\kappa=0.86$ and $\kappa=0.83$, respectively.

Adverse Events

In 303 patients, 3 serious adverse events occurred (bronchoscopy, 2/149; endosonography, 1/154) (TABLE 4). One patient developed a pneumothorax after TBLB, requiring chest tube drainage. Another patient required noninvasive ventilation (<12 hours) because of respiratory insufficiency after bronchoscopy under general anesthesia. One patient developed a mediastinal abscess after EUS fine-needle aspiration, requiring thoracotomy and prolonged antibiotic treatment.

In total, 82 adverse events occurred: 52 in 44 of 149 patients in the bronchoscopy group (30%; 95% CI,

Table 1. Baseline Characteristics of All Study Patients (N = 303)

Characteristic	No. (%)	
	Bronchoscopy (n = 149)	Endosonography (n = 154)
Age, mean (SD), y	41.2 (11.6)	44.7 (12.3)
Male sex	92 (62)	90 (58)
Symptoms		
Fatigue	99 (66)	94 (61)
Cough	79 (53)	90 (58)
Dyspnea	83 (56)	72 (47)
Arthralgia	61 (41)	58 (38)
Weight loss	32 (21)	34 (22)
Fever	19 (13)	26 (17)
Night sweats	36 (24)	25 (16)
Skin lesions	28 (19)	25 (16)
Eye lesions	22 (15)	22 (14)
Onset of symptoms, median (25th-75th percentile), mo	4.0 (2-7)	4.0 (2-6)
Smoking history		
Never	92 (62)	94 (61)
Former	39 (26)	36 (23)
Current	18 (12)	24 (15)
Chest radiograph		
Lymphadenopathy	130 (87)	140 (91)
Pulmonary opacities	79 (53)	68 (44)
CT scan of the thorax		
Lymphadenopathy[a]	147 (99)	153 (99)
Maximal nodal short axis, mean (SD), mm[b]	18.8 (6.9)	19.4 (7.0)
Pulmonary opacities	106 (71)	92 (60)
Sarcoidosis stage, based on chest radiograph		
I	69 (46)	85 (55)
II	79 (53)	68 (44)
III	1 (1)	1 (1)

Abbreviations: CT, computed tomography; EBB, endobronchial biopsy; EBUS, endobronchial ultrasonography; EUS, esophageal ultrasonography; TBLB, transbronchial lung biopsy.
Percentages may not sum to 100% because of rounding. Results on 1 patient are missing (see Figure 1).
[a] Lymphadenopathy was defined as a minimal short axis >10 mm.
[b] Mean short-axis for EUS patients was 19.0 mm(SD, 7.0); for EBUS, 20.6 mm(SD, 7.1).

Table 2. Characteristics of Endoscopy

	No. (%)			
	Bronchoscopy (n = 149)		Endosonography (n = 154)	
	TBLB	EBB	EUS-FNA	EBUS-TBNA
Procedure performed	143/149 (96)[a,b]	138/149 (93)[a]	102/154 (66)[c]	56/154 (36)[c]
No. of biopsies, mean (SD)	5.24 (1.53)	4.10 (1.03)	5.21 (1.40)	5.75 (2.01)
Patients with ≥4 biopsy specimens collected	139/149 (93)	121/149 (81)	64/68 (94)[d]	42/43 (98)[d]
Representative material[e]	138/149 (93)	132/149 (89)	97/103 (94)	51/56 (91)

Abbreviations: EBB, endobronchial biopsy; EBUS, endobronchial ultrasonography; EUS, esophageal ultrasonography; FNA, fine-needle aspiration; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration.
[a] Both TBLB and EBB were omitted in 2 patients because of restlessness.
[b] Fluoroscopy was used in 39% of patients.
[c] In 5 patients, both an EUS and an EBUS were performed.
[d] In patients without on-site cytology available (EUS: 68/103, 66% [95% CI, 56%-75%]; EBUS: 43/56, 77% [95% CI, 64%-87%]).
[e] The definition of representative material included a classifying diagnosis or nodal tissue (in case of EUS/EBUS) or respiratory epithelium (in case of TBLB/EBB).

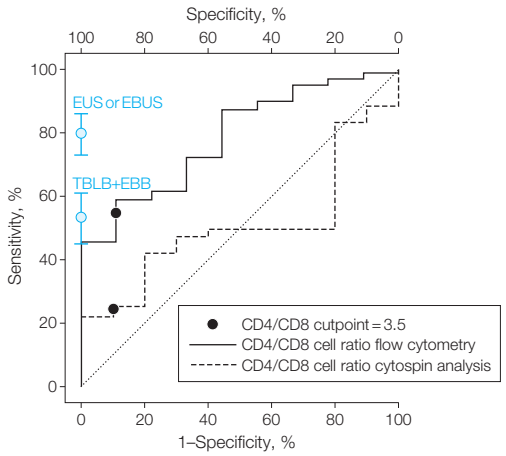
22%-38%) and 30 in 29 of 154 patients undergoing endosonography (19%; 95% CI, 13%-26%) (*P*=.03).

The most prevalent adverse event for bronchoscopy was intolerable cough (7/149; 5%; 95% CI, 2%-9%), and for endosonography, a sore throat (11/154; 7%; 95% CI, 4%-12%). All patients recovered completely.

Table 3. Granuloma Detection and Diagnostic Yield for Sarcoidosis and the Final Diagnoses by Group

	No. (%)	
	Bronchoscopy (n = 149)	Endosonography (n = 154)
Detection of granulomas, consistent with the diagnosis of sarcoidosis	72 (48)	114 (74)
Diagnostic yield of granuloma detection in patients with sarcoidosis	72/136 (53)	114/142 (80)
Final diagnosis		
Sarcoidosis	136 (91)	142 (92)
Other diagnoses	13 (9)	12 (8)
Postinflammation/reactive mediastinal nodal disease	5	7
Nonspecific interstitial pulmonary fibrosis	3	0
Tuberculosis	1	1
Lymph node metastasis of non–small cell lung cancer	0	2
Metastatic thyroid cancer	1	0
Metastatic colon cancer	0	1
Wegener disease	1	0
Pneumoconiosis	0	1
Atypical pneumonia	1	0
Atypical interstitial nodules, diagnosis unknown	1	0

Figure 2. Diagnostic Outcome of Study Procedures Based on Bronchoalveolar Lavage



A receiver operating characteristic (ROC) for the test performance of bronchoalveolar lavage (BAL). Such an ROC curve is a graphic plot that illustrates the performance of a binary classifier system as its discrimination threshold is varied. It is created by plotting the fraction of true-positives out of the positives (TPR=true-positive rate, sensitivity) vs the fraction of false-positives out of the negatives (FPR=false-positive rate, 1 − specificity), at various threshold settings. The curves for BAL (cytospin and flow cytometry analysis) show all FPR and TPR combinations that can be obtained by choosing different cutoff values for the CD4/CD8 ratios. The circles in the BAL curves represent the FPR and TPR combinations associated with a cutoff of 3.5, a diagnostic threshold often used in clinical practice. The blue circles indicate sensitivity (95% CI) of bronchoscopy and endosonography. EUS indicates transesophageal ultrasonography; EBUS, endobronchial ultrasonography; TBLB, bronchoscopy transbronchial lung biopsies; and EBB, endobronchial biopsy.

Bronchoalveolar Lavage

With a CD4/CD8 ratio cutoff value of 3.5, the sensitivity of the BAL for a final diagnosis of sarcoidosis was 54% (95% CI, 46%-62%) for flow cytometry and 24% (95% CI, 16%-34%) for cytospin analysis. The corresponding specificities were 89% (95% CI, 52%-100%) and 90% (95% CI, 56%-100%), respectively. The mean percentage of lymphocytes within inflammatory cells counted was 29.7% for flow cytometry vs 24.6% for cytospin analysis. The receiver operating characteristic curves for the sensitivity and specificity for different CD4/CD8 ratio cutoff values for flow cytometry and cytospin analysis are depicted in Figure 2.

DISCUSSION

Endosonography with sampling of intrathoracic nodes had higher diagnostic yield in comparison with bronchoscopy with TBLB and endobronchial mucosal biopsy in demonstrating granulomas in patients with presumed sarcoidosis stage I and II. Serious adverse events related to endoscopy were uncommon.

Transbronchial lung biopsies obtained during conventional bronchoscopy are regarded as the current standard to demonstrate noncaseating granulomas in patients with suspected sarcoidosis in case a tissue diagnosis is indicated.[5] The diagnostic yield of TBLB and endobronchial biopsy found in the present study (53%) is within the lower range as reported in the literature: 60% (range, 40%-90%).[7-9] In 93% of patients, at least 4 TBLB samples were obtained, showing representative alveolar tissue in 93% of cases.

TBLB can be combined with additional diagnostic modalities such as endobronchial biopsy, "blind" TBNA of mediastinal lymph nodes, or BAL. In clinical practice, TBLB is often not performed because of concern about hemoptysis (up to 4%) or pneumothoraces (up to 2%).[10]

Endosonography in the present study had a diagnostic yield of 80% to detect noncaseating granuloma in patients with suspected sarcoidosis; this is similar to

previous findings reporting a sensitivity of approximately 80% (range, 54%-100%).[11-14] A recent prospective cohort study showed that endosonography had a sensitivity of 71% in diagnosing sarcoidosis after a previous nondiagnostic bronchoscopy result.[8] Additionally, 2 small prospective studies evaluating bronchoscopy and endosonography reported a significantly higher yield for endobronchial ultrasonography-guided TBNA (85%-94%) compared with TBLB (31%-37%) to detect granulomas.[18,19]

An exploratory analysis was performed to compare endosonography and bronchoscopy stratified by stage. For stage I sarcoidosis, this study showed higher diagnostic yield of endosonography compared with bronchoscopy in granuloma detection. For stage II sarcoidosis, there was still a numeric difference but this was not statistically significant. However, our study was not formally powered for subgroup analyses, meaning that these results should be interpreted with caution.

Strengths of the present study are a high percentage of adequately performed endoscopy procedures and the international setting across 6 countries in both general and academic hospital settings, contributing to the external validity of the results. The high concordance of the reference pathologist with the initial assessment for both fine-needle nodal aspirates and histology of TBLB and endobronchial biopsy samples is an important finding, as previously observed in a small study.[20] Additionally, the availability of BAL data in addition to the granuloma detection techniques sheds light on how these different diagnostic techniques compare.

Several limitations also apply to the present study. First, granulomatous inflammation was not confirmed in all patients with the final diagnosis of sarcoidosis. However, careful 6-month follow-up limits the chance of any missed alternative diagnoses. Second, although the study was performed across Europe, it remains unknown what the outcomes are in regions with, for instance, a high prevalence of tuberculosis or histoplasmosis. Third, conventional blind TBNA was not included in the protocol. However, this technique is not widely practiced[11] and is operator dependent, and its diagnostic yield is inferior to that of endosonography-guided TBNA.[21] Fourth, because the diagnostic tests that were evaluated (TBLB, endobronchial biopsy, and endosonography) could have directly influenced the main outcome (final diagnosis of sarcoidosis at 6 months), incorporation bias is present in this study and may artifactually increase the apparent test performance characteristics of the diagnostic procedures evaluated.

Serious adverse events were uncommon and all patients recovered. One patient developed a mediastinal abscess after EUS fine-needle aspiration of a mediastinal node. Abscess formation has been reported in more cases after an esophageal[22] but never an endobronchial approach. The rate of minor adverse events was higher for bronchoscopy in comparison with endosonography, including pulmonary hemorrhage (8.1%) and pneumothoraces (4%) observed at rates similar to those reported in the literature.[10]

The value of a BAL in diagnosing sarcoidosis, as measured by CD4/CD8 ratio analysis with a cutoff value of 3.5, was limited, with a diagnostic accuracy in concordance with that in the literature.[23,24] As expected, flow cytometry provided a higher sensitivity (54%) than cytospin analysis (24%). Bronchoalveolar lavage flow cytometry outcomes showed sensitivity similar to that of the combination of TBLB and endobronchial biopsy but had a false-positive rate of 10%.

Table 4. Adverse Events in Both Groups

	Bronchoscopy (n = 149)	Endosonography (n = 154)
Serious adverse events	n = 2	n = 1
Mediastinal abscess requiring thoracotomy	0	1
Pneumothorax, drain necessary	1	0
Ventilatory insufficiency requiring noninvasive ventilation	1	0
Adverse events	52	30
Ulcer midesophageal	0	1
Pneumothorax, no drain necessary	6	0
Major agitation prohibiting adequate protocol sampling	3	0
Hemorrhage, mL		
>75	1	0
26-75	1	0
5-25	4	0
<5	6	0
Small mediastinal hematoma	0	1
Saturation decrease, %		
<60	0	1
<80	2	0
80-90	6	2
Loose tooth after endoscopy	0	1
Introduction of EUS scope into trachea	0	1
Intolerable cough	7	6
Sore throat	6	11
Dysphagia	0	2
Minor aspecific thoracic pain	3	0
Temperature <39°C	6	2
Tachycardia	1	0
Technical issues		
Early removal of scope because of technical problem	0	1
Endoscope damage	0	1

Abbreviations: EBB, endobronchial biopsy; EBUS, endobronchial ultrasonography; EUS, esophageal ultrasonography; TBLB, transbronchial lung biopsy.

How will the outcomes of this study affect future diagnostic strategies for patients with suspected sarcoidosis? Whether tissue confirmation of granulomas is indicated should be critically assessed in light of recent improvements in computed tomography–thorax imaging. For patients who require tissue sampling either to confirm sarcoidosis before treatment or to exclude similar presenting diseases such as tuberculosis and lymphoma, the outcomes of this study indicate that endosonographic evaluation is likely to have the highest diagnostic yield.

In conclusion, among patients with suspected stage I/II pulmonary sarcoidosis undergoing tissue confirmation, the use of endosonographic nodal aspiration compared with bronchoscopic biopsy resulted in greater diagnostic yield.

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