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Original Research

INTERVENTIONAL PULMONOLOGY

A Randomized Controlled Trial of Standard vs Endobronchial Ultrasonography-Guided Transbronchial Needle Aspiration in Patients With Suspected Sarcoidosis

Alain Tremblay, MDCM, FCCP; David R. Stather, MD, FCCP; Paul MacEachern, MD; Moosa Khalil, MBBCh; and Stephen K. Field, MDCM, FCCP

Background: **Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) of mediastinal lymph nodes has been found to be more accurate than standard TBNA in the setting of malignancy. In patients with suspected sarcoidosis, the smaller ultrasound needle may yield inadequate material to make a histologic diagnosis of granulomatous inflammation. The aim of this study was to compare the diagnostic yield of EBUS-guided TBNA to TBNA performed with a standard 19-gauge needle in patients with mediastinal adenopathy and a clinical suspicion of sarcoidosis.**

Methods: **A randomized controlled trial was performed in a university medical center, enrolling 50 patients (of 61 screened, 2 declined, and 9 did not meet entry criteria) with hilar and/or mediastinal adenopathy and a clinical suspicion of sarcoidosis. Twenty-four patients were randomized to undergo EBUS-guided TBNA and 26 to undergo TBNA using a standard 19-gauge needle.**

Results: **The primary outcome measure of diagnostic yield was 53.8% vs 83.3% in favor of the EBUS-guided TBNA group, an absolute increase of 29.5% ($p < 0.05$; 95% confidence interval [CI], 8.6 to 55.4%). After blinded research pathology review, diagnostic yield was 73.1% vs 95.8%, in favor of the EBUS-guided TBNA group, an absolute increase of 22.7% ($p = 0.05$; 95% CI, 1.9 to 42.2%). Sensitivity and specificity were 60.9% and 100%, respectively, in the standard TBNA group, and 83.3% and 100%, respectively, in the EBUS-guided TBNA group (absolute increase in sensitivity, 22.5%; $p = 0.085$; 95% CI, 3.2 to 44.9%).**

Conclusions: **The diagnostic yield of EBUS-guided TBNA is superior to TBNA using a standard 19-gauge needle for sampling of mediastinal lymph nodes in patients with a clinical suspicion of sarcoidosis.**

Trial registration: **ClinicalTrials.gov Identifier: NCT00373555** ***(CHEST 2009; 136:340–346)***

Abbreviations: CI = confidence interval; EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; ROSE = rapid on-site cytologic evaluation; TBNA = transbronchial needle aspiration

Sarcoidosis is a benign inflammatory condition that typically involves the lungs and mediastinal lymph nodes.[1,2] The diagnosis of sarcoidosis is usually confirmed by tissue biopsy, especially in patients in whom treatment with corticosteroids is required or the diagnosis is uncertain and confirmation is required.

Bronchoscopic samples are often preferred given their good sensitivity and low complication rates. If the diagnosis of sarcoidosis is not confirmed by bronchoscopy, more invasive surgical procedures such as mediastinoscopy[3] or open lung biopsy[4] may be required.

For editorial comment see page 327

Transbronchial needle aspiration (TBNA) with 19-gauge needles has been the standard broncho-

scopic technique for the biopsy of mediastinal lymph nodes in patients with suspected sarcoidosis and has demonstrated incremental diagnostic yield over other bronchoscopic techniques.[5–11] Endobronchial ultrasonography (EBUS)-guided TBNA was introduced into clinical practice after multiple studies[12–21] showed excellent results, mostly in patients with suspected lung malignancy. This technique allows real-time ultrasound localization and aspiration of hilar and mediastinal lymph nodes. It is not known whether this technique, which uses a smaller 22-gauge needle, will increase the diagnostic yield over that of TBNA using a standard 19-gauge needle in patients suspected of having sarcoidosis, although several case series have shown promising results with both esophageal endoscopic ultrasound (EUS)[22,23] and EBUS-guided TBNA.[24–26] This randomized study was designed to compare the diagnostic yield of TBNA using a 19-gauge needle vs EBUS-guided TBNA in patients with clinically suspected sarcoidosis and mediastinal adenopathy.

Materials and Methods

Study Design

This single-center study employed a randomized controlled design, with blinded analysis of the cytopathologic samples. The protocol was approved by the Conjoint Health Research Ethics Board of the University of Calgary, and written informed consent was obtained from all patients.

Patients were eligible for this study if they were ≥ 16 years of age, had pathologic mediastinal or hilar adenopathy (short axis, > 1 cm) confirmed on CT scan of the chest, were considered to have a likely diagnosis of sarcoidosis based on clinical and radiologic assessment, and if a clinical decision had been made by the patient and treating physician to proceed to bronchoscopy. Patients were excluded if informed consent was not obtained, if an uncontrolled coagulopathy was present (*ie*, platelets $< 100 \times 10^9$/L, international normalized ratio > 1.3, and use of clopidogrel in the 7 days prior to bronchoscopy), or if systemic treatment for sarcoidosis had been initiated > 30 days before the bronchoscopy.

Potential candidates were identified by respiratory medicine physicians and thoracic surgeons in the Calgary Health Region who were informed of the study design and entry criteria at the onset of the study and sent a monthly e-mail reminder. All study bronchoscopies were performed by the interventional pulmonary medicine group at the University of Calgary/Foothills Medical Center.

Patients were randomized at the time of bronchoscopy to undergo TBNA using a standard 19-gauge needle vs EBUS-guided TBNA in addition to other bronchoscopy procedures. A computer-generated random number list was used by an administrative assistant to generate opaque, serially numbered envelopes to ensure concealment of allocation. Block randomization in groups of 10 was performed, stratifying for chest radiograph stage I vs stage II disease. The envelopes were opened in sequential order and according to disease stage in the bronchoscopy suite immediately prior to the start of the procedure.

All bronchoscopies were performed as outpatient procedures in a dedicated bronchoscopy suite under conscious sedation and without the use of endotracheal intubation. Additional samples were collected at the discretion of the bronchoscopist as per usual clinical practice.

TBNA Group: Lymph nodes with a short-axis diameter of > 1 cm on a CT scan, accessible to TBNA at the discretion of the bronchoscopist, were punctured with a 19-gauge TBNA needle (eXcelon; Boston Scientific; Natick, MA). Three to five passes in each location were recommended.

EBUS-guided TBNA Group: Once initial bronchoscopic examination was completed, the videobronchoscope was removed and the patient was reintubated with an EBUS-guided TBNA bronchoscope (BF-UC160F; Olympus America; Melville, NY). Lymph nodes visualized by EBUS and considered appropriate for biopsy by the bronchoscopist were punctured under real-time EBUS guidance with a 22-gauge EBUS-guided TBNA needle (NA-201SX-4022-C; Olympus America; Melville, NY). Three to five passes in each location was recommended.

The sequence of sampling, number of aspirates attempted per node, and the total number of lymph node sites biopsied was left to the discretion of the bronchoscopist. All TBNA samples were placed in an alcohol fixative (CytoLyt; Cytyc Corporation; Marlborough, MA) and promptly delivered to the clinical cytology laboratory. Rapid on-site cytologic evaluation (ROSE) was not performed. Samples from each lymph node station were placed in separate containers. Visible tissue fragments and coagulated material were processed separately as paraffin-embedded cell blocks, and a 4-μm section of each cell block was stained with hematoxylin-eosin. The remaining sample was used to prepare monolayer cytology slides (ThinPrep; Cytyc Corporation), which were stained by the Papanicolaou method. Samples were reviewed initially by the assigned clinical cytopathologist. All samples were then reviewed by a research pathologist. All cytopathologists were blinded to the sampling method used. The patient's medical records were reviewed by an expert clinician, blinded to the sampling method, a minimum of 6 months after the bronchoscopy to assign a diagnosis of sarcoidosis as confirmed, excluded, or uncertain with the use of a score sheet (Appendix 1).

Outcome Measurements

The primary outcome measure for the study was the diagnostic yield of the TBNA procedure on a per-patient basis according to the clinical cytopathology report. A positive diagnostic test result was defined as the observation of noncaseating granulomatous inflammation or the observation of another specific diagnosis (*eg*, cancer or tuberculosis). The sensitivity and specificity of each of the TBNA tests for sarcoidosis were calculated according to the assignment of a final diagnosis of sarcoidosis as confirmed, excluded, or uncertain after review of the medical record by an expert clinician blinded to TBNA method, at least 6 months after

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bronchoscopy. Additional secondary outcome measures included diagnostic yield according to the research cytopathology review as well as on a "per lymph node" basis, incremental yield of TBNA above other procedures, impact of disease stage and lymph node station on diagnostic yield, procedure length, and cumulative dose of topical anesthetics and sedative medications used.

Statistical Analysis

A two-sided uncorrected χ^2 test was used to compare the diagnostic yield and other interval measurements of both groups. Ninety-five percent confidence intervals (CIs) [without continuity correction] were calculated for differences between groups to describe the effect size of the comparisons.

A sample size of 25 patients per group was calculated (uncorrected χ^2 test) based on a reported diagnostic yield of standard TBNA of 55%[5,6,9,10] in order to detect an improvement of sensitivity to 90% with EBUS-guided TBNA (based on a reported yield of esophageal EUS[22,23] in sarcoidosis patients because no published data on EBUS-guided TBNA existed at the time of study design) with a power of 0.8 and α of 0.05.

Results

Sixty-one patients were screened and 50 were randomized (Fig 1) between September 2006 and August 2007. Chart review was completed between June 2008 and August 2008. Baseline characteristics can be found in Table 1. All patients underwent mediastinal lymph node aspiration according to their assigned randomization group. Bronchoscopy was performed by interventional pulmonary medicine fellows assisted by a dedicated interventional pulmonary medicine physician in 48 of the 50 cases, with 2 cases performed without a fellow present.

Table 1—*Baseline Values*

Variables	Standard TBNA (n = 26)	EBUS-TBNA (n = 24)
Age, yr	40.8 (12.8)	39.5 (8.6)
Male gender	53.8	79.2
Disease stage		
Stage I	69.2	66.7
Stage II	30.8	33.3
Largest node size, mm	20.2 (4.7)	21.1 (5.1)
Nodes > 1 cm, No.	3.7 (1.5)	4.6 (1.8)

Values are given as mean (SD) or %.

The main results are presented in Table 2. More lymph nodes were aspirated in the EBUS-guided TBNA group (4.0 vs 2.2, respectively), but more passes per node were performed in the standard TBNA group, so that total number of passes per patient was similar (10.1 vs 8.7, respectively). Including all of the bronchoscopy samples, granulomatous inflammation was found in 21 of 26 of the patients (80.8%) randomized to the standard TBNA group vs 22 of 24 (91.7%) in the EBUS-guided TBNA group ($p > 0.05$), and a diagnosis of sarcoidosis was confirmed in 47 of 50 patients (94%), with the diagnosis remaining uncertain in 3 patients (6%). No specific

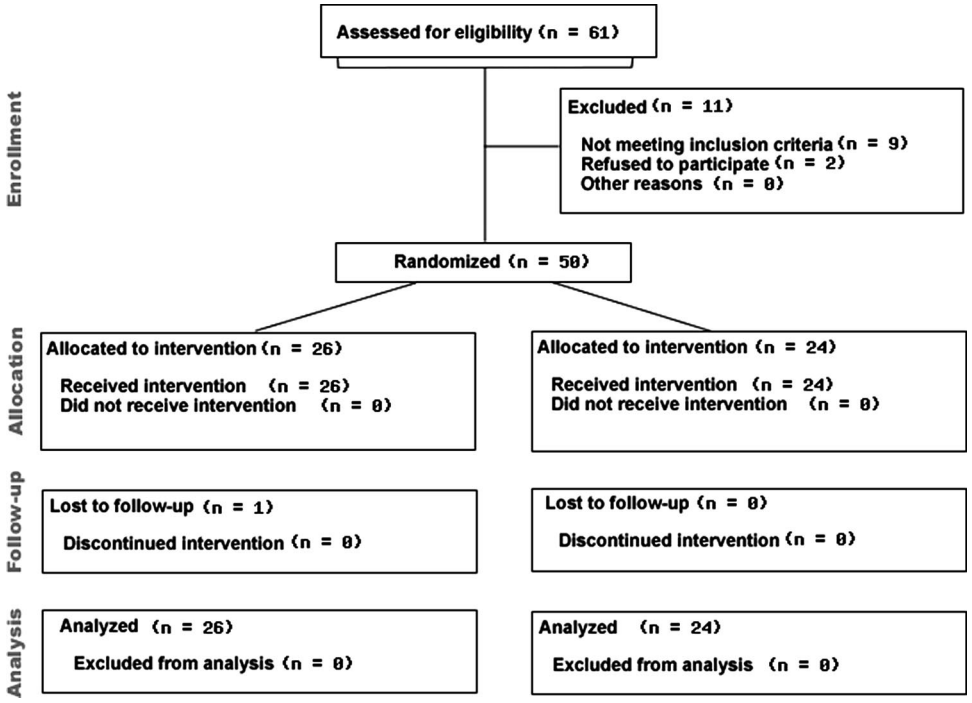

Figure 1. Study flow diagram.[38]

Table 2—*Main Results*

Variables	Standard TBNA (n = 26)	EBUS-Guided TBNA (n = 24)	Difference (95% CI)
TBNA diagnostic yield*	53.8	83.3	29.5 (8.6 to 55.4%)†
TBNA diagnostic yield (after review)	73.1	95.8	22.7 (1.9 to 42.2%)†
TBNA sensitivity for sarcoidosis	60.9	83.3	22.5 (−3.2 to 44.9%)
Node stations aspirated, No.	2.2 (0.77)	4.0 (1.0)	1.8 (1.3 to 2.3%)†
Size of nodes aspirated, mm	17.9 (4.8)	16.5 (5.0)	1.4 (−2.4 to 3.0%)
Needle passes per patient, No.	8.7 (3.3)	10.1 (2.4)	1.4 (−0.3 to 3.0%)
Total procedure length, min	34.0 (8.9)	44.2 (6.6)	10.2 (5.8 to 14.7%)†
TBNA sole diagnostic test	38.5	45.8	7.4 (−18.8 to 32.3%)

Values are given as % or mean (SD), unless otherwise indicated.
*Primary outcome measure.
†$p < 0.05$.

alternative diagnosis was made in these three patients, all of who demonstrated a benign clinical course with decisions not to pursue more invasive diagnostic testing.

The main study outcome measure of diagnostic yield was 14 of 26 procedures (53.8%) vs 20 of 24 procedure (83.3%), respectively, in the standard TBNA group and the EBUS-guided TBNA group, which is an absolute increase of 29.5%. The diagnostic yield, according to the research pathology review, was also significantly higher in the EBUS-guided TBNA group (73.1% vs 95.8%, respectively), with an absolute increase of 22.7%. The diagnostic yield on a per lymph node basis (51.7% vs 55.7%, respectively) for standard TBNA and EBUS-guided TBNA or on a per station basis (data not shown) did not reveal any significant differences between the two groups.

An absolute increased diagnostic yield of EBUS-guided TBNA over standard TBNA of 31.9% was noted in patients with stage I disease (55.6% vs 87.5%, respectively; $p = 0.041$; 95% CI, 1.1 to 55.6%), but this was not statistically significant in the smaller subset of patients with stage II disease (50% vs 75%, respectively; 95% CI, −19.4 to 58.6%). The sensitivity for sarcoidosis was 60.9% in the standard TBNA group and 83.3% in the EBUS-guided TBNA group ($p = 0.085$). The specificity for sarcoidosis was 100% in both groups, based on the final diagnosis after the follow-up period.

The transbronchial needle aspiration finding was the only positive test result in 10 of 26 cases (38.5%) and 11 of 24 cases (45.8%), respectively, in the standard TBNA vs EBUS-guided TBNA ($p > 0.05$). Endobronchial biopsies were performed in 50% of patients in both groups, and transbronchial biopsies were performed in 38.4% and 48.0% of patients, respectively. Transbronchial biopsies were performed in the majority of patients with stage II disease (93.8%). Twenty-four percent of the patients received treatment for sarcoidosis during the follow-up period.

Procedure length was 10.2 min longer and propofol was used for sedation in 26.9% more patients in the EBUS-guided TBNA group (12 of 24 patients [50.0%] vs 6 of 26 patients [23.1%], respectively; $p = 0.048$; 95% CI, 3.7 to 49.1%). The average doses of topical lidocaine, IV benzodiazepine, and opiate were similar in the two groups. Moderate bleeding was seen following two attempts at standard TBNA. No other complications were detected.

Discussion

EBUS is rapidly changing the assessment of the mediastinum, especially in patients with suspected lung malignancies in whom diagnostic yields and sensitivities of > 90% have been achieved.[12,13,15,20,21] Interestingly, there has yet to be a randomized controlled study comparing linear EBUS-guided TBNA with standard TBNA in any patient population, although one randomized study[27] did show the superiority of balloon probe radial, EBUS-guided TBNA vs standard TBNA.

In patients with suspected sarcoidosis, the role of EBUS-guided TBNA is less clear. In particular, the use of the smaller 22-gauge EBUS-guided TBNA needle could make the cytopathologic diagnosis of granulomatous inflammation more difficult than with the 19-gauge "histology" needle, which cannot be introduced through the EBUS bronchoscope. This prospective randomized study confirms the superior diagnostic yield of EBUS-guided TBNA over TBNA using a standard 19-gauge needle by demonstrating a 30% increase in diagnostic yield from aspiration of mediastinal nodes in patients with suspected sarcoidosis.

The diagnostic yields obtained in both groups were consistent with previously published case series. Several authors[5–7,9,10] have described the performance characteristics of TBNA using a standard 19-gauge needle in this patient population, with

diagnostic yields between 46% and 78% (66% pooling all studies), which is well in keeping with our results of between 54% and 73% after pathology review. One study by Wang et al[11] demonstrated a sensitivity of 90% in 20 patients using an 18-gauge needle, but 8 additional patients were reported to have "other benign disease." As such, the diagnostic yield of TBNA in this group of patients, as calculated in our study, would have been 60%, which is consistent with other reports. The higher yield of EUS-guided needle aspiration has also been noted both with EUS (82%[22] and 100%[23]) and more recently in three case series with EBUS (82%,[25] 91.8%,[26] and 93%[24]).

When analyzed on a "per-node" basis, there were no significant differences in the diagnostic yield between the two techniques. This should not suggest that the techniques are equivalent because half as many aspirations were required per node with the EBUS approach to achieve this. Should we have performed additional passes per node to match with the standard group, we likely would have seen an increased diagnostic yield on a per-node basis, as shown by Garwood et al.[25] Although the number of passes per lymph node was not specified in the protocol, we aimed to achieve at least four passes with standard TBNA for each station sampled, as recommended in the literature.[28,29] No recommendations existed at the time of study design for the number of passes to use with EBUS-guided TBNA. Based on our experience, we believed it would be more effective to do a limited number of passes in a greater number of lymph nodes in order to limit an already lengthy procedure. A recent study[30] has suggested that two or three passes are sufficient with this new technique when performed without ROSE support in patients with suspected lung malignancies, but another study[25] has suggested that in sarcoidosis patients four to five passes per node is optimal. Whether performing more aspiration procedures in fewer nodes or using ROSE in a sarcoidosis population would further increase diagnostic yield on a per-patient basis remains unknown.

Patients in the standard TBNA group had fewer lymph node stations sampled than those in the EBUS group. Although this may suggest that we were less aggressive with standard TBNA, in fact we performed more needle passes (4 per node) in more lymph node stations (2.2 per patient) than described in any of the published studies on this technique where this information is available (1 to 3 needle passes per station and 1 to 1.3 stations per patient).[6,7,10,11] This, in addition to the diagnostic yield obtained well within the range of previously published results from other centers with expertise in this technique, suggests that standard TBNA was applied at least as satisfactorily during this study compared to previous reports.

The finding of a significantly increased diagnostic yield following review by a cytopathologist with expertise in lung disease for both standard and EBUS-guided TBNA groups underscores the importance of the careful interpretation of the specimens. Interobserver and intraobserver variability is frequent in pathology and has been noted specifically with EUS and EBUS with regard to malignant diagnosis.[31] We do not believe this issue has previously been addressed in sarcoidosis patients, but variability in the interpretation of pathologic specimens may be more important in benign or preneoplastic lesions because a pathologist will always be most diligent in the detection and interpretation of malignancy. For example, in a large review of $>$ 2,000 colposcopic cytology and biopsy specimens, relatively low κ scores for reproducibility of 0.46 to 0.49[32] were reported. Regardless of this finding, the superiority of EBUS-guided TBNA persisted following the expert review.

The large incremental yield of both TBNA procedures confirms the importance of hilar and mediastinal lymph node aspiration in the bronchoscopic diagnosis of sarcoidosis, as has been previously noted in the literature,[5,8–10] even though our study was not powered adequately to show a difference in this measure between the groups. This resulted in a high overall diagnostic rate for bronchoscopy including EBUS-guided TBNA of 91.7% in a patient group with a high prevalence of stage I disease. In fact, the diagnostic yields observed following expert pathologic review of the EBUS-guided TBNA samples of 100% in patients with stage I disease and 87.5% in patients with stage II disease are comparable to that achieved with surgical mediastinoscopy,[3] and they bring into question the value of exposing patients to the additional risks of hemorrhage and pneumothorax associated with transbronchial biopsy.

One potential limitation of our study is that ROSE was not performed in either group. This may be particularly important for standard TBNA where it has been advocated by several authors based on retrospective cohort studies.[33,34] Nevertheless, ROSE has never been subjected to a randomized trial, and is not universally endorsed[35] or associated with increased yield in all studies.[36] It is also unclear whether the benefits of ROSE during TBNA yield can be extrapolated to our patient population because very few patients with sarcoidosis have been included in these studies. Previous publications[5,6,9,10] describing TBNA using a 19-gauge needle in patients with suspected sarcoidosis did not use ROSE. The utility of ROSE in the setting of EBUS-guided

TBNA remains unknown, although two of three studies[25,26] of this technique in sarcoidosis patients included this approach.

Additional biopsy procedures, such as mediastinoscopy, for patients with nondiagnostic bronchoscopy procedures were not mandated by the protocol, and these decisions were left to the treating physicians. This resulted in three patients without a confirmed diagnosis after the follow-up period. All patients had a benign course so that malignancy would appear to be unlikely. Although this could affect our sensitivity measurement should any of these patients eventually be confirmed to have sarcoidosis, it would not affect our main outcome measure of diagnostic yield.

Another limitation of our findings potentially affecting generalizability may be the specialized nature of our bronchoscopy service. Our center performed > 300 EBUS procedures during the study period with extensive prior experience with standard TBNA. This may not be representative of the experience of most bronchoscopists. Nevertheless, we believe that our results represent an optimal assessment of the true potential of both techniques in this setting.

No specific diagnosis other than sarcoidosis was confirmed during bronchoscopy or follow-up. This was likely due to our strict inclusion criteria specifying that this disease be the primary consideration based on clinical and radiologic information. In addition, only 24% of patients received specific treatment for sarcoidosis during the follow-up period. Although this raises the argument that tissue confirmation may not be required in this patient population,[1,37] the decision to proceed to biopsy was left to the discretion of the referring physician and their patients, and was made prior to the patients being referred to the investigators and was not influenced by the study. It is possible that infection remained undetected because TBNA samples were not routinely cultured, although in a 2007 series[25] of 50 similar patients, the routine culture of EBUS-guided TBNA samples did not yield a single positive result. Culturing these specimens may be more important in a patient population with a higher prevalence of mycobacterial or fungal disease.

Procedure length and amount of sedation were increased in the EBUS-guided TBNA group. Nevertheless, a 10-min increase in procedure length would appear to be reasonable to achieve these results. There were no complications related to the sedation, and all procedures were performed on an outpatient basis. In fact, the only two complications noted during the study were episodes of bleeding following standard TBNA significant enough that further passes in the lymph node station were aborted.

We conclude that EBUS-guided TBNA is the procedure of choice during bronchoscopic needle aspiration of hilar and mediastinal nodes in patients suspected of having sarcoidosis. The procedure is safe and adds a minimal amount of time to the procedure, which can be performed on an outpatient basis and can confirm the presence of granulomatous inflammation in a large proportion of patients.

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Appendix

Case review form

Case #_____

Case definitions

Study inclusion limited to patients with:

1. Pathological mediastinal or hilar adenopathy (>1 cm short axis) confirmed on Computed Tomography (CT) of the chest
2. Clinical / radiological diagnosis of sarcoidosis is considered likely diagnosis

Yes ☐ **No** ☐ **Diagnosis Confirmed**

1. **Yes** ☐ **No** ☐ Absence of a proven alternative diagnosis

AND

2. **Yes** ☐ **No** ☐ Confirmation of noncaseating granulomatous inflammation without identifiable cause on subsequent biopsy (mediastinoscopy, lung biopsy or other sites or disease involvement).

OR

3. Clinical radiological course consistent with sarcoidosis during follow-up period (specify)
   - **Yes** ☐ **No** ☐ Stability or regression of adenopathy on imaging
   - **Yes** ☐ **No** ☐ Response to corticosteroid treatment
   - **Yes** ☐ **No** ☐ Extrapulmonary manifestations compatible with sarcoidosis (see MULTIORGAN INVOLVEMENT score sheet). Specify organ and whether Definite or Probable
     - i. Specify:_____
     - ii. Specify:_____
     - iii. Specify:_____
     - iv. Specify:_____

Yes ☐ **No** ☐ **Diagnosis excluded / other diagnosis ruled-in**

Diagnosis:_____

Yes ☐ **No** ☐ **Diagnosis Uncertain**

Yes ☐ **No** ☐ **Treatment of Sarcoidosis initiated during follow-up period**

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