Respiratory Medicine (2013) **107**, 897–903

Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

CT pattern of lymphadenopathy in untreated patients undergoing bronchoscopy for suspected sarcoidosis

Rocco Trisolini [a,*], Stavros Anevlavis [a,b], Carmine Tinelli [c], Paolo Orlandi [d], Marco Patelli [a]

[a] *Thoracic Endoscopy and Pulmonology Unit, Maggiore Hospital, Largo B. Nigrisoli 2, 40133 Bologna, Italy*
[b] *Department of Pneumonology, University Hospital, Alexandroupolis, Greece*
[c] *Clinical Epidemiology & Biometry Service, IRCCS Policlinico San Matteo, Pavia, Italy*
[d] *Radiology Unit, Maggiore Hospital, Bologna, Italy*

Received 3 October 2012; accepted 27 January 2013
Available online 13 March 2013

KEYWORDS
Bronchoscopy;
Computed tomography;
Endobronchial ultrasoud-guided transbronchial needle aspiration;
Lymphadenopathy;
Sarcoidosis;
Transbronchial needle aspiration

Summary
Background and objective: Transbronchial needle aspiration procedures (TBNA, EBUS-TBNA) in sarcoidosis are associated with better results in stage I, and are preferentially performed in three lymph node stations (4R, 7, 11) as well as in the right mediastinal stations. We hypothesized that CT characteristics of lymphadenopathy, which were never systematically evaluated in untreated patients undergoing bronchoscopy for suspected sarcoidosis, could help explain the pattern of sampling and the different yield by radiographic stage of TBNA and EBUS-TBNA.
Methods: Number, size and location of lymph nodes were recorded in 74 consecutive sarcoidosis patients referred for biopsy, and were correlated with the radiographic stage.
Results: The mean number of stations harboring enlarged nodes was 8.05 per patient. Lymphadenopathy was more common in stations 7 (98.6% of patients), 11R (97.3%), 11L (86.5%), and 4R (79.7%). The overall mean size was 14.39 mm, but the largest mean size was documented in stations 7 (17.57 mm), 11R (16.83 mm), 8R (16.02 mm), and 4R (15.19 mm). The median [IQR] number of enlarged lymph node stations was significantly higher in the right than in the left mediastinum (2 [1–2] versus 0 [0–1], $p < 0.001$). No relationship was found between lymphadenopathy and sarcoidosis stage.

* Corresponding author. Tel.: +39 051 6478804; fax: +39 051 6478727.
E-mail addresses: rocco.trisolini@ausl.bologna.it (R. Trisolini), anevlavis@yahoo.com (S. Anevlavis), ctinelli@smatteo.pv.it (C. Tinelli), paolo.orlandi@ausl.bologna.it (P. Orlandi), marco.patelli@ausl.bologna.it (M. Patelli).

0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2013.01.019

Conclusions: The CT pattern of thoracic lymphadenopathy helps explain the excellent yield and the pattern of sampling of TBNA and EBUS-TBNA in sarcoidosis, but does not explain the higher yield associated with these procedures in stage I.

Introduction

Transbronchial needle aspiration procedures (TBNA and EBUS-TBNA) from hilar and mediastinal lymph nodes have become the first-step method for the pathological confirmation of sarcoidosis because of their safety and their superiority as compared to conventional endoscopic sampling methods (broncoalveolar lavage, endobronchial biopsy and transbronchial biopsy).[1–5] Beyond the very high success rate, three findings characterized most literature studies that evaluated the role of TBNA and EBUS-TBNA in sarcoidosis. First, the diagnostic yield of these procedures proved constantly higher in stage I than in stage II, by a rate ranging from 7% to 36%.[2–6] Second, the vast majority of the aspirations were performed in only 3 lymph node stations (4R, 7, 11), even in trials where EBUS-TBNA was tested.[1–10] Third, the right mediastinal stations were more frequently targeted than the left ones, by far.[1–6]

The main characteristics (number, size and location) of lymph nodes at computed tomography, and their possible differences according to the disease stage, could theoretically help explain the pattern of sampling and some specific results (e.g. higher yield in stage I) associated with TBNA and EBUS-TBNA in untreated patients undergoing biopsy for suspected sarcoidosis. Unfortunately, only two trials dating back at the '90s were specifically designed to assess the CT pattern of thoracic lymphadenopathy in sarcoidosis, to our knowledge.[11,12] These two trials provided interesting data, but they enrolled both treated and untreated patients at any time during the disease course. Furthermore, they were small-sized (25 and 40 patients), did not report the size of the lymphadenopathy, did not exclude studies lacking contrast enhancement, and used different lymph node maps to describe the lymph node location.[11,12]

The aim of the present study was to assess if the CT characteristics (size, location, number) of thoracic lymphadenopathy in untreated patients undergoing bronchoscopy for suspected sarcoidosis could help explain the pattern of sampling and some specific results (e.g. higher yield in stage I) of TBNA and EBUS-TBNA in sarcoidosis.

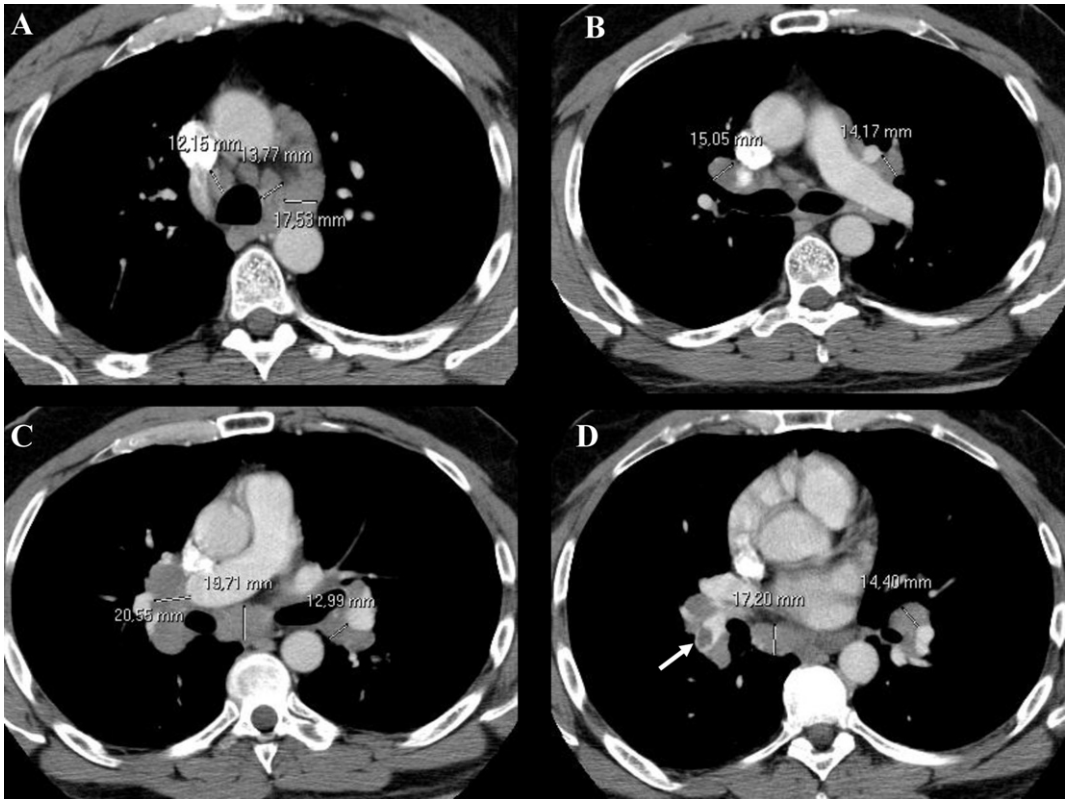

Figure 1 Contrast-enhanced CT of the chest (axial view) from a 52-yr-old male sarcoidosis patient. Enlarged lymph nodes are seen in stations (A) #4R (12.15 mm), #4L (13.77 mm), #5 (17.53 mm); (B) # 10R (15.05 mm), # 12 L (14.17 mm); (C) #11R (20.55 mm), #7 (19.71 mm), #11L (12.99 mm); (D) #8R (17.20 mm), #12L (14.40 mm). An intravascular filling defect consistent with an embolus was found, as an incidental finding, in the pulmonary artery for right lower lobe (panel D, arrow).

Methods

Study design and study population

This is a retrospective study whose protocol was approved by the Ethics Committee of the Azienda USL di Bologna (Prot. No. 803/CE). The files of the Interventional Pulmonology Unit of Maggiore Hospital (Bologna, Italy) were searched for all patients referred for the pathologic confirmation of clinically suspected sarcoidosis over a 3-year period (January 1, 2009 to December 31, 2011). Patients were included if they were 18 years or older, had sarcoidosis pathologically confirmed at the end of the diagnostic work-up, and had a contrast-enhanced CT of the chest performed before bronchoscopy. Patients were excluded if they had been given steroids or immunosuppressive drugs in the 4 weeks before bronchoscopy, as wel as if the CT they underwent before bronchoscopy was non-enhanced or was unavailable in electronic format (conditions not compatible with a reliable assessment of size, number and location of thoracic lymph nodes).

Procedures

A radiologist (P.O) and an interventional pulmonologist (R.T) jointly reviewed the contrast-enhanced CT of the chest of each patient enrolled in the study, and systematically recorded location and size of enlarged lymph nodes, as well as the number of stations harboring enlarged lymph nodes. The lymph node map recently proposed by the International Association for the Study of Lung Cancer was used to define the lymph node location.[13] Lymph nodes were considered enlarged by CT criteria if they were larger than 1 cm on their short axis. If more than one node >1 cm was present in the same station, the largest one was used for the statistical analysis. Possible disagreements between the examiners were resolved by consensus. Possible correlations between the characteristics of lymphadenopathy and sarcoiodosis stage, age, and sex were evaluated.

Statistical analysis

The Shapiro—Wilk test was used to test the normal distribution of quantitative variables. The results were expressed as mean values and standard deviation (SD), and 95% Confidence Interval were reported, as appropriate. Student *t*-test or Mann—Whitney test (if variables were all not normally distributed) were used to analyze differences between gender or sarcoidosis stage. Chi-square or Fisher exact test were used to test differences between qualitative variables. A $p < 0.05$ was considered statistically significant. All tests were two-sided. Data analysis was performed using the STATA statistical package (version 12; Stata Corporation, College Station, 2011, Texas, USA).

Table 2 Frequency and size of lymph node involvement according to the lymph node location.

Lymph node station	Frequency of involvement	Size, mm	
		Mean	SD
# 1	3/74 (4%)	16.38	6.20
# 2R	22/74 (29.7%)	12.69	2.87
# 2L	1/74 (1.3%)	10.93	NA
# 3a	6/74 (8.1%)	11.79	1.76
# 3p	10/74 (13.5%)	11.76	1.61
# 4R	59/74 (79.7%)	15.19	4.48
# 4L	31/74 (41.9%)	13.37	2.90
# 5	29/74 (39.2%)	14.33	3.69
# 6	15/74 (20.3%)	13.07	2.42
# 7	73/74 (98.6%)	17.57	5.27
# 8R	52/74 (70.3%)	16.02	4.49
# 8L	7/74 (9.5%)	13.73	2.26
# 9R	5/74 (6.8%)	13.54	3.77
# 9L	0/74 (0%)	NA	NA
# 10R	40/74 (54%)	13.64	2.91
# 10L	39/74 (52.7%)	13.24	2.20
# 11R	72/74 (97.3%)	16.83	3.89
# 11L	64/74 (86.5%)	13.60	2.69
# 12R	26/74 (35.1%)	14.38	3.90
# 12L	42/74 (56.7%)	14.07	2.30

NA: not applicable.

Results

Eighty-two patients fulfilled the inclusion criteria, but eight of them were excluded from the analysis for the following reasons: CT performed without contrast enhancement (4 patients), CT unavailable in electronic format (3 patients), and steroid treatment ongoing at the time of CT (1 patient). The main demographics of the 74 patients included in the analysis were a median [IQR] age of 45 [36—55] years, a male to female ratio of 1.05 (38/36), and a stage I to stage II ratio of 1.38 (43/31). Seventy-three patients were white, and one was black.

The mean (SD) number of all (mediastinal + hilar) stations harboring enlarged lymph nodes was 8.05 (2.83), whereas the mean (SD) number of mediastinal and hilar enlarged lymph node stations was 4.22 (1.80) and 3.82 (1.67), respectively. A combination of hilar and mediastinal lymphadenopathy was seen in 72 of 74 patients (97%)

Table 1 Mean number of enlarged LN stations according to sarcoidosis stage and sex.[a]

	Stage I	Stage II		Male	Female	
All LNs	8.20 (7.39—9.02)	7.83 (6.70—8.97)	$p = 0.58$	8.26 (7.43—9.09)	7.83 (6.76—8.89)	$p = 0.51$
Mediastinal LNs	4.13 (3.61—4.66)	4.35 (3.64—5.06)	$p = 0.61$	4.26 (3.76—4.77)	4.19 (3.49—4.89)	$p = 0.87$
Hilar LNs	4.06 (3.56—4.57)	3.48 (2.86—4.10)	$p = 0.13$	4.28 (3.43—4.57)	3.63 (3.10—4.19)	$p = 0.36$

[a] Results are expressed as mean and (95% CI).

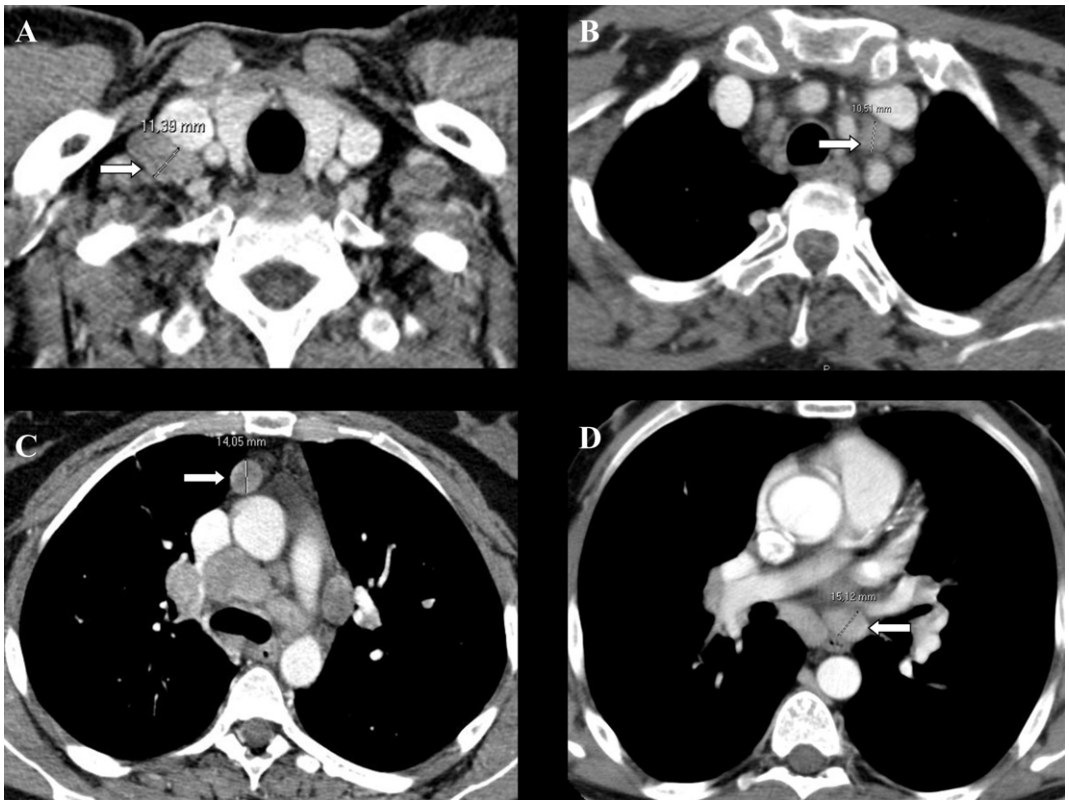

Figure 2 Contrast-enhanced CT of the chest (axial view) from 4 different sarcoidosis patients. Uncommon locations for lymphadenopathy in sarcoidosis (arrows) are stations #1 (A); #2L (B), #3a (C), and 8L (D).

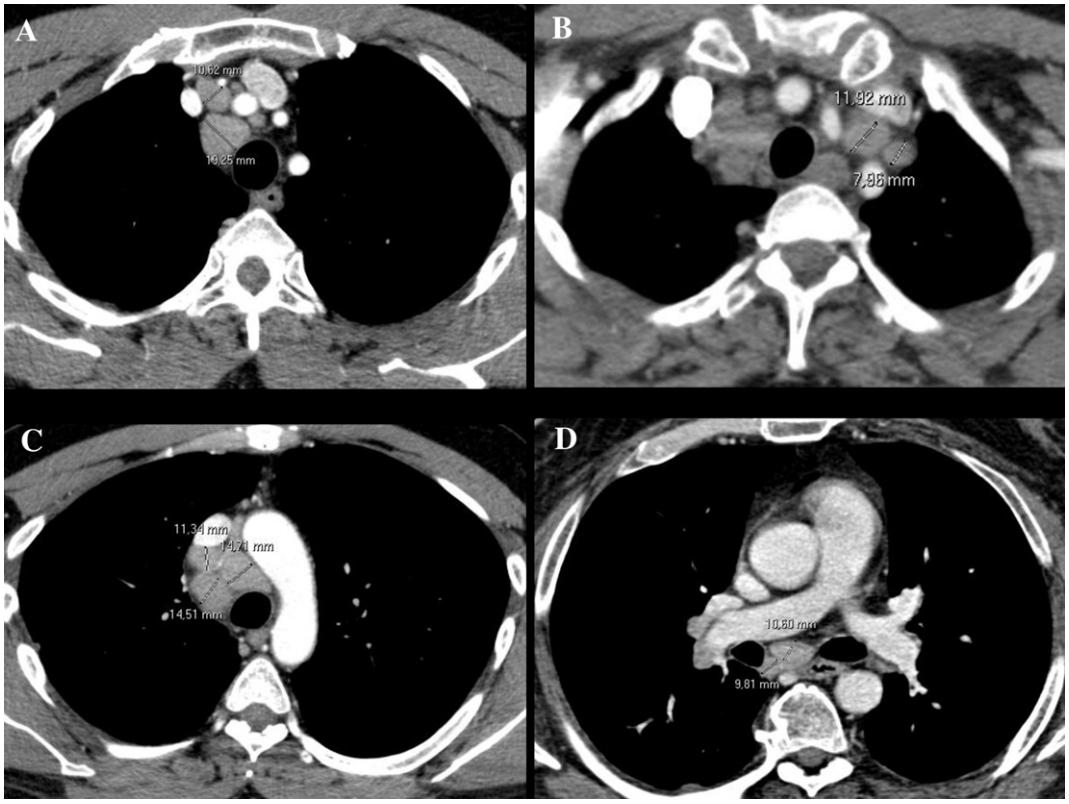

Figure 3 Contrast-enhanced CT of the chest (axial view) from 4 different sarcoidosis patients. Multiple lymph nodes are evident in stations #2R (A), #2L (B), #4R (C), and 7 (D).

(Fig. 1A–C), whereas only mediastinal nodes were enlarged in the remaining 2 patients. The mean number of stations with enlarged nodes was similar regardless of age (data not shown), sex, and sarcoidosis stage (Table 1).

Stations number 7 (98.6% of patients), 11R (97.3%), 11L (86.5%), and 4R (79.7%) were the most common location for lymphadenopathy (Table 2). Interestingly, lymph nodes in the above stations were frequently simultaneously enlarged (Fig. 1A–C). In particular, lymph nodes in stations 7 + 4R were simultaneously enlarged in 78.4% of patients, lymph nodes in stations 4R + 11 (R/L) in 71.6%, lymph nodes in stations 7 + 11 (R/L) in 85.1%, and lymph nodes in stations 4R + 7 + 11 (R/L) in 70.3%. Lymphadenopathy in stations number 1 (4% of patients), 2L (1.3%), 3a (8.1%), 8L (9.5%), and 9 (6.8%) was uncommon (Fig. 2A–C). The median [IQR] number of enlarged lymph nodes was significantly higher in the right than in the left mediastinal stations (2 [1–2] versus 0 [0–1], $p < 0.001$). The presence of several enlarged nodes in the same lymph node station was quite common (Fig. 3A–C), and a continuum of enlarged nodes without clear-cut separation between adjacent stations was frequent as well (Fig. 4). No association was seen between any single lymph node station and sex, sarcoidosis stage, and age (data not shown).

The overall mean (SD) lymph node size was 14.39 (2.14) mm (Table 2), but the mean size of lymph nodes in stations number 7 (17.57 mm), 11R (16.83 mm), 8R (16.02 mm), and 4R (15.19 mm) was larger (Table 2). The mean size of enlarged lymph nodes was similar regardless of age (data not shown), sex, and sarcoidosis stage (Table 3).

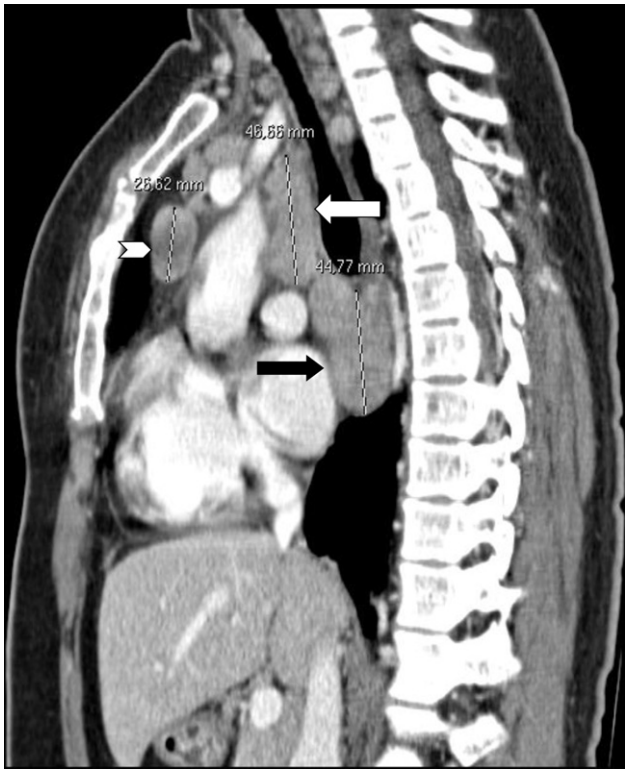

Figure 4 Contrast-enhanced CT of the chest (sagittal view) from a 41-yr-old female sarcoidosis patient showing a continuum of lymph nodes in the right paratracheal area (stations #2R through #4R, white arrow) and in the subcarinal area (stations #7 through #8R, black arrow). A long lymph node in the anterior mediastinum (station 3°, red arrow) is also visible.

Discussion

The first key characteristic of thoracic lymphadenopathy we observed at CT in our series of untreated sarcoidosis patients undergoing bronchoscopy for pathologic confirmation was the simultaneous involvement of several mediastinal and hilar stations in the vast majority (97%) of them.[11,12] A mean (SD) of 8.05 (2.83) lymph node stations per patient were, in fact, enlarged in the present series. The availability of multiple stations harboring enlarged nodes is crucial for the endoscopic diagnosis of sarcoidosis, as the number of stations sampled has been shown to influence the success rate of both TBNA and EBUS-TBNA in this setting. In a study aimed at evaluating the factors possibly predicting the yield of TBNA in sarcoidosis, Trisolini et al. demonstrated that the number of lymph node stations sampled was the only factor able to influence the diagnostic yield.[2] In particular, sampling of two lymph node stations versus one was the only variable significantly associated with a likelihood of a sarcoidosis-positive aspirate or biopsy in both univariate (odds ratio 0.15, 95% CI 0.02–0.79) and multivariate (odds ratio 0.12, 95% CI 0.02–0.70) analyses.[2] An indirect confirmation of this observation came subsequently from the randomized trial that demonstrated the superiority of EBUS-TBNA versus conventional TBNA in sarcoidosis.[14] In this study, the diagnostic yield on a per lymph node basis and on a per-station basis was not significantly different between conventional TBNA and EBUS-TBNA, and the Authors hypothesized that the true reason for the higher success rate of EBUS-TBNA over conventional TBNA was its ability to identify and sample a higher number of lymph node stations per patient (4 versus 2.2 respectively; $p < 0.05$).[14]

As for the distribution of enlarged lymph nodes, not only stations considered endoscopically "easy-to-access" (4R, 7, 11) were the most commonly involved in our series (Table 2), but the simultaneous involvement of these stations was very common as well (Fig. 1). Lymph nodes in stations 4R, 7, 11R and 11L were enlarged in 79.7%, 98.6%, 97.3%, and 86.5% of patients, respectively, and the simultaneous involvement of all these stations was found in 70.3% of patients. These figures help explain why the majority of aspirates (65%–100%) were obtained from stations 4R, 7, and 11 in all the literature studies that evaluated the role of TBNA and EBUS-TBNA in sarcoidosis.[1–10] The frequent involvement of stations 4R and 7 is of particular importance for conventional TBNA, which being a "blind" procedure, performs much better in these 2 stations due to the close proximity of the useful landmark represented by the main carina.[15–17] Curiously, we could confirm the observation, already made in previous studies,[11,12] regarding the asymmetry of the involvement of mediastinal lymph nodes in sarcoidosis. Lymph nodes belonging to stations number 2, 4, and 8 were, in fact, more commonly enlarged on the right side than on the left one (Table 2). This observation provides a plausible explanation for the fact that the right mediastinal stations were constantly more commonly targeted than their left counterpart in literature studies evaluating the role of TBNA and EBUS-TBNA in sarcoidosis.[1–10]

Table 3 Mean size of enlarged lymph nodes according to sarcoidosis stage and sex.[a]

	Stage I	Stage II		Male	Female	
All LNs	14.32 (13.71–14.93)	14.51 (13.63–15.38)	$p = 0.72$	14.60 (13.90–15.30)	14.18 (13.45–14.92)	$p = 0.41$
Mediastinal LNs	14.40 (13.61–15.18)	14.67 (13.58–15.76)	$p = 0.67$	14.78 (13.88–15.69)	14.22 (13.31–15.13)	$p = 0.38$
Hilar LNs	14.17 (13.67–14.68)	14.41 (13.53–15.29)	$p = 0.61$	14.49 (13.82–15.16)	14.05 (13.39–14.71)	$p = 0.34$

[a] Results are expressed as mean and (95% CI).

The present series provides the first estimate of the overall size of thoracic lymphadenopathy in patients undergoing biopsy for suspected sarcoiodosis, as no previous study evaluated this aspect.[11,12] Literature trials evaluating the role of transbronchial (TBNA and EBUS-TBNA) or transesophageal (EUS-NA) needle aspiration procedures in sarcoidosis provided, in fact, only the mean size of the lymph nodes that were biopsied.[1–10,17–20] The results of the present study suggest that the overall mean size of enlarged lymph node is quite smaller than the mean size of the lymph nodes that are usually sampled for diagnostic purposes. We recorded an overall mean lymph node size of 14.39 mm, but we also noticed that the mean size of the lymph nodes that are usually sampled was quite larger. The mean size of nodes in stations number 7 (17.57 mm), 4R (15.19 mm), and 11R (16.83 mm), was, in fact, larger than the overall mean lymph node size. The large size, along with the common involvement of these "easy-to-access" stations, provide more of a plausible explanation for the excellent yields obtained by the endoscopic procedures that target the mediastinum in sarcoidosis.

Age, sex, or disease stage did not influence the CT pattern of lymphadenopathy in the sarcoidosis patients of the present series. The lack of significant differences in the main characteristics (size, location, number) of enlarged nodes according to the sarcoidosis stage, in particular, tends to rule out the hypothesis that the higher yield constantly obtained by the endoscopic needle aspiration procedures in stage I of the disease could be explained by the CT pattern of lymphadenopathy. It seems more likely that a higher density of granulomas in lymph nodes of stage I patients could explain these results. Interestingly, the density of granulomas in lung tissue of sarcoidosis patients has been used to explain differences in the yield of transbronchial lung biopsy by radiographic stage. Burke and colleagues, in particular, found that the density of granulomas in transbronchial lung biopsy specimens was significantly higher in stage II and III than in stage I.[21]

In conclusion, the CT pattern of thoracic lymphadenopathy in sarcoidosis is characterized by multiple lymph node enlargements, larger size and more frequent involvement of endoscopically "easy-to-access" stations (4R, 7, 11) and predominant involvement of the right mediastinal stations. These CT findings help explain the excellent yield and the pattern of sampling of TBNA and EBUS-TBNA in sarcoidosis, but do not explain the higher yield constantly obtained by these procedures in stage I.

Conflicts of interest statement

None of the authors of the manuscript has any financial, personal, academic and/or intellectual conflict of interest. Furthermore, the study did not have any funding or sponsor.

References

1. Nakajima T, Yasufuku K, Kurosu K, et al. The role of EBUS-TBNA for the diagnosis of sarcoidosis: comparisons with other bronchoscopic diagnostic modalities. *Respir Med* 2009;**103**:1796–800.
2. Trisolini R, Tinelli C, Cancellieri A, et al. Transbronchial needle aspiration in sarcoidosis: yield and predictors of a positive aspirate. *J Thorac Cardiovasc Surg* 2008;**135**:837–42.
3. Bilaceroglu S, Perim K, Gunel O, Cagirici U, Buyuksirin M. Combining transbronchial aspiration with endobronchial and transbronchial biopsy in sarcoidosis. *Monaldi Arch Chest Dis* 1999;**54**:217–23.
4. Oki M, Saka H, Kitagawa C, et al. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. *J Thorac Cardiovasc Surg* 2012;**143**:1324–9.
5. Navani N, Booth HL, Kocjan G, 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* 2011;**16**:467–72.
6. 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.
7. Oki M, Saka H, Kitagawa C, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. *Respirology* 2007;**12**:863–8.
8. Bilaceroglu S, Mehta AC, Light R. Transbronchial needle aspiration for diagnosis of sarcoidosis. *J Bronchol* 2004;**11**:54–61.
9. Wong M, Yasufuku K, Nakajima T, Herth FJ, Sekine J, Shibuya K, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. *Eur Resp J* 2007;**29**:1182–6.
10. Fernández-Villar A, Botana MI, Leiro V, et al. Clinical utility of transbronchial needle aspiration of mediastinal lymph nodes in the diagnosis of sarcoidosis in stages I and II. *Arch Bronconeumol* 2007;**43**:495–500.
11. Sider L, Horton Jr ES. Hilar and mediastinaladenopathy in sarcoidosis as detected by computed tomography. *J Thorac Imag* 1990;**5**:77–80.
12. Patil SN, Levin DL. Distribution of thoracic lymphadenopathy in sarcoidosis using computed tomography. *J Thorac Imag* 1999;**14**:114–7.
13. Rush VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta M, Goldstraw P. The IASL Lung Cancer Staging Project. A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification of lung cancer. *J Thorac Oncol* 2009;**4**:568–77.
14. Tremblay A, Stather DR, Maceachern P, Khalil M, Field SK. A randomized controlled trial of standard versus endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. *Chest* 2009;**136**:340–6.
15. Patelli M, Lazzari Agli L, Poletti V, et al. The role of fiberscopic transbronchial needle aspiration in the staging of N2 disease due to non small cell lung cancer. *Ann Thorac Surg* 2002;**73**:407–11.

16. Harrow EM, Abi-Saleh W, Blum J, Harkin T, et al. The utility of transbronchial needle aspiration in the staging of bronchogenic carcinoma. *Am J Respir Crit Care Med* 2000;**161**:601—7.
17. Trisolini R, Lazzari Agli L, Cancellieri A, et al. The value of flexible transbronchial needle aspiration in the diagnosis of stage I sarcoidosis. *Chest* 2003;**124**:2126—30.
18. Von Bartheld MB, Veselic-Charvat M, Rabe KF, Annema JT. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcodosis. *Endoscopy* 2010;**42**:213—7.
19. Fritscher-Ravens A, Sriram PVJ, Topalidis T, Hauber H, Meyer A, Soehendra N, et al. Diagnosing sarcoidosis using endosonography-guided fine needle aspiration. *Chest* 2000; **118**:928—35.
20. Annema JT, Vaselic M, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. *Eur Resp J* 2005;**25**:405—9.
21. Burke RR, Stone CH, Havstad S, Rybicki BA. Racial differences in sarcoidosis granuloma density. *Lung* 2009;**187**:1—7.