# Tuberculosis is still the most Common Cause of Mediastinal and Intra-abdominal Lymphadenopathy by EUS-FNA in India

Manas Kumar Behera[1] Jimmy Narayan[2] Shobhit Agarwal[2] Debakanta Mishra[2] Pruthvi Reddy[2] Ayaskanta Singh[2] Girish Kumar Pati[2] Manoj Kumar Sahu[2]

[1]Department of Hepatology, SCB Medical College, Cuttack, Orrisa, India
[2]Department of Gastroenterology, Institute of Medical Sciences & SUM Hospital, Siksha O Anusandhan Deemed to be University, K8, Kalinganagar, Bhubaneswar, Orissa, India

**Address for correspondence** Manoj Kumar MD,DM Sahu, Department of Gastroenterology, Institute of Medical Sciences & SUM Hospital, Siksha O Anusandhan Deemed to be University, K8, Kalinganagar, Bhubaneswar, Orissa, 751003, India (e-mail: manojsahu@soa.ac.in).

J Digest Endosc 2021;12:133–137.

## Abstract

**Background** Lymph nodal tuberculosis is reported to occur in 4% to 7% of all tuberculosis, and mediastinal lymphadenopathy accounts for 10% of lymph nodal tuberculosis but the diagnosis still remains a challenge due to inaccessibility to these sites. There is a scarcity of recent data from India about the etiology of intra-abdominal and mediastinal lymphadenopathy despite being frequently detected in cross-sectional imaging.

**Methods** A retrospective study was conducted after reviewing hospital records over a period of 3 years from December 2017 to December 2020 who underwent endoscopic ultrasonography (EUS). A total of 126 patients with mediastinal and/or intra-abdominal lymphadenopathy detected by cross-sectional imaging were examined for clinical features, EUS, and histopathology records.

**Results** The mean age of patients was 53.12 ± 14.15 years. Seventy-one patients (56%) had intra-abdominal lymph nodes and 55 (44%) had mediastinal lymph nodes. The average number of needle passes was 2.35 ± 0.58 (range: 2–4). The majority of patients had tubercular etiology (53.2%) followed by metastatic (26.2%). Other etiologies were reactive (4.8%), lymphoma (4.8%), sarcoidosis (3.2%), and GIST (1.6%). No diagnosis could be ascertained in 6.3% of patients. The EUS features that favored tubercular etiology over metastatic were heterogeneous echotexture (72% vs. 30%), irregular shape (78% vs. 12%), indistinct borders (81% vs. 30%) and calcification (43% vs. 15%). Partial anechoic area and hyperechoic area were seen in 21% and 64% of tubercular patients, respectively. EUS only had sensitivity and specificity of 63% and 84%, respectively, and EUS FNA had a very high sensitivity and specificity of 93% and 100%, respectively.

**Conclusion** Tuberculosis is still the most common cause of lymph nodes. EUS FNA had a very high sensitivity and specificity of 93% and 100%, respectively, for the diagnosis of mediastinal and intra-abdominal lymphadenopathy.

**Keywords**
- tuberculosis
- EUS
- lymph nodes

**DOI** https://doi.org/10.1055/s-0041-1739965
**ISSN** 0976-5042



Thieme Medical and Scientific Publishers Pvt. Ltd. A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

## Introduction

Intra-abdominal and mediastinal lymph nodes are enlarged in many systemic and malignant disorders. With the advent of computed tomography (CT), ultrasonography (USG), magnetic resonance imaging (MRI), and other radiological techniques, patients with intra-abdominal and mediastinal lymph nodes are frequently referred to a gastroenterologist for evaluation. There are multiple causes of intra-abdominal and mediastinal lymphadenopathy including malignant (metastasis, lymphomas) and benign conditions (tuberculosis, sarcoidosis, reactive lymphadenopathy) and tissue diagnosis is the key to pinpointing the diagnosis. Lymph nodal tuberculosis is reported to occur in 4% to 7% of all tuberculosis and mediastinal lymphadenopathy accounts for 10% of lymph nodal tuberculosis.[1,2]

CT scan and USG-guided tissue diagnosis can be made but finding a safe percutaneous route to deep tissues (celiac, retroperitoneal node) is not always possible and aspiration of small lymph nodes is challenging.[3] Invasive procedures, such as open thoracic surgery, thoracoscopy, and laparoscopy, were previously required for histological diagnosis, but using endoscopic ultrasonography (EUS) the tissue diagnosis can be achieved easily and effectively.

EUS can easily access the lymph nodes and provide detailed information on the shape, diameter, and internal echoic features of lymph nodes. A recent meta-analysis reported that the sensitivity and specificity were 87% and 100%, respectively, for differentiating benign and malignant lymphadenopathy, respectively.[4] Malignant morphological predictors on EUS for lymph nodes include a rounded shape, size greater than 10 mm, hypoechoic echotexture, and well-defined margins. If a lymph node exhibits all four features, the accuracy of malignant diagnosis ranges from 80% to 100%.[5,6] However, only 25% of malignant lymph nodes present all four features, and benign lymph nodes are can also fulfill these criteria.[7] Several studies have shown that EUS features such as the presence of patchy anechoic/hypoechoic areas, calcifications/hyperechoic foci are predictors of tuberculosis.[8-13] There are a few studies from India, especially from the eastern region, that evaluated the etiology of abdominal and mediastinal lymphadenopathy. Hence, we felt an immense need to determine the utility of EUS-FNA in evaluating and diagnosing the etiology of intra-abdominal and mediastinal lymph nodes.

## Methods

A retrospective cohort study was conducted after reviewing the hospital records of all patients who underwent EUS at the Department of Gastroenterology IMS AND SUM hospital from December 2017 to December 2020. A total of 126 patients were available for analysis. The inclusion criterion was the presence of mediastinal or intra-abdominal lymph nodes that were detected on the CT scan and accessible from the esophagus, stomach, or duodenum. Patients were excluded if a primary lesion was identified on the CT scan of the chest, abdomen, or pelvis, and/or upper or lower gastrointestinal endoscopy. Patients were also excluded if the lymph nodes were accessible through the percutaneous route or via transabdominal ultrasonography. Data regarding the history, clinical features, and radiological investigation were retrieved.

Endoscopic ultrasound was performed using an Olympus endoscope (GF UCT 180) with a linear probe. The intra-abdominal and mediastinal lymph nodes were assessed using standard approaches. The location, number, size, margins, echogenicity, discrete or matted appearance, and presence of necrosis were noted. EUS-FNA was performed on the largest and most accessible node using an Olympus EZ Shot 3 Plus 22-gauge needle. EUS-FNA was performed under Doppler guidance to avoid intervening vascular structures. The number of passes made was recorded. No suction was used during FNA. Post-procedure, the patient was observed for 4 hours for any complication. The aspirated material was spread onto slides, which were air-dried and later alcohol-fixed and sent for cytological analysis. The final diagnosis was based on the histology of the tissue provided and response to treatment in patients where histology was inconclusive.

### Statistical Analysis

The data were analyzed using the SPSS version 20.0 (SPSS, Inc. Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation and categorical variables as the number of patients and percentages in parenthesis. Continuous data were analyzed using independent *t*-test or Mann–Whitney U test, where applicable and categorical variables were with chi-square test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of EUS and EUS FNA were calculated. *P*-values below 0.05 were considered significant.

## Results

### Clinical, Demographic, and Endosonographic Characteristics

The clinicoepidemiologic profile of patients was depicted in ►**Table 1**. Out of 126 patients, 76 (60%) were males and 50 (40%) were females. The mean age of patients was 53.12 ± 14.15 years. Clinical features of tuberculosis were seen in 82 patients. Seventy-one patients (56%) had intra-abdominal lymph nodes and 55 (44%) had mediastinal lymph nodes. The average number of needle passes was 2.35 ± 0.58 (range: 2–4). Among the mediastinal lymph nodes, the EUS FNA was done from subcarinal nodes in 34 patients, paratracheal lymph nodes in 11 patients, aortopulmonary nodes in 5 patients, paraesophageal nodes in 2 patients, and hilar nodes in 3 patients. EUS FNA in the intra-abdominal lymph node was done from peripancreatic nodes in 30 patients, periportal nodes in 24 patients, perigastric nodes in 10 patients, and celiac nodes in 7 patients. The average long axis of the lymph nodes was 2.94 ± 0.3 cm. In addition, 48% (61 patients) had irregular shape and 40% (51) had sharp margins. Echopattern distribution was heterogeneous in 60 (48%) and homogenous in 66 (52%) patients.

### Etiology of Lymphadenopathy by EUS FNA

Various etiologies are shown in ►**Fig. 1**. The majority of patients had tubercular etiology (53.2%) followed by metastatic (26.2%). Other etiologies were reactive (4.8%), lymphoma (4.8%), sarcoidosis (3.2%), and GIST (1.6%). No diagnosis could be ascertained in 6.3% of patients. Among the 82 patients clinically suspected of tuberculosis, 44 patients turned out to be lymph-node positive. The difference in endosonographic characteristics of tubercular and metastatic lymph nodes is shown in ►**Table 2**. The lymph nodes had a hyperechoic pattern in 64% of tubercular patients, while 70% of metastatic nodes were hypoechoic. Other features that favored tubercular etiology over metastatic were heterogeneous echotexture (72% vs. 30%), irregular shape (78% vs. 12%), indistinct borders (81% vs. 30%), and calcification (43% vs. 15%). A partial anechoic area was seen in 21% of tubercular patients but none in metastatic patients.

### Sensitivity and Specificity of EUS and EUS-FNA in Tuberculosis Patients

Tuberculosis was diagnosed in 53.2% of patients by EUS-FNA. (as shown in fig.2) There were eight patients in whom diagnosis could not be ascertained by EUS-FNA. Among the eight patients, five patients responded to empirical antitubercular treatment but diagnosis could not be made in the rest three patients. The sensitivity, specificity, PPV, and NPV of EUS and EUS FNA are shown in ►**Table 3**. EUS only had sensitivity and specificity of 63% and 84%, respectively, and EUS FNA had very high sensitivity and specificity of 93% and 100%, respectively.

**Table 1** Demographics and baseline endosonographic characteristics of all patients with abdominal and mediastinal lymphadenopathy

| Parameters | Values (*n* = 126) |
|---|---|
| Age (y) | 53.12 ± 14.15 |
| Gender (male:female) | 76 (60%):50 (40%) |
| Site | |
| Intraabdominal | 71 (56%) |
| Mediastinal | 55 (44%) |
| Size of nodes (cm) | 2.94 ± 3.00 |
| Homogenous | 66 (52%) |
| Heterogenous | 60 (48%) |
| Echogenicity | |
| Hypoechoic | 62 (49%) |
| Hyperechoic | 60 (51%) |
| Border | |
| Indistinct | 75 (60%) |
| Sharp | 51 (40%) |
| Shape | |
| Irregular | 61 (48%) |
| Round or oval | 65 (42%) |
| No of passes | 2.35 ± 0.58 |

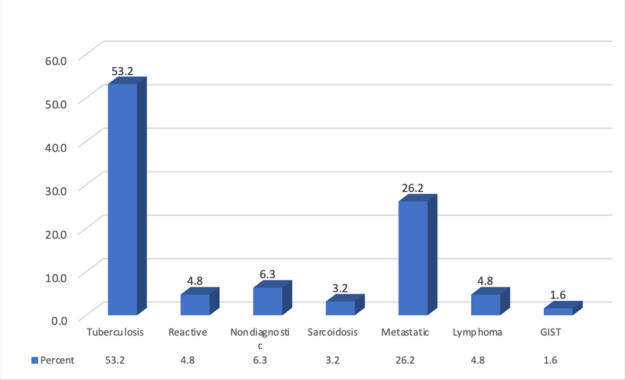



**Fig. 1** Bar diagram showing the percentage of different etiologies of abdominal and mediastinal lymphadenopathy.

## Discussion

In our study, tuberculosis (53%) and metastasis (26%) were common etiologies of mediastinal and intra-abdominal lymphadenopathy. However, other diagnoses such as reactive lymph nodes and lymphoma were also found. Tubercular lymph nodes were lesser in size, heterogenous in echotexture, indistinct border, and irregular shape as compared with metastatic lymph nodes. EUS-FNA had higher sensitivity and specificity for identifying the etiology of mediastinal and abdominal lymphadenopathy than EUS alone.

The mediastinal and intra-abdominal lymphadenopathy poses a great challenge to the gastroenterologist. Various Indian studies have found tuberculosis as the most common cause in 50 to 70% of mediastinal lymphadenopathy patients and more than 50% of abdominal lymph nodes.[8-11] However, differentiating tubercular from malignant lymph nodes by EUS is always challenging. The rounded shape, a well-defined margin of lymph nodes, size more than 10 mm along with hypoechoic echotexture can predict malignancy with an accuracy of 80 to 100%, if all these four features were present.[5,6] However, EUS alone might perhaps not be able to differentiate malignant from benign etiology as only 25% of malignant lymph nodes exhibit all these four classical features of malignancy and benign lymph nodes may also have these characteristics. Hence, EUS-FNA can reliably distinguish the etiology by obtaining tissue diagnosis. In addition, EUS-FNA can be useful in those where tissue diagnosis is not feasible due to difficult anatomical locations of lymph nodes, not amenable to other invasive investigations.[14,15]

In our study, tuberculosis was the most common etiology (53%) of mediastinal and intra-abdominal lymph nodes followed by metastatic (26%). This may be due to the high burden of tuberculosis in India. Moreover, the detection of epithelioid cell granuloma in the biopsy of lymph nodes is considered tuberculosis even if there is the absence of AFB positivity in Z-N stain due to its high endemicity in India.[16,17] A prospective study from New Delhi, India, revealed tuberculosis as the most common cause of mediastinal and intraabdominal lymph nodes in 76% of patients by EUS-FNA.[10] Another study from Mumbai, India, of 66 intra-abdominal lymph nodes revealed that EUS-FNA detected tuberculosis in 53% of patients, similar to our study.[11] EUS-FNA diagnosis of

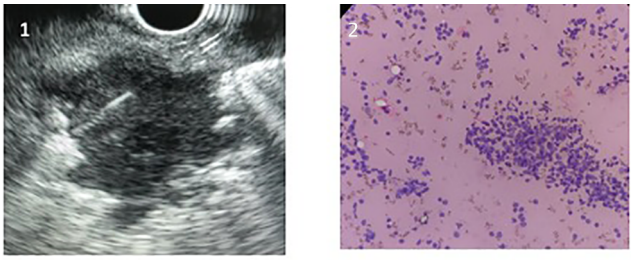
**Table 2** Comparison of demographics and endosonographic characteristics of tubercular lymph nodes and metastatic lymph nodes

| Parameters | Tuberculosis (*n* = 67) | Metastatic (*n* = 33) | *p*-Value |
|---|---|---|---|
| Age (y), mean ± SD | 48.3 ± 13.5 | 63.61 ± 13.32 | 0.001 |
| Male gender | 38 (57%) | 21 (64%) | 0.5 |
| Size of nodes (cm) | 2.37 ± 0.97 | 3.13 ± 0.64 | 0.001 |
| Homogenous | 19 (28%) | 23 (70%) | 0.001 |
| Heterogenous | 48 (72%) | 10 (30%) | |
| Echogenicity | | | 0.001 |
| Hypoechoic | 24 (35%) | 23 (70%) | |
| Hyperechoic | 43 (64%) | 10 (30%) | |
| Border | | | 0.001 |
| Indistinct | 54 (81%) | 10 (30%) | |
| Sharp | 13 (19%) | 23 (70%) | |
| Shape | | | 0.001 |
| Irregular | 52 (78%) | 4 (12%) | |
| Round or oval | 15 (22%) | 29 (88%) | |
| Partial anechoic area | 14 (21%) | 0 | 0.005 |
| Calcifications | 29 (43%) | 5 (15%) | 0.005 |
| No of passes, mean ± SD | 2.31 ± 0.52 | 2.48 ± 0.72 | 0.17 |

**Table 3** Sensitivity, specificity, positive predictive value, and negative predictive value of EUS and EUS-FNA in tuberculosis patients

| | EUS | EUS-FNA |
|---|---|---|
| Sensitivity | 62.5% | 93.1% |
| Specificity | 84.3% | 100% |
| PPV | 84.9% | 100% |
| NPV | 61.4% | 91.1% |

EUS: True-positive (TP): 45, true-negative (TN): 43, false-positive (FP): 8, false-negative (FN): 27.
EUS-FNA: True-positive (TP): 67, true-negative (TN): 51, false-positive (FP): 0, false-negative (FN): 5.




1. An ill defined and hyperechoic, heterogenous lymph node with coalescent margins seen in the hilar region
2. Smears are cellular composed of multiple epithelioid granulomas with scattered epithelioid cells and reactive lymphoid cells.

**Fig. 2** (A). An ill-defined and hyperechoic, heterogenous lymph nodes with coalescent margins seen in the hilar region. (B) Smears are cellular composed of multiple epithelioid granulomas with scattered epithelioid cells and reactive lymphoid cells.

tuberculosis was found in 62% of patients of a retrospective study from Mumbai, India.[18] Hence, despite being a high endemic region for tuberculosis, the incidence of tubercular lymphadenopathy might be decreasing in India as 40 to 50% of patients with abdominal and mediastinal lymphadenopathy had a non-tuberculosis diagnosis by EUS-FNA.

In our study, tubercular lymph nodes were lesser in size as compared with metastatic lymph nodes, with irregular margin and indistinct border and 21% had partial anechoic area. However, the partial anechoic area in the lymph node is the most discussed feature of tuberculosis in previous studies. Bodh et al and Dhir et al from India revealed a partial anechoic area in 30% of tubercular lymph nodes.[11,19] However, Rana et al from Chandigarh, India, detected this feature in 40% of tubercular lymph nodes.[8] These anechoic/hypoechoic areas represent coagulative necrosis inside tubercular lymph nodes. Another important feature of tubercular lymph nodes was an indistinct border and irregular margin, found in around 80% of tubercular lymph nodes in our study. The intense chronic inflammation in tubercular lymph nodes leads to a tendency of conglomeration to adjacent structures, hence displaying indistinct border and irregular margin in EUS.[18,20]

There are a few limitations of our study. Retrospective design is the major limitation of our study. Neither mycobacterial culture or DNA-based studies were done in our patients, other limitations of our study. There were no pathologists for rapid onsite evaluation (ROSE) in our center to strengthen our results. EUS elastography was not done in our patients to differentiate tuberculosis from malignancy. Fine needle biopsy (FNB) was not done in our study. The FNA samples were not sent for geneXpert or TB PCR. However, despite of these limitations, a large number of mediastinal and intraabdominal lymph nodes in our study evaluated by EUS and guided FNA adds significant strength to our study.

In conclusion, EUS FNA has revolutionized the evaluation of mediastinal and intra-abdominal lymph nodes by acquiring the tissue from difficult to approach locations by conventional techniques. Tuberculosis is still the most common cause of lymph nodes although nearly half of the lymph nodes were of nontuberculous origin. Smaller size, indistinct border, irregular margin, and partial anechoic areas favor the diagnosis of tuberculosis. Hence, empirical treatment of tuberculosis on the basis of imaging and clinical evidence must be strongly discouraged and EUS-FNA of lymph nodes should be done in patients when indicated prior to starting antitubercular drugs.

**Conflict of Interest**

None declared.

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