International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Role of ultrasound in differentiation between malignant and non-malignant mediastinal lymph nodes

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Abstract

Mediastinal Lymph Nodes evaluation can be done with different methods. Positron Emission Tomography (PET-CT), Magnetic Resonance Imaging (MRI), and Computed Tomography (CT) are imaging modalities with relatively high sensitivity for mediastinal disease. The gold standard for diagnosing mediastinal lesions is mediastinoscopy, but it has intraoperative and postoperative risks. Ultrasound (US) has conferred two main advantages; It is incorporated into endoscopes and allows real-time sampling of mediastinal lesions to evaluate the role of different modalities of Ultrasound in differentiation between malignant and non-malignant mediastinal lymph nodes we conducted a cross-sectional study in the Chest Department, Faculty of Medicine, Cairo University. Seventy-nine patients with CT evidence of enlarged mediastinal lymph nodes were enrolled in the study. They were subjected to neck US and Transthoracic US in parasternal areas to find accessible lymph nodes, then a transcutaneous biopsy was taken if feasible or patients referred for EBUS guided biopsy. Patients were divided into three groups, cervical, mediastinal and EBUS group The number of lymph node groups affection was significantly higher in non-malignant cases within mediastinal lymph nodes and there was insignificant difference within cervical lymph nodes. The majority of non-malignant mediastinal lymph node enlargements were due to sarcoidosis which is characterized by diffuse mediastinal lymphadenopathy, so the lymph node group number was higher in non-malignant mediastinal lymph node enlargements. The sizes of malignant mediastinal lymph nodes in ultrasonography were significantly larger than those of non-malignant lymph nodes. There weren't significant differences between the sizes of malignant and non-malignant cervical lymph nodes. Ultrasonography had detected significantly higher heterogenous texture, ill-defined borders and invasion of surrounding structures in malignant mediastinal lymph nodes in comparison to non-malignant lymph nodes. There was insignificant difference between malignant and non-malignant cervical lymph nodes as regard lymph node size. Malignant cases in mediastinal lymph nodes showed significant high vascularity with diffuse pattern during color Doppler study in comparison to non-malignant cases Ultrasound is a non-invasive, accessible, and sensitive diagnostic tool and can be used to differentiate between malignant and non-malignant mediastinal lymph nodes.

Keywords: Ultrasound, Mediastinal lymph nodes, Biopsy, Diagnosis, EBUS, TBNA.

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1. Introduction

1.1 Background

Mediastinal lymphadenopathy arises from a range of both benign and malignant causes [1]. The identification of enlarged mediastinal lymph nodes (LN) is primarily achieved through the utilization of thoracic imaging modalities [2] including; computerized tomography (CT), Magnetic resonance imaging (MRI), and Positron emission tomography (PET-CT) [5-3]. In order to establish a reliable diagnosis, the clinician is required to select from a range of available options and effectively incorporate the clinical, radiological, and pathological findings [7-6]. The final diagnosis is achieved through tissue biopsy that can be obtained via different modalities including; minimally invasive methods such as bronchoscopy/endosonography [8]or image guidance tissue sampling, and invasive methods in the form of mediastinoscopy [9] or video-assisted thoracoscopy [8]may be required in selected cases. Along with histopathological analysis of the acquired tissue sample, mediastinoscopy is the idealmethod for the diagnosi s of lesions in the mediastinum. However, it has intraoperative and postoperative hazards, and its capacity to

assess hilar nodes is restricted. These elements can make its role in mediastinal evaluation has limited applicability [10]. Over the past few decades, ultrasound imaging has become more important in pulmonary medicine, including endoscopic ultrasonography [5], conventional transcutaneous ultrasound (TUS), and endobronchial ultrasound (EBUS) [11].

The superiority of ultrasound-integrated endoscopes is mainly because they allow real-time sampling of mediastinal lesions for diagnosis and staging of malignancy [12]. EBUS-TBNA has significantly raised the ability to stage and diagnose non–small cell lung cancer with minimal invasion, and its high ability to visualize the vascular structures adjacent to area of interest. It can also obtain tissue samples of the hilar lymph nodes as well as posterior subcarinal nodes or masses [14-13]. Ultrasound-guided biopsy through the skin is an excellent method for staging of lung cancer [15]besides sampling lymph nodes that cannot be palpated in the supraclavicular, sternal notch, and lower cervical regions. It is minimally invasive, generally requires little to no anesthesia, and no radiation exposure, and is relatively affordable [16]. Thus, the study aimed to evaluate the role of different modalities of ultrasound-guided procedures in the form of cervical ultrasound (CUS), transthoracic ultrasound (TUS), and EBUS in the diagnosis of mediastinal lymphadenopathy.

2. Methods

We conducted a cross-sectional study at the Chest Department, Faculty of Medicine, Cairo University, during the period between August 2020 and July 2022. The study was performed on 79 adult subjects who were referred for clinical assessment and had CT evidence of mediastinal lymphadenopathy. Any subject with bleeding diathesis or contraindication for bronchoscopy e.g., hemodynamic instability, refractory hypoxia, recent angina, myocardial infarction, or severe pulmonary hypertension was excluded. All subjects were subjected to detailed medical history taking, and through clinical examination, computed tomography (CT) on the chest, routine laboratory workup (CBC, PT, PC, INR, Liver functions, Renal functions), and both transcutaneous cervical and transthoracic US in parasternal areas to find accessible lymph nodes. If the subject does not have enlarged lymph nodes in these areas or if the lymph node was not suitable or accessible for biopsy, he\she was referred for EBUS-guided biopsy (Fig. 1). Subjects were divided into 3 groups according to the modality of biopsy; cervical group: patients whose biopsies were taken from cervical LN, mediastinal group: patients whose biopsies were taken from mediastinal LN visualized by TUS in para-sternal areas (Internal mammary, Prevascular, and Para-Aortic LN), and EBUS group: patients whose biopsy were taken with CP-EBUS guidance. Ultrasonography was done using Hitachi EUB7000. All cases were examined by ultrasound with curvilinear transducer (3.5 MHz) and linear array transducer (13 MHz). The procedure was conducted under local anesthesia using 5 ml lidocaine (xylocaine) 2% for the skin and subcutaneous tissue.

All biopsies using true-cut needle were performed under direct ultrasound guidance and subjects were requested to remain motionless during the procedure. At least three true-cut needle biopsies were taken using a 14-gauge cutting needle under sterile technique and local anesthesia, the subjects were assessed post-biopsy to detect any complications. The biopsy specimens were kept in cups full of formalin and sent for examination by histopathology, then Hematoxylin and Eosin stains were used to stain the specimens and light microscope examination was done, some biopsies required immune-histochemical confirmation. The procedure of EBUS–TBNA was done according to CHEST guidelines [17].

2.1 Statistical analysis

The statistical analysis was conducted using IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows. Categorical variables were presented in count and percent and compared using the Pearson Chi-square test, or Fisher exact test when count less than 5. Quantitative variables were presented in mean ± standard deviation (± SD), or median, and range according to Kolmogorov Smirnov normality test. The Kruskal Wallis test was used for comparison between groups, and Wilcoxon sign rank test was used for paired comparison. Diagnostic indices were calculated using a 2x2 contingency table. All tests were two sided and p-value <0.05 was considered significant.

3. Results and Discussion

The study included 79 subjects; twenty-four patients presented with accessible cervical lesions, thirty-one by US-accessible mediastinal lesions, and twenty-four patients presented with inaccessible lesions and were indicated for EBUS. Cervical and EUBS groups were significantly older compared to mediastinal group (p-value=0.001). Smoking was more prevalent among cervical group (p-value =0.001). However there was no difference in gender distribution between groups (Table 1).Tissue biopsy was taken from all included subjects and results showed that 20 lesions were malignant and 4 were benign in the cervical group, 30 lesions were malignant in the mediastinal group and only one was a benign lesion, while EBUS showed 11 malignant lesions and 13 benign lesions. (Table 2) (Fig. 2,3,4). The study of lymph node ultrasound features in malignant versus non-malignant lymph nodes within the different groups (table 3) revealed that there were insignificant differences between malignant and non-malignant cases in cervical and mediastinal groups (p=0.081and p=0.913 respectively) as regard the number of lymph node groups affected. In EBUS group the non-malignant cases had significantly (p=0.008) higher number of lymph node groups affected than malignant cases. As EBUS group had relatively larger number of non-malignant cases and as most of the non-malignant cases were sarcoidosis, which is characterized by affection of most of mediastinal lymph node groups, so the non-malignant cases had higher number of lymph node groups affected than malignant cases.

Ultrasound had detected insignificant differences in lymph node texture between malignant and non-malignant cases in cervical and mediastinal groups (p=0.552 and p=0.677 respectively). In EBUS group there is higher percent of non-malignant cases with less lymph node breakdown so ultrasound had detected more homogenous texture in non-malignant cases than in malignant cases with significant statistical difference (p=0.007). Ultrasound had

detected insignificant differences in lymph node border between malignant and non-malignant cases in cervical and mediastinal groups (p=1 and p=0.294 respectively). In EBUS group there is higher percent of non-malignant cases with more respect of lymph node borders. Ultrasonography had visualized the whole lymph node in cervical and EBUS groups so had detected higher capsular invasion in malignant cases in comparison to non-malignant cases with significant statistical difference (p=0.012 and p=0.0001 respectively). As regard vasculature site and distribution, ultrasonography had found insignificant difference between malignant and non-malignant lymph nodes in cervical and EBUS groups (p=0.698 and p=0.542 respectively).

Mediastinal lymph nodes were examined with ultrasound in 58 cases, 44 were malignant and 14 were benign. Cervical lymph nodes were examined with ultrasound in 25 cases; 21 malignant and 4 were benign.

The comparison between ultrasound features in malignant versus non-malignant cases in mediastinal lymph nodes and cervical lymph nodes (table 4) revealed that the number of lymph node groups affection was significantly higher in non-malignant cases within mediastinal lymph nodes and there was insignificant difference within cervical lymph nodes. The majority of non-malignant mediastinal lymph node enlargements were due to sarcoidosis, which is characterized by diffuse mediastinal lymphadenopathy, so the lymph node group number was higher in non-malignant mediastinal lymph node enlargements. The sizes of malignant mediastinal lymph nodes in ultrasonography were significantly larger than those of non-malignant lymph nodes. There weren't significant differences between the sizes of malignant and non-malignant cervical lymph nodes. Ultrasonography had detected significantly higher heterogenous texture, ill-defined borders and invasion of surrounding structures in malignant mediastinal lymph nodes in comparison to non-malignant lymph nodes. There was insignificant difference between malignant and non-malignant cervical lymph nodes as regard lymph node size. Malignant cases in mediastinal lymph nodes showed significantly high vascularity with diffuse pattern during color Doppler study in comparison to non-malignant cases.

Mediastinal lymphadenopathy, paratracheal lesions, and peri-bronchial are challenging situations for clinicians due to the diversity of causes and the difficulty of obtaining tissue biopsy from these regions. Mediastinoscopy and thoracoscopy are invasive procedures that have historically served as the main methods for taking a biopsy of lesions in the mediastinum(1). We conducted a cross-sectional study to evaluate the role of different modalities of Ultrasound in differentiation between malignant and non-malignant mediastinal lymph nodes.

The study of lymph node ultrasound features in malignant versus non-malignant lymph nodes within the different groups (table 3) revealed that there were insignificant differences between malignant and non-malignant cases in cervical and mediastinal groups (p=0.081and p=0.913 respectively) as regard the number of lymph node groups affected. In EBUS group the non-malignant cases had significantly (p=0.008) higher number of lymph node groups affected than malignant cases. As EBUS group had relatively larger number of non-malignant cases and as most of the non-malignant cases were sarcoidosis, which is characterized by affection of most of mediastinal lymph node groups, so the non-malignant cases had higher number of lymph node groups affected than malignant cases.Ultrasound had detected insignificant differences in lymph node texture between malignant and non-malignant cases in cervical and mediastinal groups (p=0.552 and p=0.677 respectively). In EBUS group there is higher percent of non-malignant cases with less lymph node breakdown so ultrasound had detected more homogenous texture in non-malignant cases than in malignant cases with significant statistical difference (p=0.007). This agreed with Joseph et al. (2022), who found that Lymph nodes with heterogeneous echogenicity have a higher probability of being malignant (18) and Abedini et al. (2020), who found that heterogenous echogenicity is higher in malignant cases (19).

Bayanati et al. (2015), studied texture and shape analysis in CT for the differentiation of benign and malignant mediastinal nodes and by using optimum-threshold criteria, the combined textural and shape features identified malignant mediastinal nodes with 81% sensitivity and 80% specificity (P < 0.0001). Using this combination, 84% malignant and 71% benign nodes were classified correctly(20). Ultrasound had detected insignificant differences in lymph node border between malignant and non-malignant cases in cervical and mediastinal groups (p=1 and p=0.294 respectively). In EBUS group there is higher percentage of non-malignant cases with more respect of lymph node borders so ultrasound had detected more well defined margin in non-malignant cases than in malignant cases with significant statistical difference (p=0.00001). Jayapal et al. (2019), found that irregular margin by US has highest predictability for malignancy followed by the size but internal echo structure has highly variable correlation with histopathology(21). Ultrasonography had visualized the whole lymph node in cervical and EBUS groups so had detected higher capsular invasion in malignant cases in comparison to non-malignant cases with significant statistical difference (p=0.012 and p=0.0001 respectively). In mediastinal group ultrasonography couldn't visualize the whole mediastinal lymph node as it could be partially masked by sternum, ribs or aereated lung so couldn't detect significant difference between malignant and non-malignant cases as regard capsular invasion (p=0.294). As regard vasculature site and distribution, ultrasonography had found insignificant difference between malignant and non-malignant lymph nodes in cervical and EBUS groups (p=0.698 and p=0.542 respectively). Ultrasonography in mediastinal group had found that the malignant lymph nodes had a diffuse pattern of vasculature in comparison to non-malignant lymph with significant statistical difference (p=0.032). The presence of diffuse vascular pattern in malignant lymph nodes in mediastinal group may help them to reach large sizes. This finding was compatible with Gogia et al. (2015), found that the presence of central vasculature were predictive of a benign aetiology(22). Mediastinal lymph nodes were examined with ultrasound in 58 cases, 44 were malignant and 14 were benign. Cervical lymph nodes were examined with ultrasound in 25 cases; 21 malignant and 4 were benign.

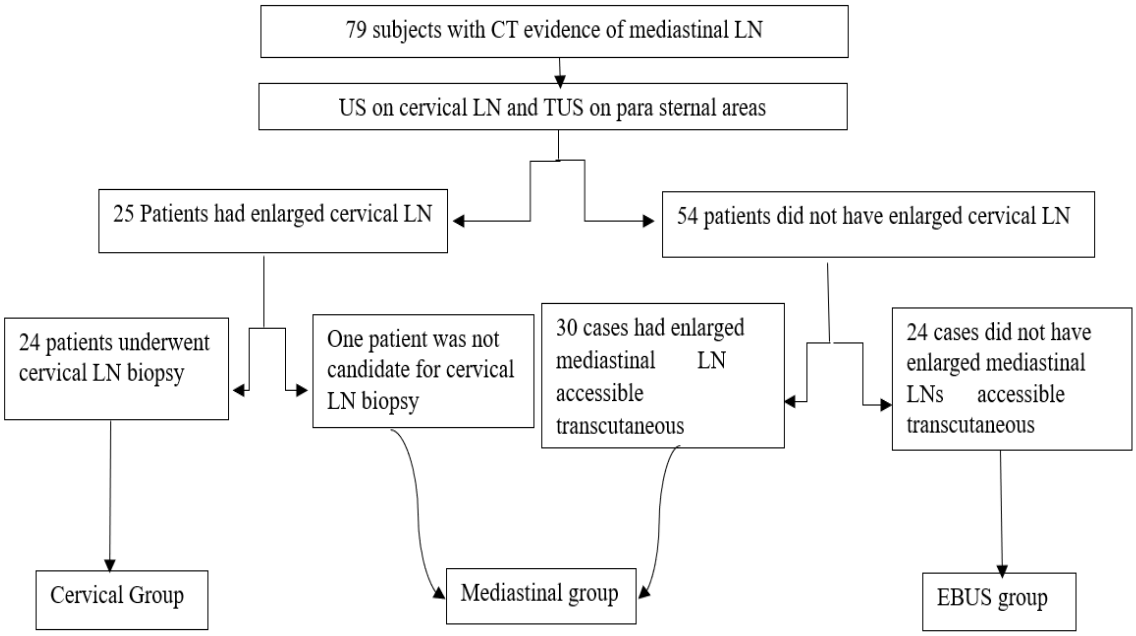

Figure 1: Patients' disposition and diagnostic approaches used for each group

Table 1: Demographics and medical history of the included patients according to the studied groups

Clinical Data	Cervical Group (n=24)	Mediastinal Group (n=31)	EBUS Group (n=24)	P-value
Sex: Male (n, %)	18 (75%)	16 (51.6%)	16 (66.7%)	0.187
Age (Mean ± SD)	48.21±15.05	36.23±14.95	49.33±16.05	0.001
Smoking (yes)	16 (66.7%)	6 (19.4%)	13 (54.2%)	0.001
Congested Non-Pulsating Neck veins (yes)	3 (12.5%)	3 (9.7%)	1 (4.2%)	0.584

Significant p-value <0.05

Table 2: Histopathology findings according to the studied groups

Diagnosis		Cervical Group (n=24)	Mediastinal Group (n=31)	EBUS Group (n=24)
Malignant	Lymphoma	10 (41.7%)	24 (77.4%)	2 (8.3%)
	Met. Adeno.	10 (41.7%)	3 (9.7%)	9 (37.5%)
	Ewing Sarcoma	0 (0.0%)	1 (3.2%)	0 (0.0%)
	Thymoma	0 (0.0%)	2 (6.5%)	0 (0.0%)
Non-Malignant	TB	1 (4.2%)	1 (3.2%)	3 (12.5%)
	Sarcoidosis	3 (12.5%)	0 (0.0%)	10 (41.7%)

Table 3: Ultrasound features in malignant versus non-malignant LN in different groups

Groups / Ultrasound Features		Cervical Group Cer. LN (24)		Mediastinal G. M. LN (31)		EBUS Group M. LN (24)	
		Malig (20)	Non-M. (4)	Malig (30)	Non-M. (1)	Malig (11)	Non-M (13)
No. of LN Groups	Mean	1.10	1.00	1.97	2	2.91	4.54
	St. d.	0.308	0	0.32	0	1.764	1.198
	p value	0.081		0.913		0.008	
Shape	Rounded	5	0	0	0	0	0
	Oval	15	4	30	1	11	13
	p value	0.544		1		1	
Size (cm)	Mean	2.01	2.00	7.69	6	4.181	3.631
	St. d.	0.591	0.707	4.11	0	1.764	1.347
	p value	0.986		0.654		0.482	
Architecture	Normal	0	0	0	0	0	1
	Abnormal	20	4	30	1	11	12
	p value	1		1		0.542	
Texture	Homogeneous	15	2	20	1	3	11
	Heterogeneous	5	2	10	0	8	2
	p value	0.552		0.677		0.007	
Border	Well Defined	20	4	14	1	1	13
	Ill Defined	0	0	16	0	10	0
	p value	1		0.294		0.00001	
Capsule	Intact	5	4	14	1	1	13
	Invaded	15	0	` 6	0	10	0
	p value	0.012		0.294		0.0001	
Invasion of Surrounding	No	20	4	17	1	9	13
	Yes	0	0	13	0	2	0
	p value	`1		0.388		0.199	
Vasculature Site	Central	2	1	0	0	0	1
	Peripheral	5	1	0	1	0	0
	Diffuse	13	2	30	0	11	12
	p value	0.698		0.032		0.542	
Vasculature Degree	Scanty	1	0	0	0	0	1
	Moderate	12	4	18	1	9	12
	High	7	0	12	0	2	0
	p value	0.301		0.613		0.194	

Cer. LN --- Cervical Lymph Nodes
M. LN --- Mediastinal Lymph Nodes

Table 4: Ultrasound features in malignant versus non-malignant cases in Mediastinal LN and Cervical LN

Groups / Ultrasound Features		Mediastinal LN (58)		Cervical LN (25)	
		Malig.(44)	Non-M. (14)	Malig. (21)	Non-M. (4)
No. of LN Groups	Mean	2.227	4.357	1.1	1
	St. d.	0.911	1.336	0.30	0
	p value	0.0001		0.528	
Shape	Rounded	0	0	5	0
	Oval	44	14	16	4
	p value	1		0.275	
Size (cm)	Mean	6.607	3.8	2.03	2
	St. d.	3.834	1.440	0.586	0.707
	p value	0.008		0.938	
Architecture	Normal	0	1	0	0
	Abnormal	44	13	21	4
	p value	0.241		1	
Texture	Homogeneous	15	11	16	2
	Heterogeneous	29	3	5	2
	p value	0.005		0.285	
Border	Well Defined	18	14	20	4
	Ill Defined	26	0	1	0
	p value	0.0001		0.656	
Capsule	Intact	17	14	5	4
	Invaded	27	0	16	0
	p value	0.0001		0.004	
Invasion of Surrounding	No	29	14	21	4
	Yes	15	0	0	0
	p value	0.012		1	
Vasculature Site	Central	0	1	2	1
	Peripheral	0	1	5	1
	Diffuse	44	12	14	2
	p value	0.039		0.664	
Vasculature Degree	Scanty	0	1	1	0
	Moderate	30	13	13	4
	High	14	0	7	0
	p value	0.014		0.326	

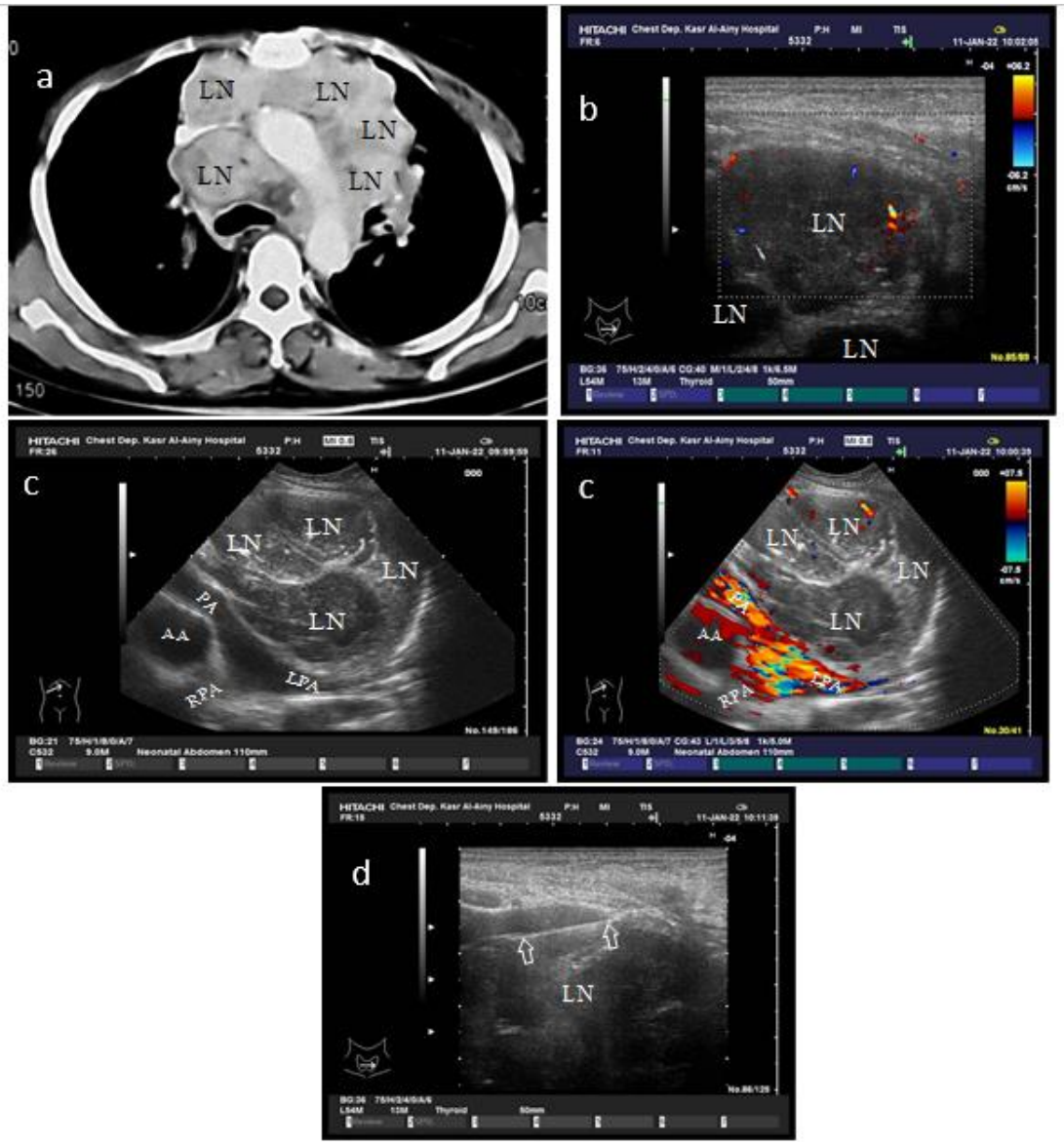

Figure 3: Mediastinal Group, Non-malignant case (TB) (a)CT: Multiple mediastinal LNs(b):US, Doppler, multiple mediastinal LNs(c): Convex probe US, color Doppler, multiple mediastinal LNs with central necrosis and peripheral vasculature(d):Linear probe US, True-cut Needle (white hollow arrows) biopsy from Lt. prevascular mediastinal LN.

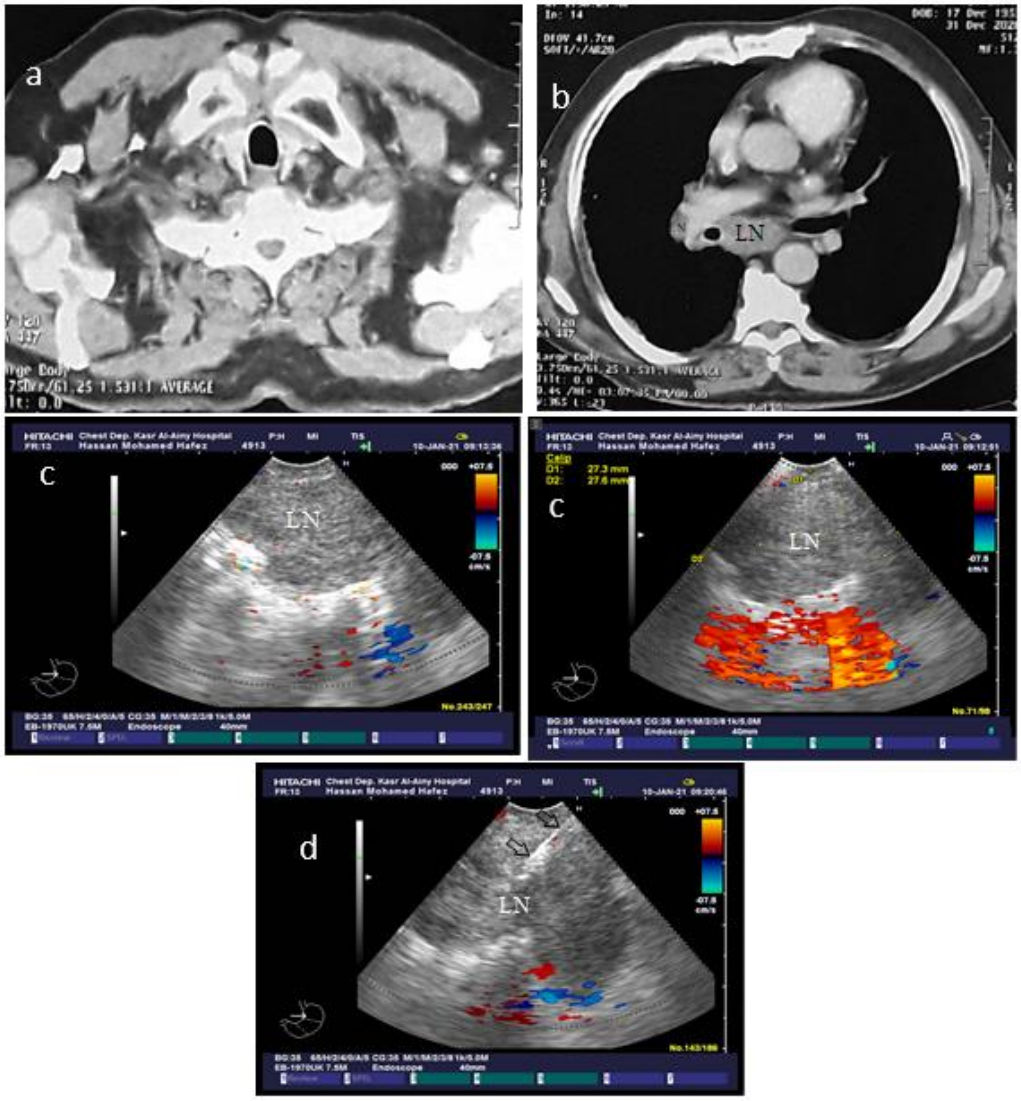

Figure 4: EBUS Group, Malignant case (Lymphoma)(a) CT: No cervical LN(b): CT: Subcarinal LN(c): EBUS: Subcarinal LN with destruction of architecture and invasion of the capsule and surrounding structures(d): CP-EBUS guided TBNA (Black hollow arrows) from Subcarinal LN

List of Abbreviations

CBC	Complete blood count
CP-EBUS	Convex probe endobronchial ultrasound
CT	Computed tomography
EBUS	Endobronchial ultrasound
EBUS-TBNA	Endobronchial ultrasound - transbronchial needle aspiration
INR	International normalized ratio
LN	Lymph Node
Met. Adeno.	Metastatic Adenocarcinoma
MRI	Magnetic resonance imaging
PC	Prothrombin concentration
Pet	Positron Emission Tomography
PT	Prothrombin time
SD	Standard deviation
TB	Tuberculosis
TBNA	Transbronchial needle aspiration
TMUS	Trans cutaneous Mediastinal Ultrasound
TUS	Thoracic Ultrasound
US	Ultrasound

The comparison between ultrasound features in malignant versus non-malignant cases in mediastinal lymph nodes and cervical lymph nodes (Table 4) revealed that the number of lymph node groups affection was significantly higher (p=0.0001) in non-malignant cases within mediastinal lymph nodes and there was insignificant difference within cervical lymph nodes (p=0.528). The majority of non-malignant mediastinal lymph node enlargements were due to sarcoidosis which is characterized by diffuse mediastinal lymph adenopathy so the lymph node group number was higher in non-malignant mediastinal lymph node enlargements. The sizes of malignant mediastinal lymph nodes in ultrasonography were significantly (p=0.008) larger than those of non-malignant lymph nodes as the growth of malignant cases is more rapid than in non-malignant cases over time, a finding that agreed with Gogia et al. (2015), who found that lymph node size was <10 mm were predictive of a benign aetiology and Joseph et al. (2022), who found that the size of lymph nodes based on a small axis diameter; >10 mm is considered to be indicative of malignancy(18, 22).

While there wasn't significant differences between the sizes of malignant and non-malignant cervical lymph nodes (p=0.938) may be due to early detection after cervical lymph node affection before reaching large sizes. There is a direct relation between lymph node size and occurrence of central breakdown, ill-defined margins and invasion of surrounding structures so ultrasonography had detected significantly higher heterogenous texture, ill-defined borders and invasion of surrounding structures (p=0.005, p=0.0001 and p=0.012 respectively) in malignant mediastinal lymph nodes in comparison to non-malignant lymph nodes. These findings agreed with Jhun et al. (2014) and Abedini et al. (2020), who reported that lymph nodal characteristics predictive of malignancy are size greater than 10 mm, round shape, heterogeneous appearance, and absence of central hilar structure, a malignant LN had at least one of these independent factors (19, 23).

There was insignificant difference between malignant and non-malignant cervical lymph nodes as regard lymph node size and so also ultrasonography couldn't detect significant difference in lymph node texture, border delineation and invasion of surrounding structures (p=0.285, p=0.656 and p=1 respectively) between malignant and non-malignant cervical lymph nodes. Ultrasonography had detected lymph node capsular invasion with significant statistical difference in malignant cases within both mediastinal lymph nodes and cervical lymph nodes (p=0.0001 and p=0.004 respectively).

Malignant cases in mediastinal lymph nodes had showed significant high vascularity with diffuse pattern (p=0.014 and p=0.039 respectively) during color Doppler study in comparison to non-malignant cases which could explain the larger sizes they had reached.

4. Conclusions

Ultrasound is a minimally invasive procedure for diagnosis of mediastinal lymphadenopathy with high diagnostic accuracy and it can differentiate between features of malignant and non-malignant mediastinal lymph nodes.

References

[1] H. Iyer, A. nand, P.B. Sryma, K. Gupta, P. Naranje, N. Damle, S. Mittal, N.K. Madan, A. Mohan, V. Hadda, P. Tiwari, R. Guleria & K. Madan. (2021). Mediastinal lymphadenopathy: a practical approach. Expert review of respiratory medicine. 15(10), 1317–1334.

[2] M. Dabrowska, K. Faber, M. Tandejko-Burdyna, P. Korczynski & R. Krenke. (2019). Etiology of mediastinal lymph node enlargement in patients who underwent EBUS-TBNA.

[3] A. Al-Ibraheem, N. Hirmas, S. Fanti, D. Paez, F. Abuhijla, D. Al-Rimawi, U. Al-Rasheed, R. Abdeljalil, F. Hawari, K. Alrabi & A. Mansour. (2021). Impact of 18F-FDG PET/CT, CT and EBUS/TBNA on preoperative mediastinal nodal staging of NSCLC. BMC medical imaging. 21(1), 49.

[4] H.A.A. Youssef, M.A. Elzorkany, S.A. Hussein, T.A. Taymour & M.H. Abdel Gawad. (2019). Evaluation of mediastinal lymphadenopathy by diffusion weighted MRI; correlation with histopathological results. Advances in respiratory medicine. 87(3), 175–183.

[5] H.J. Meyer, B. Schnarkowski, J. Pappisch, T. Kerkhoff, H. Wirtz, A.K. Höhn, S. Krämer, T. Denecke, J. Leonhardi & A. Frille. (2022). CT texture analysis and node-RADS CT score of mediastinal lymph nodes - diagnostic performance in lung cancer patients. Cancer imaging: the official publication of the International Cancer Imaging Society. 22(1), 75.

[6] P. Vilmann, P.F. Clementsen, S. Colella, M. Siemsen, P. De Leyn, J.M. Dumonceau, F.J. Herth, A. Larghi, E.L. Vazquez-Sequeiros, E., Hassan, C., Crombag, L., Korevaar, D. A., Konge & J.T. Annema. (2015). Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). The European respiratory journal. 46(1), 40–60.

[7] E.D. Crouser, L.A. Maier, K.C. Wilson, C.A. Bonham, A.S. Morgenthau, K.C. Patterson, E. Abston, R.C. Bernstein, R. Blankstein, E.S. Chen, D.A. Culver, W. Drake, M. Drent, A.K. Gerke, M. Ghobrial, P. Govender, N. Hamzeh, W.E. James, M.A. Judson, L. Kellermeyer & R.P. Baughman. (2020). Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. American journal of respiratory and critical care medicine. 201(8), e26–e51.

[8] D.A. Dziedzic, A. Peryt & T. Orlowski. (2017). The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis. The clinical respiratory journal. 11(1), 58–63

[9] S. Onat, G. Ates, A. Avcı, T. Yıldız, A. Birak, C. Akgul Ozmen & R. Ulku. (2017). The role of mediastinoscopy in the diagnosis of non-lung

cancer diseases. Therapeutics and clinical risk management. 13, 939–943.

[10] L. Socci, S. Sionis & A. Sharkey. (2021). Complications of mediastinoscopy. Shanghai Chest. 5.

[11] T.Y. Park & J.S. Moon. (2022). Outcome of Endoscopic Ultrasound-Guided Sampling of Mediastinal Lymphadenopathy. Gastroenterology research and practice. 2022, 4486241.

[12] L. Fuso, F. Varone, D. Magnini, M. Calvello, E. Lo Greco & L. Richeldi. (2018). Ultrasonography of the Mediastinum: Techniques, Current Practice, and Future Directions. Respiratory care. 63(11), 1421–1438.

[13] T. Ye, H. Hu, X. Luo & H. Chen. (2011). The role of endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) for qualitative diagnosis of mediastinal and hilar lymphadenopathy: a prospective analysis. BMC cancer. 11, 100.

[14] V. Scano, A.G. Fois, A. Manca, F. Balata, A. Zinellu, C. Chessa, P. Pirina & P. Paliogiannis. (2022). Role of EBUS-TBNA in Non-Neoplastic Mediastinal Lymphadenopathy: Review of Literature. Diagnostics (Basel, Switzerland). 12(2), 512.

[15] H.A. Abu-Youssef, K.M. Kamel, S. Selim & S.M.G. El-Deen. (2014). Study of the added value of transthoracic ultrasound in staging of lung cancer. Egyptian Journal of Chest Diseases and Tuberculosis. 63(4), 1025-1034.

[16] D. Teng, C. Dong, D. Sun, Z. Liu & H. Wang. (2022). Comparison of Ultrasound-Guided Core Needle Biopsy Under the Assistance of Hydrodissection With Fine Needle Aspiration in the Diagnosis of High-Risk Cervical Lymph Nodes: A Randomized Controlled Trial. Frontiers in oncology. 11, 799956.

[17] M.M. Wahidi, F. Herth, K. Yasufuku, R.W. Shepherd, L. Yarmus, M. Chawla, C. Lamb, K.R. Casey, S. Patel, G.A. Silvestri & D.J. Feller-Kopman. (2016). Technical Aspects of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration: CHEST Guideline and Expert Panel Report. Chest. 149(3), 816–835.

[18] T. Joseph, S. Reddy, N. Gupta, A. Perathur, A. George, V. Chandraprabha & N. Shajil. (2022). Correlating Ultrasonographic Features of Lymph Nodes During Endobronchial Ultrasound With Final Outcome. Cureus. 14(7), e26554.

[19] A. Abedini, F. Razavi, H. Mehravaran, M.P. Toutkaboni, A. Kashefizadeh, H. Emami & A. Kiani. (2020). Identification of sonographic features for predicting benign versus malignant mediastinal or hilar lymph nodes using endobronchial ultrasound. Oman Medical Journal. 35(2), e112.

[20] H.E. Bayanati, R. Thornhill, C.A. Souza, V. Sethi-Virmani, A. Gupta, D. Maziak, K. Amjadi & C. Dennie. (2015). Quantitative CT texture and shape analysis: can it differentiate benign and malignant mediastinal lymph nodes in patients with primary lung cancer?. European radiology. 25(2), 480–487.

[21] N. Jayapal, S.K.M. Ram, V.S. Murthy, S.A. Basheer, S.V. Shamsuddin & A.B. Khan. (2019). Differentiation Between Benign and Metastatic Cervical Lymph Nodes Using Ultrasound. Journal of pharmacy & bioallied sciences. 11(Suppl 2), S338–S346.

[22] P. Gogia, T.Z. Insaf, W. McNulty, A. Boutou, A.G. Nicholson, Z. Zoumot & P.L. Shah. (2016). Endobronchial ultrasound: morphological predictors of benign disease. ERJ open research. 2(1), 00053-2015.

[23] B.W. Jhun, S.W. Um, G.Y. Suh, M.P. Chung, H. Kim, O.J. Kwon, J. Han & K.J. Lee. (2014). Clinical value of endobronchial ultrasound findings for predicting nodal metastasis in patients with suspected lymphadenopathy: a prospective study. Journal of Korean medical science. 29(12), 1632–1638.