Assessment of efficacy of ultrasonography in cervical lymphadenopathy in oral malignancies

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Abstract

Aims and Objectives: To substantiate the use of ultrasonography in diagnosis of cervical lymphadenopathy in oral malignancies and to assess if ultrasonographic examination done prior to lymph node (LN) biopsy can yield important information regarding the diagnosis. **Materials and Methods:** Twenty subjects with histopathologically confirmed oral malignant lesions with clinically palpable and untreated cervical LNs included into study. These patients were subjected to clinical examination (number of LNs, shape, size, location, overlying temperature, overlying skin, tenderness, consistency, and fixity to the underlying structures), and ultrasonographic evaluation (number of LNs, shape, size (mm), location, borders, matting, peripheral halo, hilum, calcification, necrosis, reticulation, and echogenicity) of the LNs, and finally, histological assessment was done after surgical excision during the course of treatment. **Results:** Predominantly male (65%) patients were having with malignant LN involvement with age group of 60–69 years, i.e., 35%. Ultrasonogram is superior to clinical examination as it detected additional 49 nodes. Malignant nodes tend to have longest axial diameter (17 mm with standard deviation of 8.7 mm). Over all 52 malignant nodes were round, whereas 35 nodes were oval in shape. Most of the nodes were detected in submandibular region. Around 61 (70.9%) nodes had sharp borders and 26 (29.9%) had smooth borders. Loss of echogenic hilus is a common feature of malignancy showing 70% sensitivity and 67% specificity. Most of malignant nodes were hypoechoic. Around 51 (58.6%) of nodes showed intranodal necrosis, whereas it was absent in 36 (41.4%) nodes. Matting and edema were present 25 (28.7%) nodes. Intranodal calcification was present in 37 nodes. Sensitivity of USG was 90%, whereas specificity was 100%. **Conclusion:** Ultrasonographic examination of cervical LNs can yield important information regarding the diagnosis. Ultrasound examination should be done prior to FNAC and ideally an ultrasound-guided FNAC.

Keywords: Histopathology, lymphadenopathy, malignant, sensitivity, ultrasonography

Introduction

Imaging techniques play a very important role in diagnosing head and neck pathologies especially those involving deeper soft tissues. Lymphadenopathy is one such condition where critical evaluation becomes mandatory not only to assess the severity of the disease but also to determine disease prognosis and proper treatment planning. Clinical examination of cervical lymph nodes (LNs) is important in such patients but mostly remains difficult owing to their diverse location and multiple numbers. Ultrasound has higher sensitivity (96.8%) than palpation (73.3%) for detection of cervical LNs.[1]

Although computed tomography (CT) scan and magnetic resonance imaging (MRI) are valuable diagnosis aids, both are expensive and not universally available. Moreover, CT scan exposes the patient to relatively large doses of radiation, and

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MRI is expensive, time-consuming, and not suitable for every patient. Ultrasound is a useful imaging modality in assessment of soft tissue lesions. Ultrasonography is an easy, reproducible, noninvasive, no risk procedure, radiation-free imaging modality to examine the LNs. Sonography is a known modality for staging head and neck tumors and its sensitivity is greater than clinical examination and even CT scan.[2]

CT and MRI can be used for evaluation of LNs, but they are less sensitive than ultrasound in detecting nodes <5 mm in diameter, whereas ultrasound can detect nodes even <2 mm in diameter. Ultrasonography has gained recent popularity in maxillofacial imaging as it is nonionizing, noninvasive, and cost-effective.[3]

Hence, the study was designed to assess the efficacy of ultrasonography in cervical lymphadenopathy in various oral malignancies.

Materials and Methods

The recruitment of participants for the study was done at Department of Oral Medicine and Radiology, Bharati Vidyapeeth Deemed University Dental College and Hospital, Pune. The participants considered for this study had oral malignant lesions with cervical lymphadenopathy. After thorough history, clinical examination, 20 subjects were randomly selected to become part of the study.

Patients with age 18 years and above having histopathologically confirmed oral malignant lesions with clinically palpable and untreated cervical LNs included into study. Also, patients understanding the supplied information and sign informed consent to participate in the study. Exclusion Criteria includes subjects suffering from renal disease, hepatobiliary disorders, systemic lupus erythematosus, acquired immunodeficiency syndrome, psoriasis, chronic myelogenous leukemias, immunological disorders, and patients under medication for any systemic disease.

The participants were subjected to inspection, palpation, ultrasonographic evaluation of the LNs and finally, histological assessment was done after surgical excision during the course of treatment. For clinical examination number of LNs, shape, size, location, overlying temperature, overlying skin, tenderness, consistency, and fixity to the underlying structures were recorded. Ultrasonographic examination of the LNs was carried out and various parameters, such as number of LNs, shape, size (mm), location, borders, matting, peripheral halo, hilum, calcification, necrosis, reticulation, and echogenicity were recorded. The participants were further advised for surgical excision of the tumor and involved LNs. As histopathology is considered the gold standard, postsurgical biopsy reports were considered for comparison and confirmatory diagnosis of LNs. The data collected were statistically analyzed under *P* value by Wilcoxon's Signed Rank test and one sample Chi-square value test, following which graphs were plotted and tables were drawn. The mean,

median, standard deviation (SD), and average values were calculated, which were then compared for all the three methods of examination applied in the study.

Results

Total sample size for the study was 20. The patients were categorized based on clinical diagnosis and were histopathologically proven as malignant for primary tumor. Patients were in the age group of 40–79 years with maximum involvement 35% in age group of 60–69 years. The obvious difference was due to high incidence of malignancy in the older age.

Gender distribution of malignancy showed that males were more commonly affected than females, i.e., 65% involvement in males and 35% involvement in females.

Only 38 LNs were detected by clinical examination. Ultrasonogram detected an additional 49 nodes (total 87 nodes). Out of these 87 LNs detected by ultrasonography, 51 LNs were diagnosed as malignant by ultrasonography and confirmed to be malignant by histopathological diagnosis, which is a gold standard. An additional 10 LNs, which were nonmalignant by USG examination were diagnosed as malignant on histopathological examination. The mean value of LNs was 1.90 by clinical examination and 4.4 by ultrasonographic examination. *P* value was highly significant, i.e., 0.001 for clinical versus USG examination of LNs, median value of LNs detection by clinical examination was 2 and SD 0.79; by ultrasonographic examination, it was 5 and SD 2.03 [Table 1].

Assessment of size of LNs by clinical examination shows that the average long axial diameter of LNs was 15 mm (ranged from 10 to 30 mm) with SD of 5.09 mm and largest palpable node was 30 mm. By ultrasonographic examination, the longest axial diameter was 17 mm (ranged from 7–38 mm) with SD of 8.7 mm and largest node detected was 38 × 30 mm. *P* value of clinical examination versus ultrasonographic examination was 0.341, which was nonsignificant [Table 2].

Assessment of shape of LNs by clinical examination shows that majority of nodes 21 (55.3%) were round, whereas 17 (44.7%) were oval in shape. By ultrasonographic examination, 52 (59.8%) were round in shape, whereas 35 (40%) were oval in shape. *P* value was 0.695, which is statistically nonsignificant in clinical versus USG examination [Table 3].

Table 1: Descriptive statistics of total number of LN detected by clinical examination and USG (*n*=20)

Descriptive statistics (LN)	Clinical examination (*n*=20)	USG examination (*n*=20)	Clinical vs USG
Total no. of LNs	38	87	0.001[S]
Mean	1.9	4.4	
Standard deviation	0.79	2.03	
Median	2.0	5.0	
Min - Max	1-3	1-7	

LN: Lymph node; S: Significant

Region wise distribution of LNs showed that the clinical examination detected 2 (10%) in submental, 15 (75%) in submandibular, 1 in internal jugular, and 2 (10%) in submental + submandibular region. While by histopathology, 2 (10%) LNs detected in submental, 5 in submandibular, 3 in submental + submandibular, 4 in submental + submandibular + internal Jugular, and 6 in submandibular + internal Jugular.

But ultrasonographic examination detected nodes at internal jugular and cervical region also; two (10%) nodes in the submental group, eight (40%) nodes in submandibular region, one (5%) nodes in internal jugular region, two (10%) nodes in submental + submandibular, five (25%) nodes in submental + submandibular + internal jugular, one (5%) in submandibular + internal jugular, and one (5%) node in submandibular + cervical + internal jugular. *P* values for clinical versus USG examination was 0.016, which was statistically significant, 0.004 for clinical versus histopathology, which was significant and 0.310 for USG versus histopathology examination, which was non- significant.

Most of the nodes were detected in submandibular region, 75% by clinical examination, 85% by USG, and 90% by histopathology examination, as most of the nodes drain into submandibular group [Table 4].

Table 2: Comparison of size of lymph node by clinical and ultrasonographic (USG) examination (*n*=20)

Size (long axial diameter in mm)	Clinical examination (mm)	USG examination (mm)	*P* (clinical vs USG)
Mean	16.8	18.3	0.341[NS]
Standard deviation	5.9	8.7	
Median	15	17	
Min - Max	10-30	7-38	

Table 3: Comparison of shape of lymph node (LN) by clinical and ultrasonographic (USG) examination

Shape	Clinical examination (*n*=38 LNs)	USG examination (*n*=87 LNs)	*P* (clinical vs. USG)
Round	21 (55.3)	52 (59.8)	0.695[NS]
Oval	17 (44.7)	35 (40.2)	

Assessment of shape of LNs on ultrasound shows that majority of nodes 52 (59.8%) were round, whereas 35 (40.2%) were oval in shape; *P* value was 0.068, which is statistically nonsignificant. Assessment of borders in the study patients shows that only 26 (29.9%) of nodes had smooth borders, whereas 61 (70.1%) had sharp borders. The *P* value was 0.001, which proves that it is statistically highly significant. Assessment of Hilum shows that only 31 (35.6%) nodes had visible hilum, whereas 56 (64.4%) had no visible hilum. The *P* value was 0.007, which proves that it is statistically highly significant. Assessment of echogenicity of LNs shows that 64 (73.6%) nodes were hypoechoic, whereas 23 (26.4%) were hyperechoic. The *P* value was 0.001 (*P* < 0.01), which proves that it is statistically highly significant. Assessment of necrosis of LNs shows that 51 (58.6%) of nodes showed intranodal necrosis, while it was absent in 36 (41.4%) nodes. The *P* value was 0.108, which proves that it is statistically nonsignificant.

Assessment of Matting of LNs shows that 25 (28.7%) nodes showed matting and 62 (71.3%) had no matting of nodes. The *P* value was 0.001, which proves that it is statistically significant. Assessment of *Calcification* of LNs shows that calcification was present in 37 nodes. Out of 87 LNs on USG, 17 nodes had reticulation and 51 nodes showed presence of peripheral halo [Table 5].

Diagnosis by USG Examination is significantly associated with histopathology diagnosis (*P* value <0.001). Of the 10 cases who had malignant LNs by histopathological diagnosis, 9 cases (90.0%) had same malignant LNs diagnosis by USG examination; only one case (10%) had nonmalignant LN diagnosis by USG examination. Similarly, of the 10 cases who had nonmalignant LNs by histopathology, all cases, i.e., 10 cases (100.0%) had same nonmalignant LNs diagnosis by USG examination. The value of statistical measure of agreement, i.e., Kappa statistic was 0.900 (*P* value <0.001), which implies that presurgical diagnosis by USG examination is significantly associated with postsurgical confirmation by histopathology diagnosis, which is a gold standard [Table 6].

The sensitivity and specificity values: Sensitivity of USG was 90%, whereas specificity was 100%. The positive predictive value

Table 4: The distribution of location of lymph nodes by clinical examination, ultrasonography (USG), and histopathology

Location	Clinical examination	USG examination	Histopathology	*P*		
				Clinical vs USG	Clinical vs histopathology	USG vs histopathology
Submental	2 (10.0%)	2 (10.0%)	2 (10.0%)	0.016[S]	0.004[S]	0.310[NS]
Submandibular	15 (75.0%)	8 (40.0%)	5 (25.0%)			
internal jugular	1 (5.0%)	1 (5.0%)	0			
Submental + submandibular	2 (10.0%)	2 (10.0%)	3 (15.0%)			
Submental + Submandibular + internal jugular	0	5 (25.0%)	4 (20.0%)			
Submandibular + internal jugular	0	1 (5.0%)	6 (30.0%)			
Submandibular + cervical + internal jugular	0	1 (5.0%)	0			

S: Significant

of USG was 100% and negative predictive value was 90.9%. This shows that ultrasonography has 95% of accuracy in diagnosing the malignant LNs [Table 7].

Discussion

Differentiation between tubercular, metastatic, and lymphomatous cervical LNs is extremely important from the therapeutic point of view. It is also important to make the correct diagnosis at the earliest because a delayed diagnosis can lead to upstaging of the malignancy making a curable lesion incurable. Clinicians have traditionally relied on FNAC to achieve a tissue diagnosis

Table 5: Characteristics of lymph nodes (LNs) detected on ultrasonography (*n*=87 LNs)

Parameters	No. of LNs	% of LNs	Chi-square (one-sample)	*P* (one-sample)
Shape				
Round	52	59.8	3.322	0.068NS
Oval	35	40.2		
Borders				
Smooth	26	29.9	14.080	0.001***
Sharp	61	70.1		
Hilum				
Absent	56	64.4	7.184	0.007**
Present	31	35.6		
Echogenicity				
Hypoechoic	64	73.6	19.322	0.001***
Hyperechoic	23	26.4		
Necrosis				
Absent	36	41.4	2.586	0.108NS
Present	51	58.6		
Matting				
Absent	62	71.3	15.736	0.001***
Present	25	28.7		

Table 6: Comparison of diagnosis of type of lymph nodes (LNs) by ultrasonography (USG) and histopathology examination

USG diagnosis	Histopathology examination		Total
	Malignant LN	Nonmalignant LN	
Malignant LN	9 (90.0%)	0	9 (45.0%)
Non-Malignant LN	1 (10.0%)	10 (100.0%)	11 (55.0%)
Total	10 (100.0%)	10 (100.0%)	20 (100.0%)

Table 7: Sensitivity and specificity analysis of ultrasonography (USG) with histopathology (gold standard) for detecting lymph node involvement in malignancy

Diagnostic parameters of USG	Value (%)
Sensitivity of USG	90.0
Specificity of USG	100.0
Positive predictive value of USG	100.0
Negative predictive value of USG	90.9
Accuracy of USG	95.0

in cervical lymphadenopathy. The reported sensitivity and specificity of FNAC in the evaluation of cervical LNs are 82% and 97%, respectively.[4]

Thorough clinical evaluation of cervical LNs will be a difficult task as there are about 300 cervical LNs in the neck varying in size from 3 to 25 mm, which are embedded within soft tissues of the neck. Hence, cervical lymphadenopathy assessment is vital as it aids in selection of treatment modalities and predicting prognosis. Metastatic cervical LNs are site-specific. In patients with a known primary tumor, the distribution of metastatic nodes assists in tumor staging; however, if the primary tumor is not identified, the distribution of proven metastatic nodes may give a clue to identify the primary tumor.[3]

Therefore, evaluation of cervical lymphadenopathy is important for the patients with head and neck malignancies, as it helps in the assessment of prognosis and the selection of treatment method.

This study shows that the patients were in the age group of 40–79 years with maximum involvement in age group of 60–69 years, i.e., 35%, and in gender distribution, male predominance was noted, i.e., 65%. The above results were in accordance with studies done by Rahul Khanna *et al.*[4]

Clinical examination is subjective and highly inaccurate in the assessment of cervical lymphadenopathy. This fact is supported by other studies done by D'Souza *et al.*,[5] Rahul Khanna *et al.*,[4] and Venkatesh Jayaraman *et al.*[2]

In our study, whereas clinical examination detected only 38 nodes, an additional 49 nodes were detected by ultrasonography. Hence, it proves that clinically nonpalpable node (N0 node) of neck can be diagnosed with ultrasonogram as supported by study of Venkatesh Jayaraman *et al.*[2]

In our study, mean long axis diameter of LNs by clinical examination was 15 mm (ranged from 10 to 30 mm), with SD of 5.09 mm and largest palpable node was 30 mm. By ultrasonographic examination, the longest axial diameter was 17 mm (ranged from 7 to 38 mm) with SD of 8.7 mm and largest node detected was 38 × 30 mm. Study by Moritz *et al.* shows that mean long-axis diameter was 14.9 ± 9.2 mm for malignant nodes.[6]

It is agreed that larger the node, greater is the chance of lodging metastasis. However, certain benign nodes (e.g., tuberculosis) tend to be large and smaller nodes can harbor metastasis. So, instead of actual size, S/L ratio is now widely being used.

According to study, mean average size of normal cervical LNs was 0.82 cm, metastatic cervical LNs was 2.29 cm, and reactive cervical LNs was 1.24 cm.[3,7,8] The upper limit of the maximal short axial diameter for normal cervical nodes is controversial with two values being considered: 5 and 8 mm. However, Bruneton *et al.*[8] reported that normal cervical LNs had a maximal

short axial diameter of ≤8 mm. Generally, malignant nodes tend to be larger; however, inflammatory nodes can be as large as malignant nodes, and in contrast, metastatic deposit can be found in small nodes.

Malignant nodes tend to be round due to rapid growth whereas nonmalignant nodes tend to be oval in shape. This fact was clearly proven in our study; by clinical examination, 21 nodes were round and 17 were oval in shape. By USG examination, 52 malignant nodes were round, whereas 35 nodes were oval in shape. *P* value was 0.695, which is statistically nonsignificant.

Most investigators have suggested short axis/long axis ratio as the most reliable indicator for metastatic nodes.[9,10]

Based on the region wise distribution of nodes in our study, the majority of LNs was detected in submandibular region, i.e., 75% by clinical examination, 85% by USG, and 90% by histopathology examination, as most of the nodes drain into submandibular group. This could be explained by the fact that majority of patients in the malignant group had oral malignancies, which usually metastasize to submandibular and upper cervical LNs.[1,2]

Malignant nodes tend to have sharp borders, whereas reactive and normal nodes show unsharp borders. In our study, 61 (70.9%) nodes had sharp borders and 26 (29.9%) had smooth borders with *P* value being 0.001, which is statistically significant and shows that malignant nodes tend to have sharp borders. Similar results are shown by Ying and Ahuja[11] and Esen *et al.*[12]

The sharp borders in malignant nodes are believed to be due to tumor infiltration and reduced fatty deposition within the LNs, which increase the acoustic impedance difference between the LN and the surrounding tissue. Unsharp borders are common in tuberculous nodes and these are due to the edema and inflammation of the surrounding soft tissue.

Echogenic hilum is the area in which the blood and lymphatic vessels drain into the LNs. echogenic hilus corresponds to the abundance of collecting sinuses and provides acoustic interfaces to reflect a portion of the ultrasonic wave making the hilus echogenic. In this study, assessment of hilum shows that only 31 (35.6%) nodes had visible hilum, whereas 56 (64.4%) had no visible hilum. The *P* value was 0.007, which proves that it is statistically highly significant.

Khanna *et al.*[4] in their study showed an absent hilus in 83% (15/18) of metastatic nodes, while only 26% (16/62) of tubercular and 28% (4/14) of lymphomatous nodes had absent hilus. Ying *et al.*[13] found echogenic hilus to be a normal sonographic feature of normal cervical LNs in 96% of cases. They stated that although metastatic nodes lack this feature, hilum may be present in the early stage of involvement in which medullary sinuses have not been sufficiently disrupted to eradicate it. The findings in this study can be attributed to the fact that all the malignant cases were in advanced stage.

Assessment of echogenicity of LNs in this study shows that 64 (73.6%) nodes were hypoechoic, whereas 23 (26.4%) were hyperechoic. The *P* value was 0.001 (*P* < 0.01), which proves that it is statistically highly significant. Normal and reactive nodes were predominantly hypoechoic when compared with the adjacent muscles. Metastatic nodes were usually hyperechoic. Therefore, hyperechogenicity is a useful sign to identify metastatic nodes as stated by Ying and Ahuja.[14]

In this study, necrosis of LNs, i.e., 51 (58.6%) of nodes shows. In study by Venkatesh Jayaraman *et al.*,[2] necrosis was found in 4 nonmalignant and 10 nodes in malignant group intranodal necrosis, whereas it was absent in 36 (41.4%) nodes. Chintamaneni Raja Lakshmi *et al.*[3] showed intranodal necrosis was found in 26.67% of metastatic cervical LNs and there was no intranodal necrosis in reactive cervical lymph node.

Presence of intranodal necrosis is pathological. Cystic necrosis which appears as intranodal echolucent area can occur in metastatic nodes from squamous cell carcinoma, papillary carcinoma thyroid, as well as tuberculosis. So, necrosis alone cannot be used as a criterion for diagnosing malignancy.

In this study, matting of LNs shows that 25 (28.7%) nodes showed matting and 62 (71.3%) had no matting of nodes.

In study done by Venkatesh Jayaraman *et al.*,[2] three tuberculosis patients (20%) had matting, whereas only one patient (6.67%) with malignancy had matting. Soft tissue matting and edema is a common feature of tuberculosis but is less common in malignant LNs.

In this study, assessment of *calcification* of LNs shows that calcification was present in 37 nodes. Out of 87 LNs on USG, 17 nodes had reticulation and 51 nodes shows presence of peripheral halo.

Ultrasonography is increasingly being recognized as a noninvasive tool for the evaluation of cervical LNs. The sonographic appearance of normal nodes differs from those of abnormal nodes. Sonographic features, which help to identify abnormal nodes, are shape, absent hilus, intranodal necrosis, calcification, matting, peripheral halo, and a prominent vascularity. A normal node should be discoid, with a hilus, sharp margins, absence of matting, calcification, necrosis, or soft tissue edema.

Doppler ultrasonography can evaluate the vascular pattern, displacement of vascularity, vascular resistance, and pulsatility index. These features have been reported to have a sensitivity of 88% for the diagnosis of metastatic nodes and 67% for lymphoma with a specificity of 100%. The limiting feature of Doppler and power ultrasound studies is their inability to distinguish between inflammatory and neoplastic nodes reliably on the basis of their flow pattern. Also, it is costly than gray scale ultrasound. So, Doppler scan was not performed in our study.

This study shows that diagnosis by USG examination significantly tallies with histopathology diagnosis. In diagnosis of malignancy of LNs, 90% cases were diagnosed as malignant on ultrasonography, which were confirmed and proven as malignant by histopathology, which is a gold standard.

In this study, sensitivity and specificity values were calculated. Sensitivity of USG was 90%, whereas specificity was 100%. The positive predictive value of USG was 100% and negative predictive value was 90.9%. This shows that ultrasonography has 95% of accuracy in diagnosing the malignant LNs.

Matthias Beissert *et al.*[15] showed that sensitivity of EFOV-US, for the entire neck was 92%, cranial to the carotid bifurcation, it was 91%, and caudal to the carotid bifurcation it was 97%. The results show that the falsely diagnosed nodes were located mainly cranial to the carotid bifurcation.

Shivanand *et al.*[16] observed a significant association between clinical and ultrasonographic diagnosis, i.e., 100% congruency in cases of sialadenitis swellings, lymphadenitis swellings, benign, and malignant swellings.

Thus, it can be understood that a combination of clinical, ultrasonographic characteristics of head and neck LNs can differentiate malignant and nonmalignant nodes.

Conclusion

We conclude that ultrasonographic examination of cervical LNs can yield important information regarding the diagnosis. Ultrasound examination should be done prior to FNAC and ideally an ultrasound guided FNAC sample should be obtained from the most sonographically representative node to reduce the sampling error and may be especially helpful in cytologically indeterminate cases. Overall this clinical study gave very encouraging results without any radiation hazards.

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Conflicts of interest

There are no conflicts of interest.

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