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Original Article

Radiology Section

Role of Color Doppler Ultrasound in Predicting Malignancy in Cervical Lymph Nodes

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ABSTRACT

Introduction: Cervical lymphadenopathy is a common finding in clinical practice. There are various causes, which can be broadly divided into benign and malignant. Ultrasound with color Doppler is a safe, non-invasive and widely available tool for detection and characterization of cervical lymph nodes.

It can provide an insight into vascularity and flow pattern within a lymph node, thereby serving as a surrogate marker for vascular alterations seen with malignancy.

Aim: To evaluate the role of color Doppler ultrasound in predicting malignancy in cervical lymph nodes.

Materials and Methods: As a part of this prospective study, we performed ultrasound with color Doppler on 60 patients (34 males and 26 females). Inclusion criteria for the study was any patient with palpable abnormality in the neck who was detected to have cervical lymphadenopathy on ultrasound and color Doppler examination and subsequently had FNAC or excisional biopsy.

Results: Out of 98 lymph nodes evaluated in 60 patients, 30 lymph nodes in 22 patients demonstrated malignancy on pathology. Out of these 30 lymph nodes, 24 demonstrated peripheral or mixed vascularity. The Resistivity Index (RI) values in benign lymph nodes ranged from 0.40 to 0.82 with a mean of 0.60 $\pm$ 0.10. RI values in malignant lymph nodes ranged from 0.56 to 0.88 with a mean of 0.74 $\pm$ 0.08.

Conclusion: Color Doppler ultrasound plays an important adjunct role to ultrasound in differentiating benign from malignant lymph nodes. It adds to the diagnostic confidence of predicting malignancy in cervical lymph nodes. However, Color Doppler ultrasound can not replace histopathology for differentiation of benign and malignant cervical lymph nodes.

Keywords: Power Doppler, Pulsatility index, Resistivity index, Spectral Doppler.

INTRODUCTION

Cervical lymphadenopathy is a common finding in clinical practice. There are various causes of enlarged cervical lymph nodes, which can be broadly divided into benign and malignant. Clinical examination alone is suboptimal for the detection of enlarged cervical lymph nodes. Differentiation of benign and malignant lymph nodes without Fine Needle Aspiration Cytology (FNAC)/ biopsy is difficult, but crucial for patient management. Therefore, non-invasive imaging tools that can facilitate in differentiation of benign and malignant nodes are required [1,2]. In a patient without a known primary malignancy, detection of a metastatic lymph node may be the first clue of underlying occult malignancy. In a patient with known head and neck carcinoma, detection of metastatic lymph node is vital because it is the single most important factor that determines prognosis [1,3].

With advances in imaging techniques, the sensitivity of detection of cervical lymph nodes has significantly increased. Ultrasound with color Doppler is a safe, non-invasive and widely available tool for detection and characterization of cervical lymph nodes [2,3]. Various ultrasound criteria that can help in differentiation of benign and malignant lymph nodes have been well described in literature. On gray scale imaging, benign enlarged lymph nodes are hypoechoic, oval shaped with smooth border and echogenic hilum. On the other hand, malignant cervical lymph nodes are round with short axis to long axis ratio >0.5 and show loss of echogenic hilum [1,4,5]. However, color Doppler findings that can aid in differentiation of benign and malignant lymph nodes are not well established. In the present study, we aimed to evaluate the role of color Doppler ultrasound in predicting malignancy in cervical lymph nodes.

MATERIALS AND METHODS

As a part of this prospective study, we performed ultrasound with color Doppler in all patients presenting to our institute from July 2014 to January 2016. The study was conducted in ESI Medical College and PGIMSR, K K Nagar, Chennai, India. Approval from the Institutional Review Board was obtained. An informed consent was obtained from all patients for participation in this study. The study included 98 lymph nodes from 60 patients (34 male and 26 female). The inclusion criteria was any patient with palpable abnormality in the neck who was detected to have cervical lymphadenopathy on ultrasound and color Doppler examination and subsequently had FNAC or excisional biopsy. Patients who did not get FNAC and patients who were lost to follow-up were excluded from the study. After obtaining informed consent, we assessed the patients with color Doppler and ultrasound.This examination was performed on a Philips ultrasound machine unit (HD7/ Clearvue 650) using a linear, high frequency probe (3-12MHz). A curvilinear transducer (2-5MHz) was used when needed. Subsequently, the patient underwent ultrasound guided FNAC or excisional biopsy within a week after the initial ultrasound examination. The pathological specimens were evaluated by a pathologist in our institution.

The following criteria were assessed in the nodes by color Doppler:

1. Distribution of vessels on power Doppler: central, peripheral, mixed or avascular
2. Resistivity Index (RI) and Pulsatility Index (PI)
3. Peak systolic Velocity (PSV)
4. End Diastolic Velocity (EDV)

After FNAC of the lymph nodes, cytological result was obtained and statistical analysis was done to individually correlate these criteria with malignancy.

Technique of Examination

The first step was a thorough gray scale evaluation of cervical lymph nodes. For Doppler evaluation of neck nodes, we optimized the following machine settings for detecting vascularization: maximum gain settings (85-90%), PRF between 700-1.000 MHz, wall filter as low as possible (50 to 100Hz max), appropriate algorithm to remove motion artifacts with medium persistence. The color gain was initially increased to a level which shows color noise, and then decreased to the level where the noise just disappears. With the use of color Doppler, the vascular pattern and distribution were assessed. The vascular pattern of the lymph nodes is classified into four categories as per the distribution of vascularity [1,2,4]:

- Hilar pattern with blood flow branching radially from the center of the node.
- Peripheral pattern with blood flow limited to the periphery of the node. No vessels arise from the central hilar vessels.
- Mixed pattern of vascularity with blood flow detected in the peripheral and central part of the node.
- Avascular with no apparent vascularity detected in the node on color and power Doppler.

Spectral Doppler was used to assess intranodal vascular resistance and evaluation of RI and PI was done. Measurements are obtained from three consecutive waveforms and the smallest sample volumes were used. When measuring blood flow velocity (PSV and EDV), angle correction was made at an angle of 60 degree or less.

STATISTICAL ANALYSIS

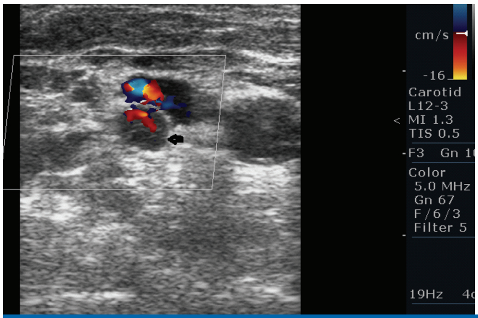
The statistical test used was Fisher`s exact probability test (chi square test). This test was used to find the difference between benign and malignant pathologies for evaluating the significance of differences in the parameters observed in the two groups. Qualitative data was expressed in percentage. Quantitative data was expressed in mean and standard deviation.

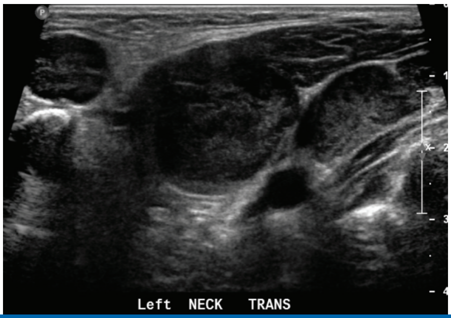
RESULTS

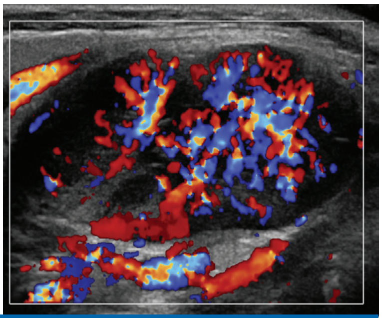
The age group of our patients ranged from 12 to 76 years. There were 34 males and 26 females. Sixteen patients had a known malignancy at the time of ultrasound examination. Out of 98 lymph nodes evaluated in 60 patients, 30 lymph nodes in 22 patients demonstrated malignancy on pathology. 68 lymph nodes in 38 patients were benign, either reactive or tubercular in etiology [Table/Fig-1]. Among these 22 patients, 16 had a known diagnosis of malignancy, while the cervical lymph node of 6 patients was the harbinger of malignancy. The distribution of blood vessels within a lymph node as well as spectral Doppler parameters were correlated with histopathology findings. Malignancy was seen in 30 of the 98 lymph nodes on cytology/ histopathology (31%). Out of these 30 lymph nodes, 24 demonstrated peripheral (10 lymph nodes) [Table/Fig-2] or mixed vascularity (14 lymph nodes) [Table/Fig-3,4]. 3 of the 30 lymph nodes demonstrated central vascularity only, while 3 lymph nodes were avascular [Table/Fig-5]. Twenty four of the 30 malignant lymph nodes demonstrated mixed or peripheral vascularity, with 3 lymph nodes demonstrating central vascularity and 3 lymph nodes demonstrating lack of vascularity. Out of 68 benign lymph nodes, central vascularity was observed in 60 lymph nodes (88.2%) [Table/Fig-6,7] and mixed in 4 lymph nodes (5.8%) [Table/Fig-8]. In our study, both reactive as well as tubercular lymph nodes demonstrated

Serial No.	Pathological Diagnosis	No.of Patients	No. of Nodes		Percentage of Nodes
1	Metastasis	14	18	30	18.36%
2	Lymphoma	8	12		12.24%
3	Tuberculosis	16	30	68	30.61%
4	Reactive LN	22	38		38.79%
Total		60	98		100

[Table/Fig-1]: Spectrum of diseases in our study of cervical lymphadenopathy.





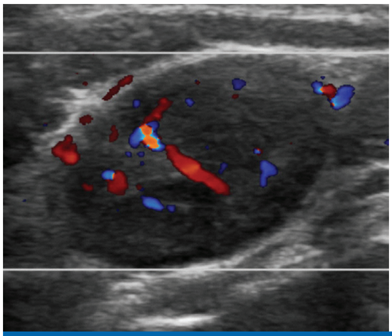
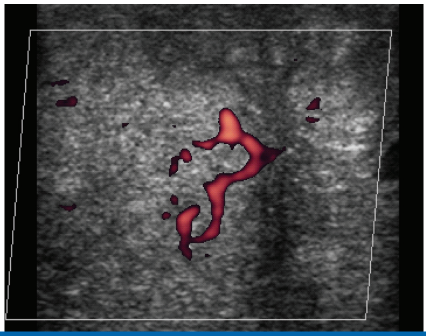
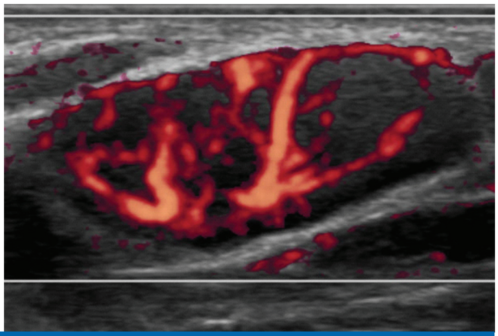


[Table/Fig-2]: A case of malignant node (metastatic adenocarcinoma) showing the presence of peripheral vascularity on color Doppler ultrasound. **[Table/Fig-3]:** A case of malignant lymph nodes (Non-Hodgkin's lymphoma) demonstrating gray scale ultrasound appearance of enlarged cervical lymph nodes. Note the round shape and lack of an echogenic hilum. **[Table/Fig-4]:** A case of malignant node (Non-Hodgkin's lymphoma) showing the presence of mixed (peripheral and central) vascularity on color Doppler ultrasound.

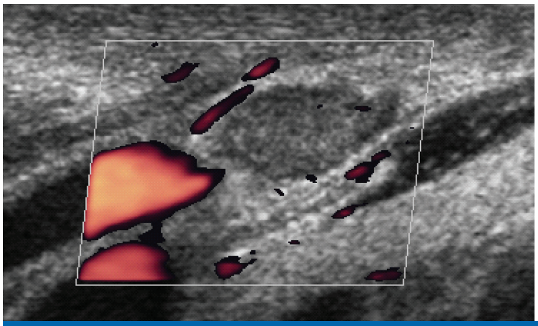
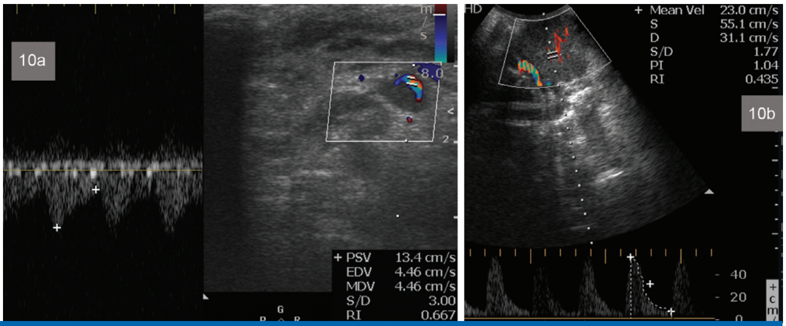
Distribution of Vascularity	Pathological Diagnosis		Total
	No. of Malignant Nodes	No. of Benign Nodes	
Peripheral	10 (83.3%)	2 (16.7%)	12 (100%)
Mixed	14 (77.8%)	4 (22.2%)	18 (100%)
Central	3 (4.8%)	60 (95.2%)	63 (100%)
No Flow	3 (60%)	2 (40%)	5 (100%)
Total	30 (31%)	68 (69%)	98 (100%)

[Table/Fig-5]: Vascular distribution on color Doppler flow in malignant and benign cervical lymph nodes.

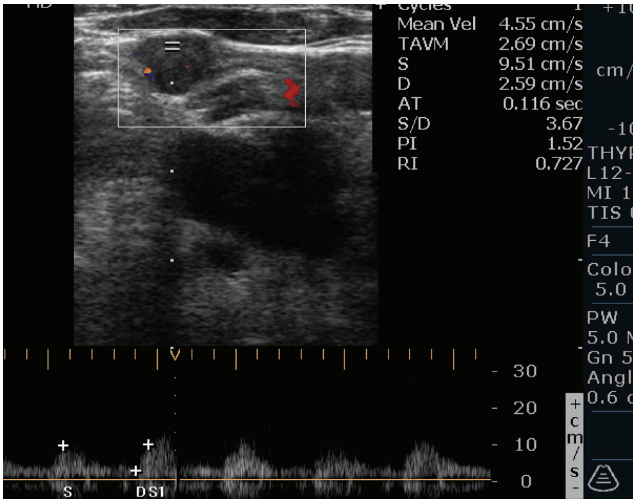
central vascularity [Table/Fig-6,7]. Out of the 8 benign lymph nodes that did not demonstrate central vascularity, 6 were reactive and 2 tubercular lymph nodes [Table/Fig-9]. The RI values in benign lymph nodes ranged from 0.40 to 0.82 with a mean of 0.60 $\pm$ 0.10. RI values in malignant lymph nodes ranged from 0.56 to 0.88 with a mean of 0.74 $\pm$ 0.08 [Table/Fig-10a,10b,11]. Similarly, the PI values in benign lymph nodes ranged from 0. 38 to 2.20 with a mean of 1.60 $\pm$/0.32. PI values in malignant lymph nodes ranged from 0. 46 to 3.48 with a mean of 2.24 $\pm$/0.44 [Table/Fig-11,12].

[Table/Fig-6]: A case of reactive node showing the presence of central vascularity on color Doppler ultrasound. **[Table/Fig-7]:** A case of tuberculous node showing the presence of central vascularity on power Doppler ultrasound. **[Table/Fig-8]:** A case of reactive node showing the presence of mixed (peripheral and central) vascularity on power Doppler ultrasound.

[Table/Fig-9]: A case of tuberculous node showing the lack of vascularity on power Doppler ultrasound.
[Table/Fig-10]: Spectral Doppler of a malignant node with metastatic adenocarcinoma (10a) and a benign (tuberculous) lymph node (10b).
*Note the relatively higher RI in the malignant lymph node (10a).



[Table/Fig-11]: Spectral Doppler of a metastatic cervical lymph node with papillary carcinoma of the thyroid (operated).

Vascular Resistance	Malignant LN		Benign LN	
	Mean	Range	Mean	Range
RI	0.74±0.08	0.56 to 0.88	0.60±0.10	0.40 to 0.82
PI	2.24±0.44	0. 46 to 3.48	1.6±0.32	0. 38 to 2.20

[Table/Fig-12]: Spectral analysis with mean values of intranodal vascular resistance in malignant and benign cervical lymph nodes.

Doppler Findings in Malignant Nodes	SB Dangore et al., [5]	Giorgio de Stefano et al.,[2]	Present Study*
Peripheral Pattern of Vascularization	62.85%	24%	33.34%
Mixed Pattern of Vascularization	25.71%	32%	46.67%
No Flow with Absence of Signal	5.7%	14%	10%

[Table/Fig-13]: Pattern of vascularization of malignant nodes on color Doppler evaluation in our study as compared to previous studies.

*Considering that we are not including the central pattern of vascularity as a factor to compare with other studies. 3 out of 30 malignant cases showed central vascularity, which makes it 10%. Therefore, all the rest constitute 90%.

Spectral Analysis	SB Dangore et al., [5]	Mahyar Ghafoori et al.,[6]	Present Study
Resistivity Index (RI) of Malignant Nodes	0.73 ± 0.16	0.79 ± 0.08	0.74+0.08
Pulsatility Index (PI) of Malignant Nodes	1.76 ± 0.66	1.83 ± 0.52	2.24+0.44
Resistivity Index (RI) of Benign Nodes	0.65 ± 0.18	0.64 ± 0.08	0.60+0.10
Pulsatility Index (PI) of Benign Nodes	1.13 ± 0.48	1.18 ± 0.38	1.6+0.32

[Table/Fig-14]: Intranodal resistance on spectral Doppler evaluation of cervical lymph nodes in our study as compared to previous studies.

DISCUSSION

Cervical lymphadenopathy can be evaluated by various diagnostic tools such as ultrasound, color Doppler, CT-scan, MRI and PET CT. Each of these modalities have their strengths and limitations, ultrasound having the highest sensitivity in detection of malignant nodes, while PET CT offers the highest specificity [1,6]. Ultrasound and color Doppler are cheap, easily available and radiation free. The excellent resolution of ultrasound makes it an ideal modality for assessment of cervical lymphnodes. Various sonographic criteria for differentiation of benign and malignant cervical lymph nodes have been well established by prior studies. Gray scale imaging assesses well the morphological nodal aspects as shape, size, border, echogenicity, echogenic hilus and presence/absence of calcifications [1,4,7]. Malignant nodes are noted to be larger in size in comparison to reactive nodes with different cut offs (5mm, 8mm, 10mm) described previously in literature to differentiate the two [1]. Benign nodes generally have oval shapes with smooth borders. Neither nodal size nor border is however a reliable criterion to distinguish the two. Normal and reactive nodes tend to have short axis to long axis ratio <0.5 with echogenic hilum preserved [3,4]. Malignant nodes tend to be round in shape with short axis/ long axis ≥0.5, hypoechoic with absence of echogenic hilum [6,8,9]. Tumor growth results in distortion of internal architecture, tumorous infiltration of the sinuses, thus resulting in loss of echogenic hilum [8,10]. Malignant nodes may have sharp borders considering the theory that intranodal tumor infiltration results in increased acoustic impedance between involved node and the surrounding area [1,4]. A proven metastatic node with ill-defined border indicates extracapsular extension. Intranodal necrosis is common in metastatic nodes from squamous cell carcinoma [3,4,10]. Calcifications, though rare in metastatic nodes, are frequently present in metastatic nodes of papillary carcinoma [4,7]. Color and power Doppler assesses the pattern of vascularity of lymph nodes and provides useful supplementary information to assess the nature of cervical lymph nodes in vivo. While color Doppler and power Doppler detects the presence and distribution of vascularity, spectral Doppler ultrasound is used for assessment of intranodal vascular resistance [1]. The specificity of ultrasound combined with FNAC for the detection of malignant lymph nodes is as high as 93.7% [1]. For evaluation of lymph nodes for malignancy, Doppler assesses two major features:

1. Distribution of vessels within the lymph node.
2. Vascular flow pattern with parameters such as RI and PI.

Distribution of Vessels

On color Doppler, presence of central blood flow within a lymph node suggests the presence of a hilum and correlates with a benign or reactive lymph node [2,3]. However, presence of peripheral vessels or mixed vascularity suggests malignancy [4,5]. This peripheral vascularity is thought to result from tumor infiltration of lymph nodes which provides Tumor Angiogenetic Factor (TAF), resulting in angiogenesis and recruitment of peripheral vessels [6]. On color and power Doppler malignant nodes usually show peripheral or mixed vascularity, hence peripheral vascularity in a cervical lymph node, with or without hilar vascularity is highly predictable of malignancy [1,3,8]. Using the criteria of peripheral or mixed vascularity, we obtained a positive predictive value of 80 percent in predicting malignancy. As stated above, in this study, 24 of 30 malignant lymph nodes demonstrated mixed or peripheral vascularity, with 3 lymph nodes demonstrating central vascularity and 3 lymph nodes demonstrating lack of vascularity. Interestingly, all these 3 lymph nodes demonstrating central vascularity were seen in patients with Non-Hodgkin's lymphoma [Table/Fig-3,4]. This finding has been reported in the past by previous researchers. The presence of central vessels in lymphomatous lymph nodes is thought to be related to the fact that intranodal necrosis is not common in lymphoma and so hilar vessels are preserved [5,9] [Table/Fig-13]. Furthermore, the lack of vascularity in 3 malignant lymph nodes likely reflect the complete replacement of nodal tissue by tumor cells. Furthermore, out of the 68 benign lymph nodes, central vascularity was observed in 60 lymphnodes (88%) [Table/Fig-5,6]. and mixed in 4 lymph nodes (5.8%) [Table/Fig-5,8]. This confirms the findings on prior studies that presence of central vessels is a sign of benign lymph nodes. In our study, both reactive as well as tubercular lymph nodes demonstrated central vascularity [Table/Fig-6,7]. Out of the 8 benign lymph nodes that did not demonstrate central vascularity, 6 were reactive and 2 tubercular lymph nodes [Table/Fig-9].

Vascular Flow Pattern

The flow pattern within cervical lymph nodes can be assessed by parameters such as RI, PI, PSV and EDV. Out of these parameters, RI has been most commonly used to differentiate benign from malignant cervical lymph nodes. However, some prior reports suggest that malignant lymph nodes have higher RI than benign lymph nodes [5], while others seem to suggest lower or similar RI values [6] [Table/Fig-14]. The theory for increased RI is that with growth of tumor cells,the normal part of a node is replaced, thus resulting in compression of its blood vessels, increased vascular resistance and increased RI [6,9]. Ahuja et al., however suggest lowering of RI in malignant lymph nodes due to absence of smooth muscle layer in malignant neoangiogenesis and the arterio venous shunting [7,9].

A criteria for optimum cut-off values for RI and PI as 0.7 and 1.4, with a sensitivity of 86% and 80%, and a specificity of 70% and 86%, respectively has been proposed [9,11]. Using this criteria, we found a sensitivity of 83.3% and 74% and a specificity of 68% and 75% respectively.

The positive predictive value was approximately 65% and 59% respectively. No positive or negative correlation was observed in PSV and EDV values with malignancy. As demonstrated by these results, there is a general trend towards high RI and PI values in malignant lymph nodes as compared to benign lymph nodes [6,11]. However, there are a lot of overlapping values and the predictive value of these parameters individually is low. In our study, 5 lymphoma nodes demonstrated low RI and PI values (mean RI 0.68 and mean PI 1.2). These findings are similar to a prior study by Brnic et al., [12]. This can be explained by the fact that the normal nodal architecture is not disrupted in lymphoma, similar to chronic lymphadenitis.

One of the limitations of our study is a low sample size. However, we only included patients with a confirmatory diagnosis on cytology/histopathology. Many patients with suboptimal tissue samples on cytology/ histopathology were excluded from this study. Additionally, many patients with cervical lymph nodes, especially the ones with known malignancy were evaluated with other techniques such as CT and MRI. Another limitation of this technique is that deep lymph nodes, such as retropharyngeal lymph nodes cannot be assessed by ultrasound and color Doppler. Retropharyngeal lymph nodes are common sites of metastases in head and neck cancers such as nasopharyngeal carcinoma, and these lymph nodes are optimally evaluated with computed tomography or magnetic resonance imaging. A modality specific limitation of ultrasonography is its inability to detect micro metastasis in non enlarged lymph nodes.

CONCLUSION

Color Doppler ultrasound is a useful exam that provides an insight into the vascularity of a lymph node, thereby serving as a surrogate marker for in vivo assessment of neovascularity. The vascular hemodynamics within a lymph node can also be assessed by this technique. It can help in the detection of abnormal lymph nodes and can be used for deciding which node to biopsy.

Color Doppler ultrasound does play an important adjunct role to ultrasound in differentiating benign from malignant lymph nodes. It adds to the diagnostic confidence of predicting malignancy in cervical lymph nodes. It is also useful if gray scale ultrasound findings are equivocal, and it improves diagnostic accuracy. However, color Doppler ultrasound can neither replace histopathology for differentiation of benign and malignant cervical lymph nodes, nor can it eliminate the need for biopsy.

Advances in Knowledge

- Peripheral or mixed vascularity in a cervical lymph node pertains to a high positive predictive value for predicting malignancy. Conversely, presence of central vessels is a sign of benign lymph nodes.

- There is a general trend towards high RI and PI values in malignant lymph nodes as compared to benign lymph nodes, however no definite cut-off values can be ascertained.

Implications in Patient Care and Management

- When ultrasound is done for evaluation of cervical lymphadenopathy, the addition of Doppler can help to further characterize the node and add to the degree of confidence in differentiating benign and malignant lymph nodes.

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