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Role of spectral doppler in the differentiation of benign and malignant cervical lymphadenopathy

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Abstract: *Introduction:* Differentiating benign from malignant lymphadenopathy is often a diagnostic challenge to medical professionals and multiple non invasive modalities from palpation to MRI have been used. Histopathology remains the gold standard but imaging modalities are frequently used. The main objective of our study is to assess the accuracy of spectral Doppler in differentiating benign and malignant lymphadenopathy. *Methods:* A prospective study was done in patients with cervical nodes and the Doppler study was done primarily assessing the spectral doppler features and the diagnosis was compared with histopathology. *Results:* Reactive nodes usually showed hilar vascularity. Metastatic nodes showed Peripheral and chaotic multifocal vascular signals. Resistive Index and Pulsatility Index were the most important markers among the spectral parameters for the differentiation of benign and malignant lymphadenopathy. RI and PI of malignant nodes was significantly higher than benign nodes. PSV of the nodes was not much different but EDV was low in metastatic nodes. EDV> 11.1 cm/s has 100% negative predictive value for nodal metastasis, and EDV<3.4 cm/s has 100% specificity and PPV for metastasis. Tubercular nodes shows indeterminate doppler characteristics. *Conclusion:* Colour doppler sonography is a highly efficacious investigation for differentiation of benign and malignant lymphadenopathy Colour doppler can be used to prevent unnecessary invasive biopsy in many patients particularly in those patients where we get very low values of RI and PI and very high values for EDV. RI is the single most important parameter in the differentiation of benign and malignant lymphadenopathy. Cut off value of 0.7 for RI and 1.3 for PI, yield acceptable sensitivity, specificity and accuracy.

Keywords: Lymphadenopathy, Doppler. Resistive Index, Pulsatility Index.

Introduction

Examination of the neck nodes has traditionally been performed with palpation. In case of non palpable nodes, metastasis has been presumed to be absent. However, during the past two decades, results have shown that palpation is an unreliable method for the assessment of metastasis. Investigators have suggested that noninvasive imaging techniques such as CT and US be used for improved detection of metastasis in lymph nodes [1].

Sonography has proved highly effective for detection, localization and delineation of enlarged lymph nodes of the neck. Infiltration of adjacent structures, specifically the common, internal and external carotid arteries and the neck muscles are reliably demonstrated. AJCC is most commonly used nodal classification but a different nodal classification for use in sonography has been developed and include 8 groups [2].

1) Submental
2) Submandibular
3) Parotid
4) Upper cervical
5) Middle cervical
6) Lower cervical
7) Supraclavicular fossa
8) Posterior triangle

In some metastatic carcinomas, the tumour cells infiltrate and invade the lymph node only partially and peripherally with no increase in nodal size. The metastasis may have increased vascularity and by applying color-coded

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duplex sonography (CCDS), it is possible to demonstrate the pathologic increased vascularity even in small lymph node metastases of 3 to 4 mm in diameter [3]. Although CDUS evaluation cannot replace histopathological procedure, it plays a definite role as an adjunct to the clinical evaluation of cervical lymphadenopathy & proves its value as an important investigation for differentiating between benign and malignant lymphadenopathy [4].

The main objective of our study was to specify the role of spectral parameters in distinguishing benign from malignant nodes. The results obtained were correlated with histopathological findings and specificity and sensitivity of colour Doppler parameters in differentiation of benign and malignant lymphadenopathy was determined.

Material and Methods

This study was conducted in the Postgraduate Department of Radiodiagnosis, Government Medical College, Jammu on 50 patients who presented with Cervical Lymphadenopathy and were referred from departments of Government Medical College, Jammu during the period of study. All studies were done on TOSHIBA XARIO Ultrasound Scanner with a linear probe with 7.5 MHz frequency. Doppler examination was preceded by grey scale sonography and we looked for size (L/S ratio), shape, echogenicity, nodal border and echogenicity of hilus. Calcification, intra nodal necrosis, matting and adjacent soft tissue edema if present were also noted.

Colour Doppler parameters were adjusted for detection of low-velocity or low- volume flow and included:

- wall filter = low (1 or 2)
- gate = 1
- velocity scale = 6 cm/sec
- PRF = 500 – 750 Hz
- Persistence = mid level
- The colour gain was first increased to a level which shows colour noise, and then decreased to the level where the noise just disappeared.
- In measuring the vascular resistance (RI and PI), the more prominent vessels were selected.
- In case of blood flow velocity (peak systolic velocity, PSV and end diastolic velocity, EDV), angle correction was made to an angle of 60 degree or less.
- Chi-square test was used for overall efficacy of Doppler and spectral parameters in accurate differentiation of benign and malignant lymphadenopathy and student's t-test was used for determining signifance of difference of means of roundness index, RI /PI in benign and malignant nodes.
- All the cases underwent FNAC/Biopsy and the results were compared with doppler findings.

Results

The present study was undertaken in the department of Radiodiagnosis and Imaging, Government Medical College, Jammu on fifty patients having nodal masses in neck who were referred to our department for Doppler Ultrasonography.

Malignant nodes outnumbered benign cases in our study as patients who were very sick and admitted on inpatient basis were usually referred to us. 29 of 50 cases in our study were malignant with metastatic and lymphomatous nodes accounting for 19 and 10 cases respectively.

Table-1: Grey scale features

Diagnosis	mean Roundness index (L/S)	Hilar features			Necrosis
		Normal	Absent	Displaced	
Reactive (n = 11)	2.12	9	0	2	1
Tuberculosis (n = 10)	1.87	3	2	5	5
Lymphoma(n = 10)	1.56	6	4	0	0
Metastatic(n = 19)	1.41	2	14	3	3

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Solbiati index or roundness index of lymph nodes is most important grey scale feature in differentiating benign from malignant nodes Mean Roundness index in benign nodes was 2 and in malignant nodes was 1.46. Highest index was 2.86 in benign node and lowest index in benign node was 1.67, highest index in malignant node was 1.87 and lowest index of 1.11 was seen in malignant node. The difference was statistically significant with p value < 0.05. However, 3 out of 11 reactive nodes i.e 27% and 5 out of 10 tubercular nodes i.e 50% had SI < 2. None of malignant node had SI > 2 in our study. So 19 of 27 nodes (70%) having SI < 2 were malignant. So there was high false positive rate for predicting malignant nodes using roundness index as the only criteria. Necrosis and displaced hilum as a feature was seen more frequently in tubercular nodes and necrosis was not seen in any of the lymphomatous lymph nodes.

Vascular Distribution in Nodes: Vascular distribution has been classified differently by different researchers. In our study, we have taken classification of Wu et al [5] who in addition to Avascular group classified vascularity into four types as-

- *Hilar type:* A simple short feeding vessel, or a central longitudinal vessel, or a hilar vessel with regular and symmetric centrifugal branching.
- *Spotted or multifocal type:* Scattered specks or segments of vessel signals distributed chaotically within the node.
- *Peripheral type:* Vascular signals distributed only around the node or in a basket pattern with centripetal branching.
- *Mixed type:* A mixture of more than one of the foregoing types.

Hilar vascularity was common in reactive and lymphomatous nodes and mixed pattern was frequently seen in metastatic nodes (figure 1,2,3).

Table-2: Vascular Distribution

Type of Vascularity	Patients with reactive (n =11)	Patients with tuberculosis (n =10)	Patients with metastasis (n =19)	Patients with lymphoma (n =10)
Hilar	9	4	1(5.26%)	4
Multifocal	1	2	1(5.26%)	0
Peripheral	0	0	1(5.26%)	0
Avascular	0	3	1(5.26%)	0
Hilar, peripheral and multifocal	0	0	2(10.52%)	0
Peripheral and multifocal	0	0	10(52.6%)	0
Hilar and peripheral	1	1	1(5.26%)	5
Hilar and multifocal	0	0	2(10.52%)	1

Figure-1: Colour Doppler of a reactive node showing single hilar vessel

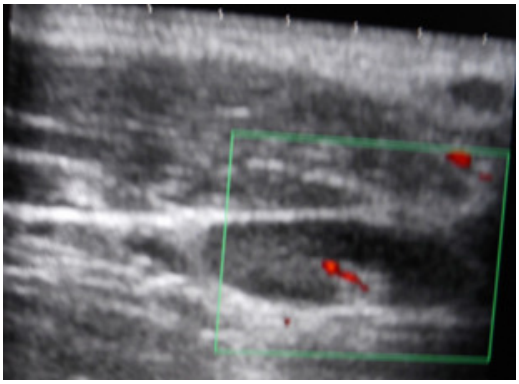

Figure-2: Power Doppler of a lymphomatous node with activated hilar vascularity

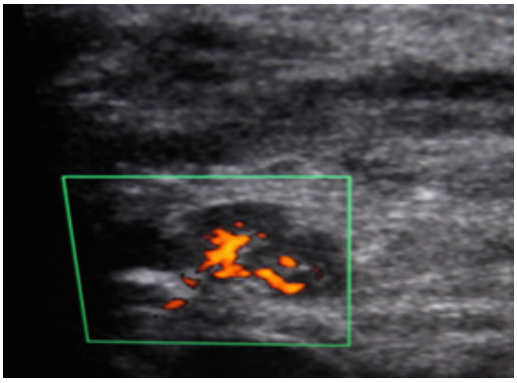

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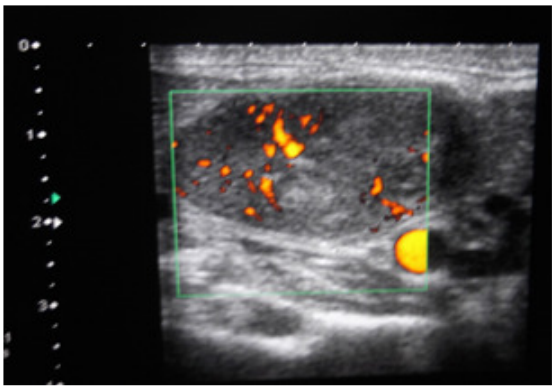
Figure-3: Power Doppler of a Metastatic node with multicentric and peripheral vascularity



Spectral Indices Of Nodal Vessels: Resitive index of benign nodes was low with minimum value of 0.33 and maximum value of 0.7 while as Resistive index of malignant nodes was high with minimum value of 0.65 and maximum value of 1.15 Most of malignant nodes have RI value more than 0.7 and most of the benign nodes have RI value less than 0.7. Pulsatility index of benign nodes was low with minimum value of 0.42 and maximum value of 1.3 while as Pulsatility index of malignant nodes was high with minimum value of 1.1 and maximum value of 4.5 Most of malignant nodes have RI value more than 1.3 and most of the benign nodes have RI value less than 1.3.

Table-3: Spectral Indices		
Diagnosis	**Mean RI**	**Mean PI**
Benign	0.58	0.85
Malignant	0.86	1.76

There was a significant difference in the mean RI and PI values of benign and malignant values with mean RI and PI of malignant nodes as 0.86(SD=0.11) and 1.76 (SD=0.72) respectively and mean RI and PI of benign nodes as 0.58(SD=0.1) and 0.85(SD=0.23) respectively. Difference of means were found statistically significant using student's t-test with a p-value < 0.0001.

Table-4: Spectral Indices		
Diagnosis	**Mean RI**	**Mean PI**
Metastasis	0.86	1.72
Lymphoma	0.86	1.83
Reactive	0.54	0.77
Tuberculosis	0.65	1.03

Mean RI and PI of lymphoma and metastatic nodes was almost similar with no significant difference. Mean RI and PI of tubercular nodes is more than reactive nodes but less than malignant nodes.

Table-5: EDV of lymph nodes		
EDV(cm/s)	**Benign**	**Malignant**
< 0	0	2
0-4.9	3	21
5-9.9	12	4
>=10	3	1

EDV of malignant nodes varied from -4.6 to 11.1 cm/s with mean of 2.8cm/s and EDV of benign nodes varied from 3.4 to 19.4 cm/s with mean value of 7.5cm/s. 23 of 28 vascular malignant nodes showed EDV < 5cm/s and 15 of 18 vascular benign nodes showed EDV >/= 5cm/s. None of the benign node had EDV < 3.4 and none of the malignant node had EDV > 11.1cm/s. (figure 4,5,6,7).

Figure-4: Spectral trace of a reactive node showing low RI, PI

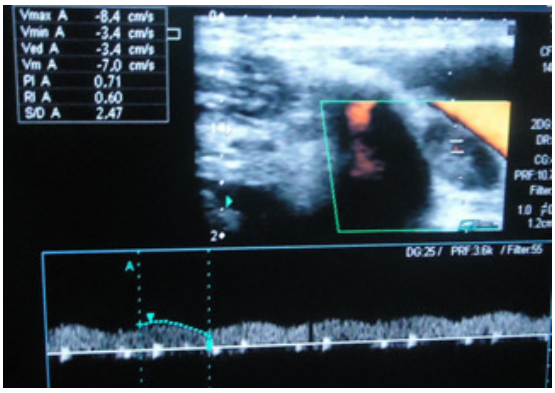


Figure-5: Spectral Doppler of lymphomatous node seen in Figure 2 shows high RI and PI

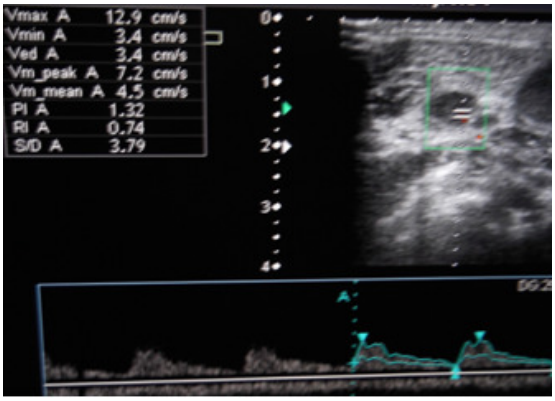


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Figure-6: Spectral doppler of Metastatic node (Figure 3) shows high RI, PI and low EDV

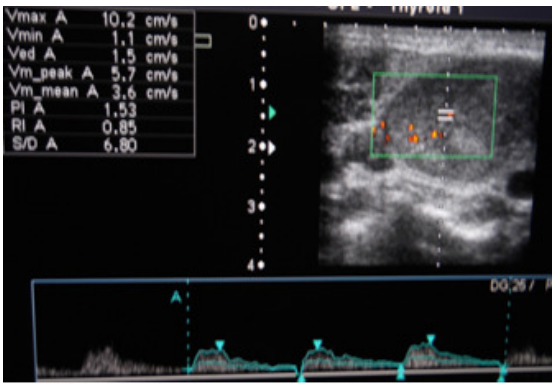
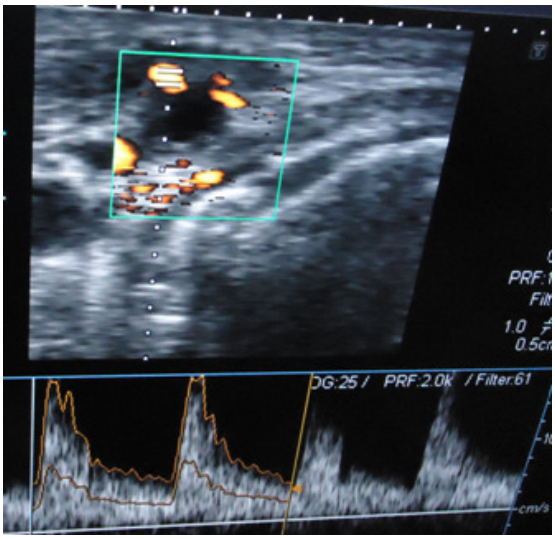


Figure-7: Doppler of a tubercular node with necrosis and multifocal vascularity and spectral trace also being indeterminate



PSV of lymph nodes: PSV of malignant nodes varied from 7.79 to 43 cm/s with mean of 19.84cm/s and PSV of benign nodes varied from 8.4 to 29.4 cm/s with mean value of 17.37cm/s

Discussion

Grey scale features most important in differentiation of benign and malignant lymphadenopathy were roundness index and hilum changes. Grey scale features had acceptable sensitivity for detecting a malignant node but had low specificity as half of tubercular nodes and 18% of reactive nodes had SI< 2. Hilar vascularity is commonly seen in reactive lymphadenopathy. 82% of cases in our study showed hilar vascularity. Ayata et al [6] noticed hilar vascularity in 88% of reactive lymph nodes. Ahuja et al [7] noticed hilar vascularity in 96% of reactive nodes. Tubercular nodes usually have variable vascularity. In the present study, hilar (40%) and avascular (30%) forms were most common together accounting for 70% of cases. Multifocal and mixed vascularity was seen in 20% and 10% of cases respectively. In a study conducted by Wu et al [5] they found 72% of tuberculous lymphadenopathy lesions revealed either an avascular pattern or a hilar vascular pattern.

Malignant nodes are characterized by extrahilar vessels which are induced by neovascularisation however incidence of extrahilar vessels in lymphoma is lower than metastatic nodes [8]. In the present study, vascular distribution was variable with mixed vascularity being the most common form of vascularity in metastatic nodes and was found in 79% of cases. Wu et al [5] also found mixed vascularity the most common form and was seen in 53% of cases. Na et al [9] also noticed mixed vascularity in 82% of malignant nodes. Spotted/ Multifocal and Peripheral vascularity were the main vascular components present in the metastatic nodes with 15 of 19 nodes (79%) showing multifocal and 14 of 19 (74%) showing peripheral with both being together in mixed form usually. Only peripheral vascularity was only seen in 5.3% of cases. Na et al [9] also noticed similar findings with 47 of 52 nodes (90%) showing peripheral and 42 of 52(81%) showing multifocal with both forms being together usually in mixed form, they noticed pure peripheral vascularity in 6% of cases.

Lymphomatous nodes usually showed hilar preponderance. In our study, 40% of nodes showed only hilar vascularity and 60% showed mixed vascularity with hilar component seen in all the cases showing mixed vascularity.Hilar vascularity in lymphoma was different from benign nodes in being more profuse and showing few large branches and it was also noticed by Giovagnorio et al [10] and they called it hilar activated or type 2 hilar vascularity. They also concluded that lymphoma and metastatic node can be differentiated by vascular pattern as hilar vascularity is more common in lymphoma and peripheral subcapsular vascularity is more a feature of metastasis.

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Wu et al [5] also found that hilar vascularity is the most common vascularity seen in lymphoma and is different from benign hilar vascularity as high vascular density is seen in lymphoma cases.

Lymphadenopathy due to benign and malignant diseases can be distinguished with a high degree of accuracy by means of spectral waveform analysis. RI and PI of malignant nodes is significantly higher than benign nodes. In the present study, RI values ranged from 0.33 to 0.7 in benign nodes and 0.65 to 1.15 in malignant nodes and Mean RI of benign and malignant nodes in our study was 0.58 and 0.86 respectively. Choi et al [11] in their study noticed that RI ranged from 0.38 to 0.82 in benign nodes and 0.44 to 1.24 in malignant nodes with a mean RI of 0.59 in benign nodes and 0.92 in malignant nodes. Ferrari et al [12] found mean RI of 0.58 and 0.84 in benign and malignant lymph nodes respectively almost in close agreement with the present study. PI values ranged from 0.42 to 1.3 in benign nodes and 1.1 to 4.5 in malignant nodes and mean PI of benign and malignant nodes in our study was 0.85 and 1.76 respectively. Choi et al [11] in their study noticed that PI ranged from 0.46 to 1.43 in benign nodes and 0.59 to 6.16 in malignant nodes with a mean PI of 0.90 in benign nodes and 2.66 in malignant nodes. Ahuja et al [7] found a mean PI of 1.89 for malignant nodes and 1.07 for reactive nodes almost close to the values obtained in the present study.

In the present study, mean RI and PI in reactive nodes was 0.54 and 0.77, in tubercular nodes was 0.65 and 1.03,in lymphomatous nodes was 0.86 and 1.83 and in metastatic nodes was 0.86 and 1.72 respectively. Na et al [9] found mean RI and PI of 0.57 and 0.85 in reactive nodes, 0.64 and 1.03 in tubercular nodes, 0.7 and 1.2 in lymphoma and 0.83 and 1.62 in metastatic nodes which.. In our study mean RI and PI of lymphoma cases was not much different from metastasis because most of our lymphoma cases were aggressive Non Hodgkin lymphoma as has been noticed by Picardi et al [13], that mean RI value of aggressive NHL was 0.85 and was significantly higher than the mean values of 0.74 in Hodgkin lymphoma. Different researchers have suggested different cut off for RI and PI for differentiating benign and malignant lymphadenopathy. Wu et al [5] suggested cut off of 0.7 for RI and 1.1 for PI and found that accuracy was 73% and 76%, respectively. Chang et al [14] suggested a cut off of 0.6 for RI and 1.2 for PI and found sensitivity and specificity of 81% each. However, they had selected the lowest indices from each node. Shirakawa et al [8] suggested cut off of 0.72 for RI and 1.3 for PI and found it appropriate for acceptable sensitivity, specificity and Ahuja et al [15] suggested the cut off of 0.7 for RI and 1.4 for PI.

In the present study sensitivity and specificity was seen at three different values of RI and PI and it was noticed that at RI of 0.7 and PI of 1.3 high sensitivity (93%,89%) and specificity (94%,94%) was obtained with a p-value <0.0001 (using Chi Square test) while increasing the cut off to 0.8 for RI increased the specificity to 100% but reduced sensitivity to 68% and by decreasing cut off to 0.6 sensitivity increased to 100% but specificity was reduced to 45. Na et al [9] also looked for sensitivity and specificity at different cut off values and found sensitivity for labeling a node malignant at RI of 0.6 was >90% but specificity was 50%, at RI of 0.8 sensitivity reduced to around 50% but specificity was 100%. Likewise, for a cut off PI value of 1.1, sensitivity was > 80% but specificity was around 70% but at a cut off value of 1.5 sensitivity reduced to 55% but specificity reached 100%.

Mean Peak systolic velocity in the present study was similar in benign and malignant lymph nodes with malignant nodes showing mean PSV of 19.84cm/s and benign nodes showing mean PSV of 17.37cm/s and mean End diastolic velocity in malignant nodes was 2.8cm/s which was significantly lower than mean EDV of benign nodes which was 7.5 cm/s. EDV in malignant nodes varied from -4.6 to 11.1cm/s and EDV in benign nodes ranged from 3.4 to 19.4 cm/s. So in our study EDV> 11.1 cm/s has 100% negative predictive value for nodal metastasis, and EDV<3.4 cm/s has 100% specificity and PPV for metastasis.

Choi et al [11] also found mean PSV similar in two groups with mean PSV of 25cm/s in malignant and 24cm/s in benign nodes. Mean EDV of malignant and benign nodes was

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2cm/s and 10cm/s respectively. EDV in benign nodes varied from -10cm/s to 14cm/s and EDV in benign nodes ranged from 3cm/s to 51 cm/s. Brnic and Hebrang [16] also noticed that EDV>9 cm/s has 100% negative predictive value for nodal metastasis, and EDV<1 cm/s has 100% specificity and PPV for metastasis. Most important marker for differentiation of benign and malignant node in our study was RI with a sensitivity of 93%, specificity of 94% and accuracy of 93.5% at a cut off value of 0.7 with a p-value of < 0.0001. Issing et al [17] also concluded that most valuable parameter was Pourcelot index (RI) with a specificity of 92% for detecting malignant node. Ayata et al [6] also suggested RI as the most important marker with a sensitivity of 84.6, specificity of 100% and accuracy of 95.7% at a cut off value of 0.7 for differentiating benign from neoplastic lymphadenopathy.

Summary

Grey scale features most important in differentiation of benign and malignant lymphadenopathy was roundness index. Roundness index had acceptable sensitivity for detecting a malignant node but had low specificity as half of tubercular nodes and 18% of reactive nodes had SI< 2. Colour doppler features important in differentiation of benign and malignant lymphadenopathy were spectral parameters and vascular distribution. Reactive nodes usually showed hilar vascularity and in tubercular nodes, hilar vascularity and avascular forms constituted 3/4th of cases. Metastatic nodes showed mixed vascularity in most of the cases with peripheral and multifocal vascular signals being the most common while as lymphomatous nodes behaved differently by showing preponderance of type 2 hilar vascularity either in pure or mixed forms. Tubercular nodes showed features in between reactive and malignant nodes. RI and PI were the most important markers among the spectral parameters for the differentiation of benign and malignant lymphadenopathy. RI and PI of malignant nodes was significantly higher than benign nodes with p-value < 0.0001. At a cut off value of 0.7 for RI, sensitivity, specificity and accuracy were 93%, 94% and 93.5% respectively and at a cut off value of 1.3 for PI, sensitivity, specificity and accuracy were 89%, 94% and 91.3% respectively. PSV was similar in two groups and did not have any role but EDV of the malignant nodes was significantly lower than benign nodes. Although there was overlap in the values of EDV in the two groups but EDV> 11.1 cm/s has 100% negative predictive value for nodal metastasis, and EDV<3.4 cm/s has 100% specificity and PPV for metastasis. Main pitfall with doppler was the group of avascular nodes where diagnosis was based on grey scale features only.

Conclusion

Colour doppler sonography is a highly efficacious investigation for differentiation of benign and malignant lymphadenopathy Colour doppler can be used to prevent unnecessary invasive biopsy in many patients particularly in those patients where in addition to favorable grey scale features, we get very low values of RI and PI and very high values for EDV. Peripheral and chaotic multifocal vascular signals are strongly predictive of metastatic nodes. RI is the single most important parameter in the differentiation of benign and malignant lymphadenopathy. Cut off value of 0.7 for RI and 1.3 for PI, yield acceptable sensitivity, specificity and accuracy.

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