

The value of Doppler sonography in differential diagnosis of cervical lymphadenopathy

Dr. eaman muhsin Ali

FICMS MBCHB , Diagnostic radiology, dept. of surgery

College of medicine, Al-kufa university

Dr. Saad Al-Lamie

HDOS MBCHB general surgery

Abstract

In this prospective study we evaluate Doppler spectral parameters in lymphomatous, reactive , metastatic and acute inflammatory lymph nodes & evaluated the pulsed Doppler sonography as a technique to distinguish between different causes of cervical lymphadenopathy. Spectral Doppler analysis with measurement of resistance index (RI) , pulsatility index (PI) , peak systolic velocity (PSV) &End diastolic velocity (EDV) was performed in 100 patients with cervical lymphadenopathy . The results of Doppler analysis were compared with findings of cytology & histology or with clinical presentation & follow up . T-test was used to assess statistical significance of differences in Doppler parameters between groups of patients . Significant differences in RI & PI were shown between all groups of patients except between lymphomatous & reactive lymph nodes. Specificity of 100% for metastatic nodal involvement was shown for cutoff values $RI > 0.80$ & $PI > 1.80$. A positive predictive value (PPV) of 100% for acute lymphadenitis was shown for cutoff values $RI < 0.50$ & $PI < 0.60$. An $EDV > 10$ cm/s has 100% negative predictive value for nodal metastasis , & $EDV < 2$ cm/s has 100% specificity & PPV for metastases . Although there exist differences in RI , PI , PSV & EDV between different nodal diseases , unfortunately, only extreme cutoff values may occasionally be helpful in differential diagnosis. Doppler spectral analysis is a valuable noninvasive adjunct which can help in differentiation between metastatic , lymphomatous , acute inflammatory & reactive lymphadenopathy , but cannot eliminate the need for biopsy in the majority of cases.

Introduction

The inaccuracies in physical examination of cervical lymph nodes are well documented and all diagnostic imaging modalities have been shown to have superior diagnostic accuracy .Ultrasound is being increasingly used to assess cervical nodes . It has the benefits of not using ionizing radiation or intravenous contrast medium but it is generally accepted that it is less able to stage most primary tumors at the same time , and deep lymph nodes , for example in the retropharyngeal region , cannot be assessed by ultrasound . The optimal size criteria to define pathological lymph nodes at ultrasound are minimum diameter of 9 mm for level 2 nodes and 8mm for the remaining levels .These measurements offer a sensitivity of 74% and specificity of 78%. The ratio of minimal to maximal axial diameter has been reported to be a valuable predictor of malignancy , a ratio of greater than 0.55 indicating malignancy , with a specificity of 63%and sensitivity of 92%. Ultrasound has potential advantages over MRI and CT in the evaluation of nodal shape , with its ability to rotate the probe at ultrasound and select true minimal and maximal diameters . Ultrasound also has the advantage of demonstrating the normal nodal architecture with the presence in the normal node of an echogenic lymph node hilum and surrounding hypoechoic cortex. This has been shown to be helpful in distinguishing malignant from benign normal- sized nodes. Central necrosis will be identified by areas of low echogenicity with posterior acoustic enhancement. The rim of the node will usually be thick and irregular . Coagulative necrosis can also give the appearance of a very heterogeneous nodal architecture , with areas of increased reflectivity within the nodes. The distribution of blood flow in lymph nodes has also been evaluated using color Doppler ultrasound . It has been shown that areas of vascular sparing and isolated peripheral flow are suggestive of malignancy . Ultrasound contrast medium may contribute to such Doppler assessment in the future . Nodes involved by lymphoma may appear of very low

reflectivity with through transmission and thus mimic cysts . Increasing the gain setting will demonstrate low-level echoes within the node and color flow can be demonstrated within the node to differentiate it from a cyst. The most promising contribution of ultrasound is in the guidance of FNAC. This increases the specificity of ultrasound detection of lymph node metastases to 100% but reported sensitivities remain between 50 and 98%. These results do depend on whether the study population includes patients with No necks (those patients who clinically have no palpable disease), as these nodes will be smaller and more difficult to aspirate . Some papers performing direct comparison of ultrasound –guided FNAC with CT and MRI have shown it to be the most accurate technique in staging both the clinically metastatic and normal neck . The major drawback of using ultrasound in the staging of nodal metastases in the neck is the inability in most cases to stage the primary site of disease. The presence of extra capsular spread of disease does have major prognostic implication but is also less well seen with ultrasound than with CT.[1]

Analysis of blood flow may help to detect malignancy in lymph nodes , as has been demonstrated in many tumors . Both the angioarchitecture [2,3,4,5,6,7,8, 9,10,11] & the hemodynamics [2,3,4,5,8,10,11,12,13,14,15] differ among various cervical & axillary nodal diseases . Blood vessel morphology in metastatic nodes is usually deranged as internal nodal architecture is destroyed by neoplastic infiltration. Small arteries in metastatic nodes may be destroyed by tumor tissues [6], whereas severe inflammation causes dilatation of intranodal vessels due to local humoral agents.

Aim of the study

This prospective study

- 1-To determine whether Doppler spectral analysis could enable distinction between lymphomatous , metastatic , chronic inflammatory & acute inflammatory lymph nodes in patients with neck nodal disorders .
- 2- Whether it might be a valuable non-invasive adjunct to other diagnostic methods in work up of oncologic patients.

Materials and methods

Population study:

One hundred untreated patients with cervical lymphadenopathy (age range 8-70 years) (mean age 49.1 ± 11.9 years) were examined with color and spectral Doppler analysis over the period from 2008-2010.

In order to ensure that the examined lymph node exactly matched the removed /biopsied node , only one node in each patient with typical localization or morphology was included in the study . With such "one patient – one node approach" the possibility for confusion among the nodes was reduced to the minimum.

Four groups of subjects were included in the study : patients with suspected malignant lymphomas & chronic lymphatic leukemia , carcinomas with neck metastases , acute inflammations in oropharyngo-facial region, and reactive cervical lymph nodes. The later group consisted of outpatients , examined using ultrasound for reasons other than lymph node swelling , in whom chronic inflammatory cervical lymph nodes were found incidentally (Table 1).

We compared Doppler spectral findings with findings of histology & cytology in malignant nodes , or with clinical presentation & follow-up in benign nodes.

The US examination were performed using sonoline versa pro. Machine with a linear 7.5 MHz transducer with color Doppler & power Doppler capabilities . Following conventional ultrasonic morphologic analysis of the lymph node , we performed pulsed Doppler examination guided by color Doppler . Power Doppler was used to identify faint flow signals in small lymph nodes, if it was undetectable by color Doppler. Probe pressure to the skin , which could obliterate flow in superficial nodes was strictly avoided . Angle of correction was kept at less than 60° in all analysis of spectra , with angle correction providing accurate velocity measurements. Peak systolic velocity (PSV) , end diastolic velocity (EDV) , resistance index (RI) , & pulsatility index (PI) were measured. Spectra were derived from three different vessels in each node. The highest PSV & EDV values & the mean RI & PI values are taken as representative so as to minimize possible effect of compression with transducer. The RI & PI were calculated by use of US machine software , with manual tracing of spectral profiles.

All US examination were performed by the same radiologist (the author), hence the interobserver variability is excluded. Although the examiner was not aware of the final diagnosis at the moment of Doppler US examination , the study might be biased to some extent by the knowledge of clinical and conventional US findings , which could not be avoided.

Histologic & cytologic evaluation

The etiology of lymph node enlargement is confirmed by histopathology , cytology , or clinical follow up. Excisional or US- guided needle biopsy was done in patients in whom malignant nodes were suspected . In patients with low suspicion of malignancy , fine needle aspiration cytology (FNAC) with consecutive clinical follow- up was performed . In some cases histology was done in addition to FNAC. When benign morphology of lymph node was recognized on conventional US , in the patient with no suspicion for malignancy , and if rapid regression was evident under antibiotic treatment , only clinical & US follow-up of 3-6 months was considered to be sufficient for diagnosis . Histologic analysis was conducted by an experienced pathologist who evaluated the material gained by node biopsies or neck dissections. The same pathologist performed cytologic analysis of fine needle aspirate.

Statistical evaluation

Student's *t*-test was used to assess the statistical significance of differences of Doppler parameters among the groups of patients . The sensitivity & specificity of cutoff values of Doppler parameters were calculated and charted as receiver operating characteristics curves (ROC).

Results

Sixty nine benign and thirty one malignant cervical lymph nodes were included in our series. Patients diagnoses in each of four study groups are shown in Table1. Doppler parameters of all lymph nodes are summarized in Table 2.

Doppler arterial waveforms showed a wide spectrum of pulsatility, from low-impedance configuration with relatively high diastolic flow (mainly in acute lymphadenitis; Figure 1; Table 2) to high – impedance configuration with low diastolic flow (predominantly in metastatic lymph nodes ; Figure2 ; Table2) .

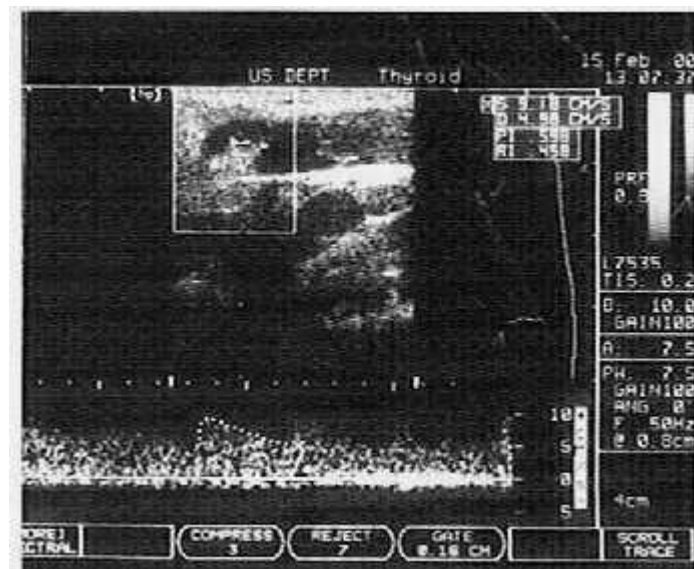


Fig.1 low - impedance configuration of intranodal spectrum with high diastolic flow in acute lymphadenitis :RI=0.46 ,PI=0.60.

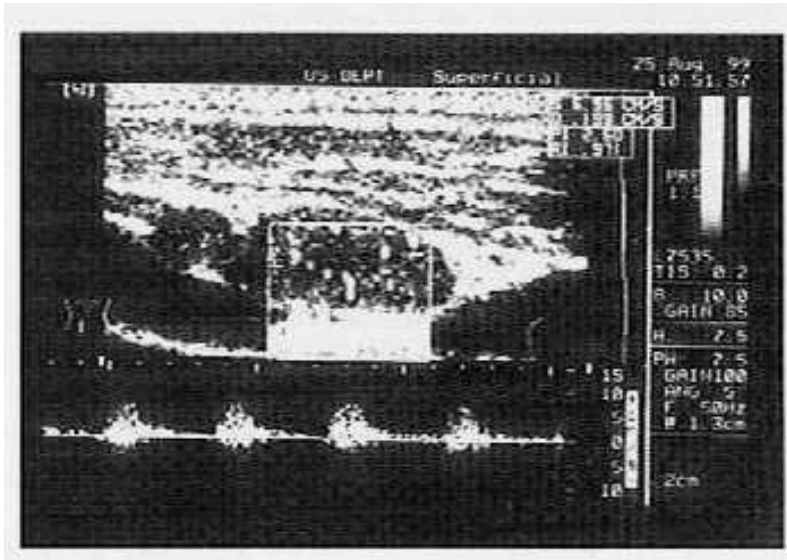


Fig.2 high-impedance configuration of intranodal spectrum with low diastolic flow in metastatic lymph node : RI =0.97 , PI =2.60.

The significance of differences between groups of subjects for each Doppler US parameter is shown in Table 3. Doppler indices RI & PI were significantly different between all compared groups , except between malignant lymphomas & reactive nodes (between the two groups , however , differences in PSV & EDV were significant).

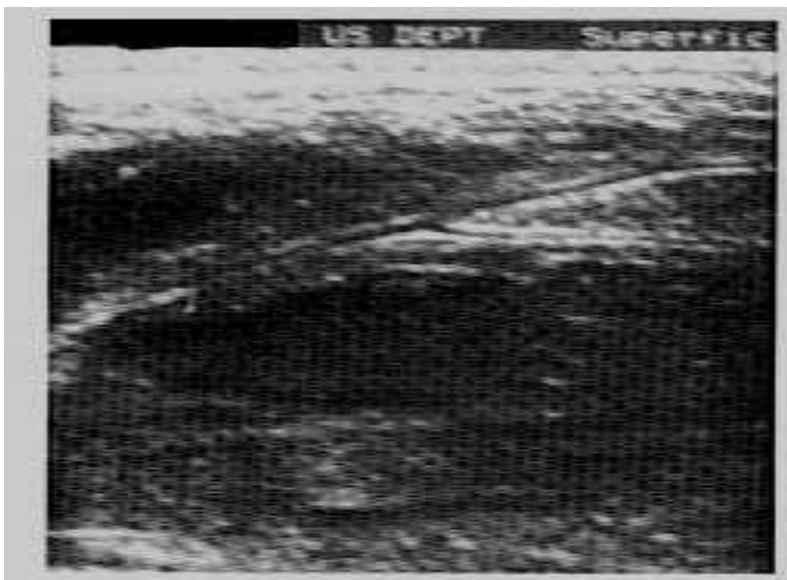


Fig.3- small vessels within lymphomatous nodes are clearly visible with high-frequency transducer as echogenic double-lined structures within thickened echo-poor nodal cortex.

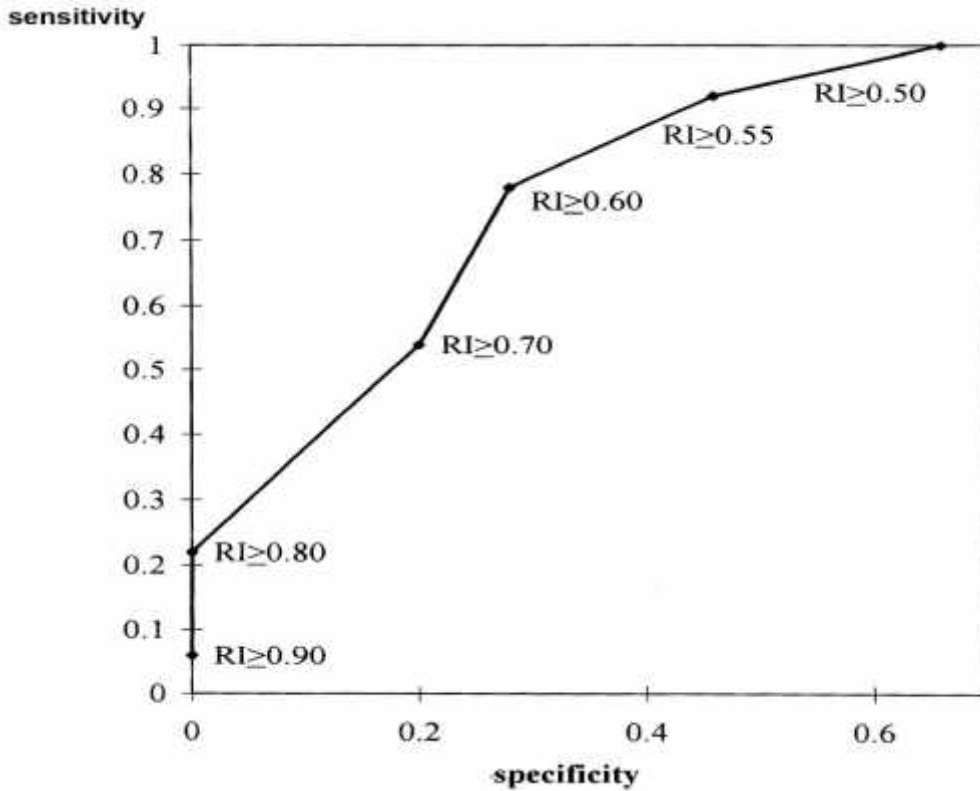


Fig.4 Receiver operating characteristic curve shows relationship between sensitivity and specificity of RI for each cut off value . Although high values of RI are highly specific for malignancy the corresponding sensitivities are not satisfactory.

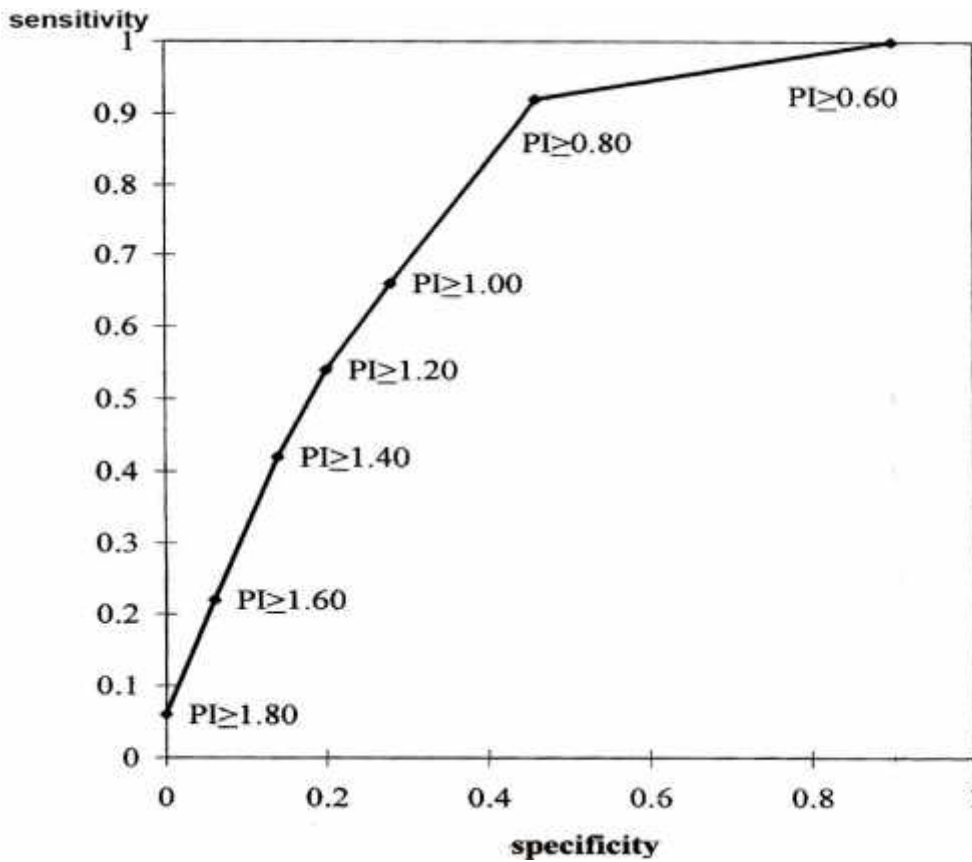


Fig.5 Receiver operating characteristic curve shows relationship between sensitivity and specificity of PI for each cut off value . Although PI is more valid criterion because are under curve is larger than that of RI, sensitivities are not satisfactory

The cut off values of RI & PI in differentiating benign (acute inflammatory & reactive) from malignant (lymphomatous & metastatic) nodes are charted as ROC curves shown in Figures 4 and 5. As none of lymph nodes affected by malignant processes had RI lower than 0.50, cutoff values $RI > 0.50$ and $PI > 0.60$ has sensitivity and negative predictive value (NPV) of 100% for malignancy. Cutoff values of $RI < 0.50$ & $PI < 0.60$ has positive predictive value (PPV) of 100% for acute lymphadenitis. An $RI > 0.80$ has PPV and specificity of 100% for metastasis. Relatively high PPV of 86% and specificity of 100% for metastases were shown for $PI > 1.80$. The cutoff values $RI > 0.70$ and $PI > 0.90$ are of highest accuracy of 75% and 77%, respectively.

Despite the high specificity and PPV of high Doppler indices for malignancy, our results overlapped considerably between malignant and benign nodes in the lower range of both RI and PI, which preclude accurate distinction based exclusively on RI and PI. No cutoff value for either index has both high sensitivity & specificity for malignancy. High specificity & PPV of $RI > 0.80$ & $PI > 1.80$ cutoffs, however, enabled us to predict malignancy in nodes which can occasionally be mistaken as benign using other diagnostic methods.

The PSV was significantly different between group of lymphomas & reactive nodes, lymphomas & acute inflammatory nodes, and metastatic and reactive nodes.

The difference between acute inflammatory and reactive nodes was near the level $p = 0.50$ (Table3). The EDV was significantly different between lymphomas & metastases, lymphomas & reactive nodes, metastatic & acute inflammatory nodes, and reactive and acute inflammatory nodes. In all reactive and metastatic nodes $EDV < 5\text{cm/s}$ was observed (whereas in 25% of lymphomas and 25% of acute inflammatory nodes $EDV > 9\text{cm/s}$). An $EDV > 10\text{cm/s}$ is a valuable cutoff for excluding metastasis, leaving the possibility for the diagnosis of lymphoma or acute lymphadenitis (sensitivity 100%, specificity 17%, PPV 27%, NPV 100%). No one reactive lymph node in our study had $EDV < 2\text{cm/s}$, whereas 16% of metastatic nodes had very low EDVs

, even 0.2 cm/s; hence, EDV<2 cm/s is 100% specific for metastatic involvement of lymph node (sensitivity 16%, PPV 100% , NPV 77%; Figure 2).

Table 1 : four groups of patients according to etiology of lymph node enlargement . in patients with reactive nodes, US examinations (in italics) were done for reasons other than lymphadenopathy.

Study group	Diagnosis	No. of patients
Malignant lymphoma (n=12)	Non-Hodgkin's lymphoma	6
	Hodgkin's disease	4
	Chronic lymphatic leukemia	2
Metastatic lymph nodes(n=19)	Upper respiratory cancer	9
	Parotid cancer	4
	Lung cancer	3
	Carcinoma of unknown origin	3
Reactive(chronic inflammatory)lymph nodes(n=30)@	<i>Thyroid US</i>	13
	<i>Carotid Doppler US</i>	7
	<i>Salivary glands US</i>	4
	<i>Breast US</i>	4
	<i>neck US, unspecified</i>	2
Acute lymphadenitis (n=39)	Acute bacterial tonsilo-pharyngitis	12
	Upper respiratory infection	9
	Acute sialoadenitis	3
	Dental inflammation or abscess	5
	Aphous stomatitis	3
	Furuncle. Acne vulgares.	7

@lymph node was considered "reactive" if signs of chronic inflammation were found.

Table 2: Results of spectral Doppler US analysis . Data are given as means \pm SD . RI resistance index ; PI pulsatility index; PSV peak systolic velocity ; EDV end diastolic velocity.

Doppler parameters	Malignant lymphomas	Metastatic lymph nodes	Reactive lymph nodes	Acute lymphadenitis
RI	0.65 \pm 0.07	0.77 \pm 0.10	0.66 \pm 0.07	0.48 \pm 0.04
PI	1.04 \pm 0.32	1.51 \pm 0.40	1.14 \pm 0.35	0.64 \pm 0.09
PSV (cm/s)	18.19 \pm 6.94	16.46 \pm 6.16	11.64 \pm 5.17	14.13 \pm 5.46
EDV (cm/s)	6.89 \pm 3.70	3.67 \pm 2.84	4.06 \pm 2.15	7.04 \pm 2.76

Table 3: Significance of differences between compared groups of patients for each Doppler US parameters. ML malignant lymphoma , MT metastatic lymph nodes , RE reactive lymph nodes, AC acute lymphadenitis.

Compared groups	RI	PI	PSV	EDV
ML vs MT	$< 10^{-5}$	$< 10^{-3}$	0.55@	$<10^{-3}$
ML vs RE	0.29 @	0.34 @	10-4	$<10^{-3}$
ML vs AC	$< 10^{-9}$	$<10^{-5}$	0.04	0.84@
MT vs RE	$< 10^{-4}$	0.01	0.01	0.96@
MT vs AC	$< 10^{-13}$	10^{-6}	0.31@	10^{-4}
RE vs AC	10^{-9}	$< 10^{-6}$	0.06@	$<10^{-2}$

@ non significant

Discussion

The reliability of Doppler US in differentiating malignant from benign lymph nodes is still a matter of debate. Authors who have analyzed vascular resistance in cervical lymph nodes have mostly found higher Doppler indices in malignant than in benign nodes [2 , 3 , 4 , 5 , 8 , 11 , 12 , 13,14] None of them have analyzed acute lymphadenitis separately from chronic inflammatory lymph nodes , whereas in several studies metastatic & lymphomatous nodes have been considered simply as "malignant nodes" , even though their Doppler parameters differed considerably [2,4,13].

The sensitivity of Doppler US equipment has greatly improved in the past two decades, and blood flow has become detectable nearly in all superficial lymph nodes. Since 1991 several studies have aimed to prove the value of Doppler spectral analysis in predicting the cause of lymph node enlargement [3,4,5,8,10,11,12,13,14,15]. The authors have investigated vascular resistance in

superficial lymph nodes , and have shown that resistance is lower in benign than in malignant – especially metastatic – lymph nodes. In some papers significantly higher Doppler indexes in metastatic than in lymphomatous nodes have also been reported [2,4,6]. Only in one study was very low resistance in malignant nodes shown [3] , but these results were not corroborated in later studies, just as arteriovenous shunts were not found in metastatic nodes.

Some authors initially believed that superficial lymphadenopathy due to benign and malignant disease could be noninvasively distinguished by means of Doppler waveform analysis, but many agreed that because of significant overlap of both RI & PI values between benign & malignant nodes , it was unlikely that Doppler US would eliminate the need for biopsy in the majority of patients [3,14]; however , the analysis of most series has demonstrated that RI & PI above the certain cutoff values might predict malignancy in lymph nodes with satisfactory confidence [2,4,5,12].

Our study supports the results of previous reports that malignant nodes have higher RI & PI than benign nodes. We observed significant differences between all groups except between malignant lymphomas & chronic inflammatory nodes for both indexes. Similar intranodal resistance in the latter two groups can be explained by the fact that the normal intranodal structure in lymphomas has not been damaged by the growth of neoplastic tissues, which is lodged in mainly intact nodal fibroepithelial skeleton. According to the investigation by Majer et al [16] and to our experience , intact small vessels in lymphomatous nodes can be clearly visible with high-frequency transducers as echoic double – lined structures within expanded thickened echo-poor nodal cortex (Figure 3). Apart from this , metastatic involvement results in distortion of intranodal architectural network , along with damage and/or compression of blood vessels shown in one histologic study [6,12].

Doppler arterial waveform in acute lymphadenitis in our series consistently showed low-impedance pulsatile pattern , with RI & PI significantly lower than in reactive nodes & malignant nodes ($p < 10^{-9}$). Cutoff values of RI < 0.50 & PI

< 0.60 have reached PPV of 100% for acute lymphadenitis. Consequently , when clinical & grey-scale US features of the node are equivocal , very low Doppler indexes strongly suggest benign nature of lymphadenopathy. Even inadequate examination technique (e.g.; compression with the probe) , which occasionally may lead to falsely higher Doppler indexes , will not reduce such a high PPV since PPV is independent of the false-negative rate.

In our study , as in the majority of studies published previously , considerable overlap in the lower range of RI & PI between benign & malignant nodes was observed. For this reason, RI & PI may be helpful in differential diagnosis of neck lymphadenopathy only when higher or lower than certain cutoff values. According to our results , Doppler indexes RI > 0.80 & PI > 1.80 are 100% specific for metastases. Specificity of 100% for RI > 0.80 & PI > 1.50 in the detection of malignancy, shown previously [5], appeared to be lower (88%) in our study. In another paper [16] accuracy for RI > 0.80 and PI > 1.60 was 91% in differentiation of reactive from metastatic nodes (our results; 62%). Although their sensitivity is low (Figs .4 &5), high specificity of these cutoffs may be helpful in selecting nodes for the biopsy. This may decrease the number of negative punctures or reveal metastatic nodes mistaken for benign using other diagnostic methods. As none of the nodes affected by malignant processes in our series had PI < 0.60 , this cutoff value has NPV of 100% for malignancy. As a consequence, if PI < 0.60 is observed, the node is not likely to be malignant and has no priority for puncture or biopsy.

In addition to Doppler indexes , extreme EDV values may also indicate the diagnosis in some cases of lymphadenopathy [12]. According to our results, cutoff value EDV > 10cm/s can reliably exclude metastasis (NPV 100%) and EDV < 2 cm/s is of 100% specificity and PPV for metastasis. Doppler spectrum derived with angle correction reveals low or high EDV at a glance, which helps in deciding instantaneously which node to puncture, when several nodes are present at the neck. We must, however, be aware of whether the spectrum really originates from within the node, because extranodal muscular artery with low or

absent diastolic flow can occasionally be misunderstood as a highly resistant intranodal vessel.

The ROC analyses of Doppler parameters (Fig.4,5) showed that none of these parameters offer both good specificity & sensitivity , and reliable differential diagnosis of cervical lymphadenopathy is not possible with Doppler measurements alone.

Our study has a limitation in that we did not analyze the degree of nodal neoplastic invasion nor correlate it with intranodal hemodynamics. Although we did include several small malignant nodes in our material, we did not systematically deal with early- stage malignant infiltration of lymph nodes and cannot discuss about changes of intranodal blood flow in small nodal metastases , which probably do not induce significant changes in nodal vascular structure. Further studies are required to investigate how large portions of lymph node need to be replaced by tumor cells for increased vascular resistance to occur.

Conclusion

We conclude that although there exist differences in RI , PI , PSV & EDV between different nodal diseases, none of these parameters (alone) offer both good sensitivity and good specificity , and only extreme cutoff values are helpful in differential diagnosis.

Doppler spectral analysis is a valuable noninvasive adjunct to gray-scale US, and may help differentiate the causes of nodal swelling, but cannot obviate biopsy in the majority of cases.

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قيمة الدوبلر الطيفي والملون في تشخيص أمراض العقد اللمفاوية العنقية.

تشتمل هذه الدراسة على مقارنة قيم الدوبلر الطيفي والملون في تمييز أسباب تورم العقد اللمفاوية في الرقبة متضمنا الالتهابية ، التفاعلية ، السرطان اللمفي والسرطان الثانوي المنتشر.

قيم الدوبلر الطيفية المستخدمة تتضمن الآتي : ١. معامل المقاومة ٢. معامل النبضات ٣. قمة السرعة الانقباضية ٤. نهاية السرعة الانبساطية .

أجريت الدراسة على مئة مريض مصاب بتورم العقد اللمفاوية في الرقبة مستخدمين السونار العادي والملون والطيفي، كما قورنت نتائج الدوبلر بنتائج الزرع النسيجي والخلوي والمتابعة السريرية ، ولقد تبين بان هناك فرق واضح في معامل المقاومة و معامل النبضات بين كل مجاميع المرضى ماعدا السرطان اللمفي والتورم التفاعلي للغدد اللمفاوية . أما القيم الأخرى فهي كالآتي :

١. قيمة الخصوصية ١٠٠% للعقد المتأثرة بالسرطان المنتشر للقيم القطعية : معامل المقاومة $0,80 <$ ومعامل النبضات $1,80 <$

٢. القيم الايجابية المتوقعة ١٠٠% للعقد المتأثرة بالالتهابات الحادة للقيم القطعية : معامل المقاومة $0,50 >$ ومعامل النبضات $0,60 >$

٣. القيم السلبية المتوقعة ١٠٠% للعقد المتأثرة بالسرطان المنتشر للقيم القطعية: معامل نهاية سرعة الدم الانبساطية $10 \text{ سم/ثا} <$

٤. القيم الايجابية المتوقعة وقيمة الخصوصية ١٠٠% للعقد المتأثرة بالسرطان المنتشر للقيم القطعية: معامل نهاية سرعة الدم الانبساطية $2 \text{ سم/ثا} >$

على الرغم مما ظهر في نتائج دراستنا التي تبين وجود فرق في قيم معامل المقاومة ومعامل النبضات ، قمة سرعة الدم الانقباضية ونهاية سرعة الدم الانبساطية في مختلف أسباب تورم العقد اللمفاوية (العنقية) ، لاتوجد هناك قيمة واحدة بحد ذاتها توفر كل الشروط لتشخيص سبب تورم العقد اللمفاوية ، باستثناء استخدام قيم قطعية عالية جدا ، قد تكون في بعض الأحيان عاملا مساعدا في تشخيص تلك الأسباب .

كما أظهرت دراستنا أيضا بان تحليل الدوبلر الطيفي يعتبر عامل تشخيصي غير تداخلي يساعد في تشخيص عقد الرقبة اللمفاوية ، لكن لاتنفي الحاجة إلى الخزعة (أي الزرع النسيجي) في أكثر الحالات .