

The Role Of High Resolution Ultrasonography To Differentiate Between Benign And Malignant Cervical Lymph Nodes In Oral Squamous Cell Carcinoma

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Received: 18.09.2017

Accepted: 16.11.2017

Abstract:

*Objectives:*The purpose of the study was to evaluate the role of high resolution ultrasonography to differentiate between benign and malignant cervical lymph nodes in oral squamous cell carcinoma.

*Materials & Methods:*The study was conducted in the Department of Oral and Maxillofacial Surgery, BSMMU, Dhaka, Bangladesh, during a period of January -2010 to December - 2011. A total number of 41 patients with clinical evidence of palpable cervical lymph nodes in oral squamous cell carcinoma were evaluated with high resolution ultrasonography. To evaluate the diagnostic accuracy of high resolution ultrasonography, the high resolution ultrasonography findings were compared and correlated with histopathological examination after neck dissection.

Results: All patients were pre-operatively examined by palpation and high resolution ultrasonography evaluation was done. Among them 41 study subjects, on high resolution ultrasonography evaluation 23(56.09%) lymph nodes were metastatic and 18(43.90%) lymph nodes were reactive. After postoperative excisional histopathology examination 22(53.66%) lymph nodes were metastatic and 19(46.34%) lymph nodes were reactive in nature. Correlation of vascular flow pattern with histopathological diagnosis showed that central flow for benign nodes, mixed & peripheral flow for malignant nodes were highly significant parameters ($P < 0.001$). High resolution ultrasonography has specificity 78.94%, sensitivity 86.36% and diagnostic accuracy of the high resolution ultrasonography was 82.92%.

Conclusion: High resolution ultrasonography can play a definite role as an adjunct to the clinical evaluation of palpable cervical lymph nodes and proves its value as an important noninvasive investigation procedure for differentiating between benign and malignant cervical lymph nodes in oral squamous cell carcinoma.

Key words: High resolution ultrasonography, palpable cervical lymph nodes, oral squamous cell carcinoma, histopathology

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Introduction

Squamous cell carcinoma is the most common malignant tumor in the head and neck region.¹ Approximately 90 % of oral cancers are squamous cell carcinoma.² Assessment and early detection would drastically bring down the morbidity and mortality associated with advanced stages of oral cancer.³ In the treatment of patients with oral squamous cell carcinoma of the oral cavity size of primary lesion, site, thickness, histological staging and presence or absence of metastatic spread are important to formulate a treatment plan.⁴

Lymphatic spread is the most important mechanism in the spread of the head and neck squamous cell carcinomas.⁵ The presence or absence of lymph node metastasis has a great impact on the prognosis and survival of patients with oral cancer. Nodal metastasis to one side decreases the survival rate by 50%, while bilateral metastasis decreases survival by a further 25%.^{4,6,7,8} The neck status is the single most important indicator of prognosis in head and neck cancers.⁹

Management of the lymph node in neck region in patients with oral squamous cell carcinoma is controversial. Some surgeon's advice elective treatment of the neck while others do not support that.⁴ It is possible to reduce the risk of undiagnosed metastasis with accurate imaging techniques and thus probably reduce the number of elective neck treatments.¹⁰ Several imaging modalities have been used in evaluating the status of cervical lymph nodes in oral squamous cell carcinoma. Ultrasonography, ultrasound-guided fine needle aspiration cytology (FNAC), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Lymphoscintigraphy. The continuous advanced techniques lead to an increasing sensitivity of the imaging modalities in the detection of lymph nodes. However, differentiation between benign and malignant lymph nodes is not possible as far as conventional ultrasound examination, CT and MRI are concerned.^{11,12,13} Though ultrasound - guided fine needle aspiration cytology (FNAC) has a higher diagnostic accuracy^{11,14} but puncturing the metastatic lymph node with the risk of micro dissemination of cancer cells, rupturing the capsule of the metastatic node and infection may occur following the FNAC procedure.¹⁵

High-resolution ultrasonography has been commonly used to evaluate cervical lymphadenopathy and the role of gray-scale ultrasonography in the assessment of cervical lymph nodes is well established.^{16,17,18}

Gray-scale ultrasonography is widely used to assess cervical nodes for their number, site, size, nodal boundary, hilum, adjacent soft tissue edema and other internal nodal echo patterns.^{16,17} But gray-scale ultrasonography is not sensitive enough in differentiation of malignant and benign lymph nodes.^{13,19} The application fields of color Doppler and power Doppler ultrasonography are broad and Doppler ultrasonography was suggested to be used for differentiation of benign and malignant lymph nodes.

Color Doppler ultrasonography is a medical imaging technique which is used to provide visualization of the blood flow, using color processing to add color to the image so that we can clearly see what is happening inside the body. Color Doppler ultrasonography is a non-invasive investigation procedure that can define the morphological and vascular characteristics of lymph nodes. The presence of intra nodal vascularity, its distribution and estimates of the intravascular resistance and spectral Doppler analysis are evaluated with color Doppler.¹⁴ All these intra nodal vascular alterations helps in differentiating benign from malignant lymph nodes.^{20,21} With the development of technology and the introduction of power Doppler ultrasonography, assessment of the vascularity of lymph nodes by ultrasound has become more accurate.^{21,22,23} In comparison with color Doppler ultrasonography, power Doppler ultrasonography is more sensitive in detection of structures with low volume of fluid^{24,25} and it is more accurate in the assessment of small vessels, those found in lymph nodes.²⁶

In this article we evaluated the role of high resolution ultrasonography characteristics of cervical lymph nodes in patients with oral squamous cell carcinoma to determine a more reliable method of distinguishing benign from malignant lymph nodes in oral squamous cell carcinoma.

Aims & Objectives

1. To evaluate the role of high resolution ultrasonography to differentiate between benign and malignant cervical lymph nodes in oral squamous cell carcinoma.
2. To evaluate the Doppler recorded blood flow patterns increases the diagnostic accuracy of detecting metastatic lymph nodes.
3. To assess the reactive and metastatic features of cervical lymph nodes in oral squamous cell carcinoma by high resolution ultrasonography.
4. To correlate between the ultrasonography findings and histopathology findings of palpable cervical lymph nodes in oral squamous cell carcinoma.

Materials & Methods

A prospective cross sectional observational study was designed.

Study population: The study was performed in Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, BSMMU, Dhaka, Bangladesh from January - 2010 to December - 2011, where a significant number of oral squamous cell carcinoma patients were admitted regularly. Among them 41 study subjects were selected, who fulfilled the inclusion criteria. Inclusion Criteria: I) All admitted patients diagnosed histopathologically as squamous cell carcinoma in oral cavity. II) Patients of oral squamous cell carcinoma with clinical evidence of palpable cervical lymph nodes. Exclusion Criteria: I) Patients of oral squamous cell carcinoma was declared as inoperable for the primary tumor. II) Inoperable for advanced neck metastasis. III) Inoperable for systemic diseases. IV) Patients who received previous radiotherapy.

Study Procedure: Diagnosis was made by accurate history, clinical examination, histopathological examination from the primary lesion and high resolution ultrasonography examination. After obtained an informed written consent all patients were evaluated with high resolution ultrasonography by an experienced radiologist.

The high resolution ultrasonography study was conducted with Siemens Acouson Antares equipped with broadband (frequency bands 5-10 MHz) linear array transducer. The Doppler parameter was adjusted for low velocity or low volume flow or both. PRF 800 kHz, Band pass filter was 62/75 Hz.

The patient should be supine in positioned with the neck hyper-extended. A pillow should be placed under the shoulders for support the lower neck region. The patient was remained in this position for 5 minutes before the examination was started to ensure the blood flow was measured at rest in position.

The examination was started with a transverse scan of the sub mental area. The transducer was then swept laterally to one side of the neck while the patient's head rotates towards the opposite side to allow free manipulation of the transducer. The submandibular region was examined with a transverse scan along the inferior border of the mandibular body. The internal jugular chain nodes were examined in transverse scan along the internal jugular vein and common carotid artery from the tail of parotid gland to the junction between internal jugular vein and the subclavian vein. The posterior triangle nodes

were examined. The same scanning protocol was used on the opposite side of the neck so that the major nodal chain in the neck was covered.

All cervical lymph nodes in each region were assessed for size, shape, echogenic hilum and vascularity. The vascular pattern of each cervical lymph node was determined and classified according to the location of the vascularity. (1) Central (hilar) flow with a single vascular signal branching radially from the center, originating symmetrically and showing a regular course from the lymph nodal hilum (2) Peripheral (capsular) flow signals along the periphery of the lymph nodes, with branches perforating the periphery of the lymph node and not arising from the hilar vessels (3) Mixed the presence of central and peripheral vascular flow patterns (4) Absent or no vascular signals within the lymph nodes. The blood flow pattern and vascular resistance (Resistive index and Pulsatility index) were measured and recorded. Histopathological diagnosis was performed after neck dissection that was done by the Oral and Maxillofacial surgeon and after that each cervical lymph node was histopathologically determined to be metastatic or reactive. Then a correlation was done between the high resolution ultrasonography findings and histopathological findings of palpable cervical lymph nodes in oral squamous cell carcinoma.

Data Processing and Analysis

Data were processed and analyzed by using computer software SPSS version 19 for windows. Level of significance was set at 0.05 and p value < 0.05 was considered significant.

Results

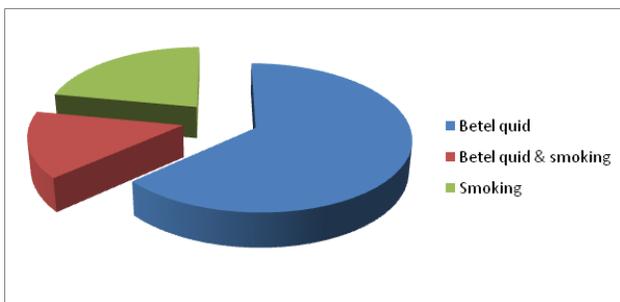
The study was performed in Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, BSMMU, Dhaka, Bangladesh from January-2010 to December-2011, where a significant number of oral squamous cell carcinoma patients were admitted regularly. Among them 41 study subjects, on high resolution ultrasonography evaluation 23(56.09%) lymph nodes were metastatic 18(43.90%) lymph nodes were reactive. After postoperative excisional histopathology examination 22(53.66%) lymph nodes were metastatic and 19(46.34%) lymph nodes were reactive in nature.

Table 1: Distribution of the study subjects by age.

Age group	Frequency	Percentage (%)
30 - 40 years	12	29.3
41 - 50 years	10	24.39
51 - 60 years	11	26.8
> 60 years	08	19.51
Total	41	100.0
Mean (±SD)	51.70 (±11.11)	Range 35-70

The table shows the age distribution of the study subjects. Out of 41 subjects 12 (29.3%) were between 30-40 years, 10 (24.39%) were 41-50 years, 11 (26.8%) were 51- 60 years and 08 (19.51%) were above 60 years. The age of the study subjects ranged from 35 - 70 years Mean age (+/-SD) = 51.70 (± 11.11) years.

Figure 1: Distribution of study subjects by their habits.



This pie diagram shows distribution of study subjects by their habits. Among them 26 (63.4%) were habituated to betel quid chewing, 06 (14.6%) were habituated both betel quid and smoking, 09 (22.0%) were smoking respectively.

Table 2: Evaluation of cervical lymph nodes in the study subjects.

Evaluation of lymph nodes	Metastatic	Reactive	Total
Clinical evaluation	25(60.98%)	16(39.02%)	41(100.0%)
Ultrasonography evaluation	23(56.09%)	18(43.90%)	41(100.0%)
Excisional Histopathology	22(53.66%)	19(46.34%)	41(100.0%)

Table 3: Distribution of vascular flow pattern in cervical lymph nodes by Doppler ultrasonography.

Vascular flow pattern	Excisional Histopathology		Total	P value
	Metastatic	Reactive		
Peripheral & mixed flow pattern	19(86.37%)	04(21.05%)	23(56.10%)	<0.001 ^s
Centralflow pattern	03(13.63%)	15(78.95%)	18(43.90%)	
Total	22(100%)	19(100%)	41(100%)	

The table shows vascular flow pattern in cervical lymph nodes. Among 22 metastatic nodes, 19 (86.37%) metastatic nodes had a mixed and peripheral pattern of blood flow and 03 (13.63%) metastatic nodes had a central pattern of blood flow within the lymph nodes. Among 19 reactive nodes, 04 (21.05%) reactive nodes had a mixed and peripheral pattern of blood flow and 15 (78.95%) reactive nodes had a central pattern of blood flow. Significant differences were found in different outcome of vascular flow pattern (p < 0.05) in chi- square test.

Table 4: Distribution of Resistive index (RI) in cervical lymph nodes by Doppler ultrasonography.

Resistive index	Excisional Histopathology			P value
	Metastatic	Reactive	Total	
RI > 0.6	20 (90.9%)	07 (36.84%)	27 (65.85%)	0.001 ^s
RI ≤ 0.6	02 (9.10%)	12 (63.16%)	14 (34.15%)	
Total	22 (100.0%)	19 (100.0%)	41(100.0%)	

The table shows the resistive index (RI) in cervical lymph nodes. Among the 22 metastatic nodes R.I. >0.6 was observed in 20(90.9%) metastatic nodes and R.I. < 0.6 was observed in 02(9.10%) metastatic nodes. Among the 19 reactive nodes R.I. >0.6 was observed in 07(36.84%) reactive nodes and R.I. < 0.6 was observed in 12(63.16%) reactive. Significant differences were found in different outcome of RI (p < 0.05) in chi- square test.

Table 5: Distribution of Pulsatility index (PI) in cervical lymph nodes by Doppler ultrasonography.

Pulsatility index	Excisional Histopathology			P value
	Metastatic	Reactive	Total	
PI > 1.1	21 (95.45%)	07 (36.84%)	28 (68.30%)	< 0.001 ^s
PI < 1.1	01 (04.55%)	12 (63.16%)	13 (31.70%)	
Total	22 (100%)	19 (100%)	41 (100%)	

The table shows the pulsatility index (PI) in cervical lymph nodes. Among the 22 metastatic nodes P.I >1.1 was observed in 21(95.45%) metastatic nodes and P.I.< 1.1 was observed in 01(04.55%) metastatic nodes. Among the 19 reactive nodes P.I.>1.1 was observed in 07(36.84%) reactive nodes and P.I. < 1.1 was observed in 12(63.16%) reactive nodes. Significant differences were found in (p < 0.05) chi-square test.

Table 6: Diagnostic accuracy of vascular pattern, Resistive index, Pulsatility index.

Diagnostic Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
Vascular pattern	86.36%	78.94%	86.36%	83.33%	82.92%
Resistive index (RI)	90.91%	63.16%	74.07%	85.71%	78.04%
Pulsatility index (PI)	95.45%	63.16%	75.0%	92.31%	80.48%

The above table shows the diagnostic accuracy of vascular pattern, RI and PI. Sensitivity of vascular pattern were 86.36% Specificity 78.94% predictive value for a positive test 86.36% and predictive value for a negative test 83.33% respectively. Sensitivity of resistive index (RI) were 90.91%, Specificity 63.16%, predictive value for a positive test and predictive value for a negative test were found 74.07% and 85.71% respectively. Sensitivity of pulsatility index (PI) were 95.45%, Specificity 63.16%, predictive value for a positive test and predictive value for a negative test were found 75.0% and 92.31% respectively. In the analysis the accuracy of vascular pattern, RI and PI of color Doppler ultrasonography were, 82.92 %, 78.04 %, 80.48 % respectively.

Table7: Correlation of high resolution ultrasonography evaluation with histopathology examination.

High resolution ultrasonography evaluation	Excisional Histopathology		Total	P value
	Metastasis	Reactive		
Metastasis	19(86.37%)	04(21.05%)	23(56.10%)	0.001 ^s
Reactive	03(13.63%)	15(78.95%)	18(43.90%)	
Total	22 (100%)	19 (100%)	41(100%)	

The above table shows the diagnostic accuracy of vascular pattern, RI and PI. Sensitivity of vascular pattern were 86.36% Specificity 78.94% predictive value for a positive test 86.36% and predictive value for a negative test 83.33% respectively. Sensitivity of resistive index (RI) were 90.91%, Specificity 63.16%, predictive value for a positive test and predictive value for a negative test were found 74.07% and 85.71% respectively. Sensitivity of pulsatility index (PI) were 95.45%, Specificity 63.16%, predictive value for a positive test and predictive value for a negative test were found 75.0% and 92.31% respectively. In the analysis the accuracy of vascular pattern, RI and PI of color Doppler ultrasonography were, 82.92 %, 78.04 %, 80.48 % respectively.

Table7: Correlation of high resolution ultrasonogra-

phy evaluation with histopathology examination.

Diagnostic Accuracy	Sensitivity	Specificity	PPV	NPV	Accuracy
High-resolution ultrasonography	86.36%	78.94%	86.36%	83.33%	82.92%

The above table shows the diagnostic accuracy of high resolution ultrasonography. Sensitivity of high resolution ultrasonography were 86.36%, Specificity 78.94%, predictive value for a positive test 86.36%, and predictive value for a negative test 83.33% were found and respectively. In the analysis the accuracy of color Doppler ultrasonography were 82.92% respectively.

Discussion

High-resolution ultrasonography is preferred over other imaging methods in determination of lymph nodes and in pursuit of the disease.^{27, 28}

The role of high resolution Doppler ultrasound in the evaluation of metastatic lymph nodes is based on the fact that tumors larger than a few millimeters in diameter stimulate the growth of new vessels. This tumor neo - vascularity has certain characteristics that enable a presumptive diagnosis of malignancy to be made.²⁹ In evaluating nodal vascularity, Doppler ultrasound assesses two main feature.^{14,21,26,27,30,31}

1. Distribution of vessels within the lymph node.
2. Vascular parameters detecting intravascular resistance (RI, PI).

The vascular pattern of the enlarged lymph nodes was classified into the following four groups according to the location of the vascularity (1) Central flow signals branching radially from the center (2) Peripheral flow signals along the periphery of the lymph nodes, with branches perforating the periphery of the node and not arising from the hilar vessels (3) Mixed the presence of central and peripheral flow signals (4) No flow or apparent avascular, absence of vascular signals within the lymph nodes.³⁰ (Fig:1, 2, 3)

Normal and reactive lymph nodes tend to show hilar vascularity / central vascularity.^{23,27,31} Peripheral or mixed nodal vascularity are common in metastatic nodes. The peripheral vascularity in metastatic nodes is believed to be related to tumor infiltration of the lymph nodes in which the tumor cells produce tumor angiogenesis factor (TAF) which causes angiogenesis and recruitment of peripheral vessels.^{21,22,23} Mixed flow of the metastatic node was explained by two pathogeneses. First, as the tumor nests replace the lymph node, the pre-existing nodal vessels may be

proliferated and transformed into feeding vessels by tumor angiogenesis, resulting in central aberrant nodal vessels. Second, advanced tumor infiltration of a lymph node will destroy the hilar blood supply, resulting in induction of the vascular supply from the peripheral pre-existing vessels in perinodal connective tissue, which may be accelerated by extra capsular invasion.²¹

Many studies stated that, absence of perfusion in a lymph node is an important feature suggesting its malignant nature because total replacement of the whole lymph node by necrosed and keratinized tumors tissue.^{15,22}

In our study the distribution of vascular flow pattern in cervical lymph nodes shows in excellent result. Among 22 metastatic nodes, 19(86.37%) metastatic nodes had a mixed and peripheral pattern of blood flow and 03(13.63%) metastatic nodes had a central pattern of blood flow within the lymph nodes. Among 19 reactive nodes, 04(21.05%) reactive nodes had a mixed and peripheral pattern of blood flow and 15(78.95%) reactive nodes had a central pattern of blood flow statistically highly significant in this study. The vascular resistance in terms of resistive index (RI) and pulsatility index (PI) can be evaluated with the use of color Doppler ultrasonography.(Fig: 4, 5, 6) We know, metastatic lymph nodes involved in a pattern by which metastatic tumors enter the lymph nodes through the afferent lymphatic vessels and colonize the marginal sinuses and then enter the medulla and the hilum in the end.³² As tumor cells spread into the lymph nodes, they grow and replace a large portion of the lymph node and at last the lymph node is totally replaced by tumor cells. At this stage tumor cells compress vessels in the lymph node because a limited space is there. This vascular compression by tumor cells increases vascular resistance, causing an increase in the RI.¹⁴ The vascular resistance of metastatic nodes is higher than that of reactive nodes.^{21,23,31,33} However some studies suggested that the vessels in a metastatic lymph node had lower vascular resistance due to the absence of a muscle layer in tumor vessels and the presence of arteriovenous shunting.^{14,33,34}

Different cut-off values of RI (0.6, 0.7 and 0.8) and PI (1.1, 1.5 and 1.6) in differentiating metastatic and reactive lymph nodes have been reported.^{21,22,23,34} In this study, we applied the cut-off points (RI 0.6 and PI 1.1) and observed that among the 22 metastatic nodes R.I. > 0.6 was observed in 20(90.9%) metastatic nodes and R.I. < 0.6 was observed in 02(9.10%) metastatic nodes. Among the 19 reactive

nodes R.I. > 0.6 was observed in 07(36.84%) reactive nodes and R.I. < 0.6 was observed in 12(63.16%) reactive nodes. Among the 22 metastatic nodes P.I. > 1.1 was observed in 21(95.45%) metastatic nodes and P.I. < 1.1 was observed in 01(04.55%) metastatic nodes. Among the 19 reactive nodes P.I.>1.1 was observed in 07(36.84%) reactive nodes and P.I. < 1.1 was observed in 12(63.16%) reactive nodes.

The analysis of patterns of nodal vascularity along with R.I. and P.I can be used to differentiate benign from malignant cervical lymph nodes in oral squamous cell carcinoma with high sensitivity and high specificity. On the basis of the presence of color flow pattern, the sensitivity and specificity in this study were (86.36%) and (78.94%) respectively, which were nearly similar to Dangoreet al.²⁹ (87.60%) and (91.66%) respectively. Overall results of color Doppler flow criteria were statistically highly significant in this study (P < 0.01).

In this study we found that sensitivity (90.91%), specificity (63.16%) and accuracy (78.04%) for RI and sensitivity (95.45%), specificity (63.16%) and accuracy (80.48%) for PI. Dangoreet al.²⁹ applied the cut-off points (RI 0.7 and PI 1.5 for malignant nodes) and found that the sensitivity (64%) and specificity (81.18%) respectively. The results of our study showed that there was a statistically significant which was comparable with previous studies by Steinkamp et al.²²

In this study the sensitivity, specificity and accuracy of the high resolution ultrasonography was sensitivity (86.36%) specificity (78.94%) and accuracy (82.92%) which is comparable to Dangoreet al.²⁹ where accuracy was (92.85%) and specificity was (94.28%). Haberal (2004) et al.⁸ found (85%) accuracy with sensitivity (72%) specificity (96%). Sadat et al.³⁵ found (72.4%) accuracy with sensitivity (93.33%) specificity (50%).

Giovagnorio et al.¹² reported that color Doppler ultrasound is promising because it is easily applicable and does not require calculations. Some study stated that tissue characterization is not possible by ultrasound and it cannot detect early-stage of malignant lymphadenopathy.²¹ The use of high-frequency transducers has improved the ability to detect and interrogate the vascular signals. Dragoniet al.³¹ investigated superficial lymph node enlargement in 71 patients undergoing surgical biopsy at the onset of lymphadenopathy with high resolution pulsed and color Doppler ultrasonography. They observed volume, vascularization score, pulsatility index, and resistive index were significantly higher in their study. They

concluded that high resolution pulsed and color Doppler ultrasound may provide information that is useful in making correct differential diagnoses of malignant or benign lymphadenopathy. The combined use of high resolution ultrasonography with Doppler spectral waveform analysis by means of color Doppler and power Doppler ultrasonography will improve the diagnostic accuracy in differentiating benign from malignant lymph nodes in oral squamous cell carcinoma.



Fig: 1. Doppler ultra sonogram analysis of a lymph node with central pattern of vascular flow.

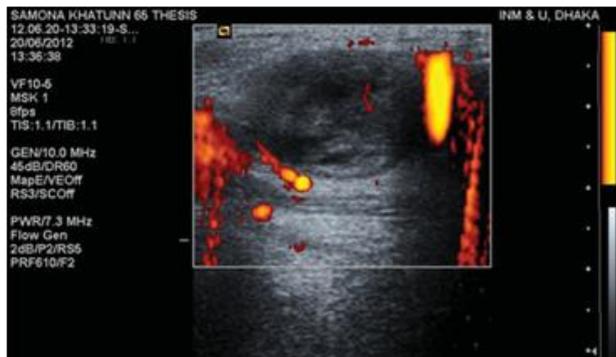


Fig: 2. Doppler ultra sonogram analysis of a lymph node with peripheral pattern of vascular flow.

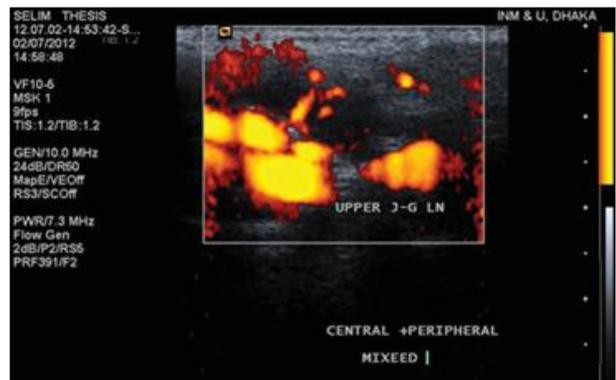


Fig: 3. Doppler ultrasonogram analysis of a lymph node with mixed pattern of vascular flow.

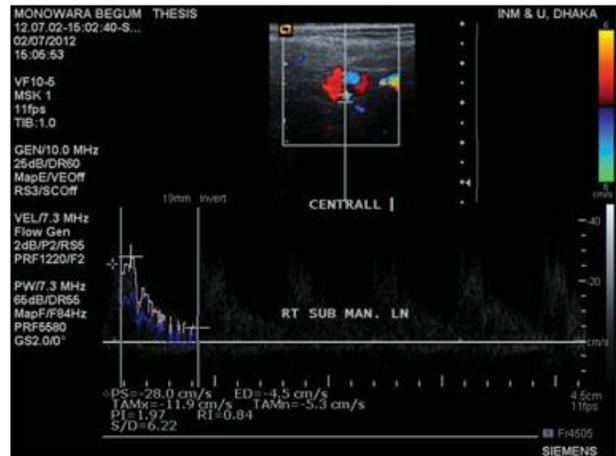


Fig: 4. Doppler ultra sonogram with spectral wave form analysis with central pattern of vascular flow

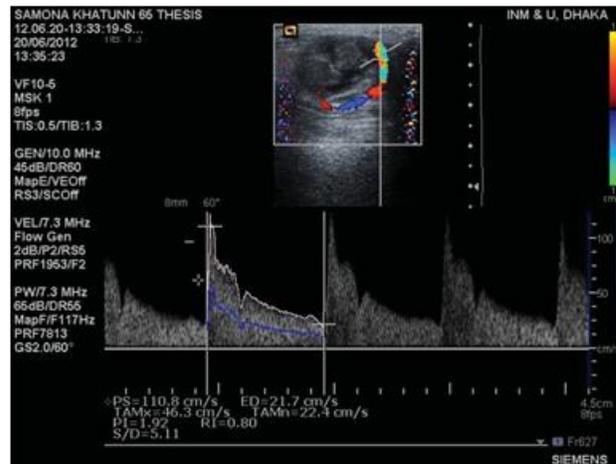


Fig: 5. Doppler ultra sonogram with spectral wave form analysis with peripheral pattern of vascular flow

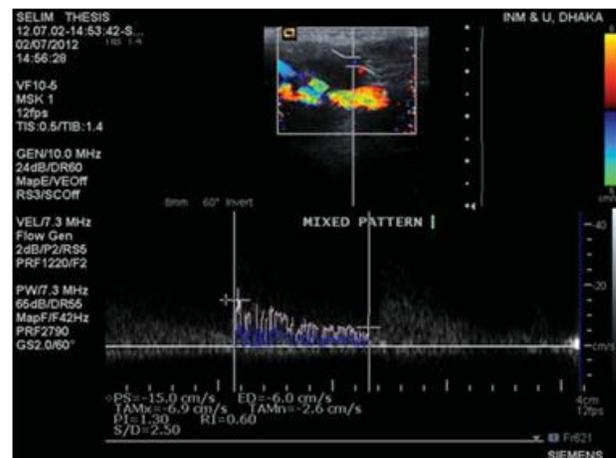


Fig: 6. Doppler ultra sonogram with spectral wave form analysis with mixed pattern of vascular flow.

Conclusion

High resolution ultrasonography with Doppler spectral waveform analysis by means of color Doppler and power Doppler ultrasonography plays a definite role as an adjunct to the clinical evaluation of cervical lymphadenopathy and proves its value as an important noninvasive investigation procedure for differentiating between benign and malignant cervical lymph nodes in oral squamous cell carcinoma and its high diagnostic accuracy can improve the performance for the diagnosis of palpable cervical lymph nodes in oral squamous cell carcinoma and we recommend it in regular clinical practice.

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