Nodal vascularity as an indicator of cervicofacial metastasis in oral cancer: A Doppler sonographic study

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ABSTRACT

Background: The objective of this study was to assess nodal vascularity by Doppler sonography and to find out the correlation between clinical and various Doppler sonographic features for the detection of the metastatic nodes in oral cancer patients. Patients and Methods: A total number of 55 patients of histopathologically proven oral cancer presenting with enlarged superficial cervicofacial lymph nodes were included in the study. Patients were subjected to clinical examination according to a specially designed proforma and the TNM staging was done. If more than one enlarged nodes were present, then the node with the largest diameter was chosen for further Doppler ultrasonographic examination followed by fine needle aspiration cytology test of the same node. Results: Correlations of patterns of color Doppler flow signals with cytological diagnosis showed that central type of vascular pattern was statistically significant parameter for benign lymph nodes and peripheral type of vascularity was highly significant parameter for malignant lymphadenopathy. It was found that the cut-off value of resistive index ≥0.6 was statistically significant in the assessment of metastatic node (P < 0.01) with a sensitivity of 45.5% and specificity of 93.9%. On comparison of the clinical features (TNM staging) with Doppler sonographic features, it was found that the characteristic features suggestive of malignant lymph nodes on Doppler sonography such as peripheral blood flow and high resistive index were more consistently and frequently associated with the higher sub-stages of T3 and T4 and N2b and N2c of TNM staging system. Conclusion: Nodal vascularity may be used to differentiate benign from malignant lymphadenopathy. Proper judicious use of non-invasive color Doppler ultrasonographic examination provides an opportunity to eliminate the need for biopsy in reactive nodes and provide treatment in a more precise manner.

Key words: Cervical lymphadenopathy, color Doppler ultrasound, metastasis, oral cancer

INTRODUCTION

Oral squamous cell carcinoma is the most common malignant tumour of the oral cavity. Cervicofacial lymph node status has been shown to be prognostically important in head and neck cancer outcome. It has been found that if the metastasis involves the ipsilateral lymph nodes, then the prognosis is 50% and if it involves contralateral lymph nodes, then it further reduces down to only to 25%.¹ Traditionally, only the enlargement in the size of the lymph node was assessed by grey scale ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) scan to predict the metastatic nodes. However, using the size criteria alone to detect the metastatic nodes is not found to be very effective.

More recently, Doppler sonographic evaluation of lymph nodes for patients with head and neck cancers showed that certain intra-nodal angioarchitectural changes are reliable and reproducible indicators of metastatic lymph nodes. Doppler sonography is a non-invasive procedure that can define the morphologic and vascular characteristics of the lymphadenopathies. Both the angioarchitecture and the haemodynamics differ among various cervical nodal diseases. Blood vessel morphology in metastatic nodes is usually deranged by neoplastic infiltration. A normal node has vascularity that appears as a radial and longitudinal configuration with symmetric distribution on color Doppler sonography. The increase in nodal vascularity in
metastatic nodes occurs because tumours larger than a few millimeters in diameter stimulate the growth of new vessels by secreting an angiogenesis factor. As the node is progressively involved, increased vascularity is seen in the central and peripheral parts. These changes, therefore, are reflected on color Doppler sonography by a qualitative increase in peripheral vascularity. Hence the study was undertaken to assess nodal vascularity by Doppler sonography for detection of cervicofacial metastasis in oral cancer patients and to correlate clinical and various Doppler sonographic features. We also aimed to validate the role of Doppler sonography as a non-invasive diagnostic tool for the detection of the metastatic nodes.

**PATIENTS AND METHODS**

The study group comprised 55 patients of oral cancer presenting with enlarged superficial cervicofacial lymph nodes who reported from November 2009 to March 2011, prospectively to the department of Oral Medicine and Radiology, Mahatma Gandhi Postgraduate Institute of Dental Sciences, Puducherry. The study was approved by the Ethics and Research committee of the Institution. Patients in the study group were selected based on the following inclusion and exclusion criteria. Individuals with clinical evidence and histopathologically proven oral cancer and individuals presenting with enlarged, palpable superficial lymph nodes in head and neck region were included in the study. Individuals presenting with other known causes of cervical lymphadenopathy such as oral infections, tuberculosis, granulomatous diseases like sarcoidosis were excluded from the study sample.

Patients with oral cancer presenting with enlarged palpable cervicofacial lymph node were subjected to clinical examination according to a specially designed proforma and the TNM staging was done. The regional lymph nodes were assessed for the number, size, consistency and mobility parameters. TNM staging was done according to American Joint Committee on Cancer (AJCC) 2010.

If more than one enlarged nodes were present, then the node with the largest diameter was chosen for further Doppler ultrasonographic examination. The largest lymph node (size approximately ≥1 cm in diameter) palpable was taken for further investigation. If more than one lymph node was palpable satisfying size criteria, the lymph node, which was hard or fixed, was subjected to further investigation.

In this prospective study, the perfusion patterns of metastases and reactively enlarged nodes in patients with known squamous cell carcinoma of oral cavity were examined. The subjects lay supine on the examination couch, with the shoulders supported by a soft pad, and the neck was hyper-extended. The subjects lay in this position for 5 min before the commencement of the examination, to ensure that the blood flow is measured at rest. Grey scale and power Doppler sonography were performed using an L&T Medical Sequina unit equipped with a wide bandwidth (range 5-10 MHz) transducer. All examinations were performed by a single examiner experienced in head and neck sonography and Doppler sonography techniques. Grey scale ultrasonography was performed at 8 MHz, and the standard Doppler settings were chosen for optimal detection of the signals from the lymph node vessels, which had low velocity flow.

On the grey scale ultrasonography, the largest transverse diameter of the lymph node was measured and the echogenicity was assessed. The echogenicity was classified into homogenous and heterogeneous types [Figures 1 and 2] based on internal architecture of lymph node. If the lymph node is uniformly hypo-echoic, then it was designated as homogenous and if it is showing the presence of both hyper-echoic as well as hypo-echoic areas then it was considered to be heterogeneous node. Lymph node with heterogeneous echo pattern showing areas of cystic necrosis was considered as one of the factor indicating the involvement of the node by metastatic cells. Settings of the Doppler ultrasonographic unit were standardised for high sensitivity, with a low wall filter to allow detection of vessels with low blood flow. The vascular pattern of each lymph node was determined and classified according to the location of the vascularity:

1. **Central (hilary) — A single vascular signal or vascular signal branching radially, originating symmetrically, and showing a regular course from the nodal hilum [Figure 3].**
2. **Mixed — Presence of central and peripheral vascular patterns [Figure 4].**
3. **Peripheral (capsular) — Flow signals along the periphery of the lymph nodes, with or without branches into the nodes [Figure 5].**
4. **Absent.**

In evaluating the vascular pattern, the hilar vascular pattern was considered to be suggestive of benignity, whereas...
Peripheral and mixed vascular patterns were considered to be suggestive of a malignant node. The angle independent velocimetric indexes, resistive index (RI) and pulsatility index (PI) were also calculated. RI and PI were measured using on board software as follows: RI = (peak systolic velocity — end diastolic velocity)/peak systolic velocity; PI = (peak systolic velocity — end diastolic velocity)/time-averaged maximum velocity.

After the ultrasonographic examination of the lymph node, the same node was subjected to fine needle aspiration cytology (FNAC) test. Patient consent was taken prior to biopsy. The slides were examined by the experienced oral pathologist for the presence of metastatic cells [Figure 6]. Some cases where smear was having insufficient material and were not of good quality were made again after recalling the patient. Only those reports were included as positive finding on FNAC where frank metastatic cells were seen in smear by cytopathologist.

The correlation between the FNAC findings and Doppler sonographic examination were subjected to suitable statistical methods.

**RESULTS**

A total of 55 patients fulfilling the inclusion and exclusion criteria were included in the study. Age of the study group ranged from 28 to 80 years including 28 males and 27 females. The mean age of male patients was 55.21 and 56.22 for females [Table 1].

After the clinical examination, ultrasonographic examination of the neck was done and assessed for echogenicity, blood flow, intra-nodal vascular resistance.

Echogenicity: Out of 55 lymph nodes, 32 were homogenous and 23 were found to be heterogeneous. On FNAC examination, 78.1% of homogenous nodes were found to be non–metastatic, whereas 65.2% of heterogeneous nodes were found to be metastatic [Table 2 and Figure 7].

For assessment of correlation between echogenicity and FNAC of lymph nodes, Fisher exact test was done. It was found that homogeneity for benign lymph nodes and heterogeneity for malignant lymph nodes was a highly significant parameter ($P < 0.01$), with a sensitivity of 68.18% and specificity of 75.76%, respectively. Area under the ROC
(Receiver Operating Characteristic) curve came out to be 0.72 indicating that the randomly selected individual from the positive group (homogenous and non-metastatic node; heterogeneous and metastatic node) has a test value larger than that for a randomly chosen individual from negative group (homogenous and metastatic node; heterogeneous and non-metastatic node) 72% of the times [Figure 8].

Color flow pattern showed 33 centrally perfused lymph nodes, that is color Doppler ultrasonographic finding suggestive of benign lymphadenopathy, 7 nodes with peripheral flow, that is color Doppler ultrasonographic finding suggestive of malignant lymphadenopathy, 10 lymph nodes with mixed vascularity and 5 lymph nodes with no flow [Table 3].

For comparing the vascular flow patterns with echogenicity, chi-square test was done. Among the group of lymph nodes showing central/hilar flow, 82% (27 out of 33) were found to have homogenous internal architecture. In contrast, all the lymph nodes showing the peripheral vascularity (seven nodes) were found to exhibit heterogeneous architecture. The study showed that there was a significant correlation between the echogenicity and vascular pattern of lymph nodes with homogeneous nodes exhibiting central flow and heterogeneous node associated with peripheral flow ($P < 0.05$) [Table 4].

Comparison of vascular flow patterns with FNAC findings was done by chi-square test. Among the group of lymph nodes showing central/hilar flow, 72.7% (24 out of 33)
were found to be benign on FNAC examination. In contrast, 85.7% (6 out of 7) of the lymph nodes showing the peripheral vascularity were found to be malignant on FNAC examination [Table 5 and Figure 9].

The study showed that central type of vascular pattern was statistically significant parameter for benign lymph nodes ($P < 0.01$) with a sensitivity of 69.1% and specificity of 73.5%. The study also showed that peripheral type of vascularity was highly significant parameter for malignant lymphadenopathy ($P < 0.01$) with a sensitivity of 68.2% and specificity of 75.8%.

In the study the RI ranged from 0.4 to 0.75. Fisher exact test was applied to find the significance of RI in assessing the metastatic nodes. Out of total 12 nodes having value of resistivity index greater than 0.6, 10 (83.3%) were found to be metastatic on FNAC examination [Figure 10]. We found that the cut-off value of RI 0.6 was statistically significant in the assessment of metastatic node ($P < 0.01$) with a sensitivity of 45.5% and specificity of 93.9% [Table 6 and Figure 10].

**DISCUSSION**

For many years, regional lymph nodes in tumour bearing hosts have been considered to be anatomic barriers to the systemic dissemination of tumour cells. The characteristic in tumour formation is angiogenesis and therefore the morphologic and hemodynamic changes that occur in tumour vessels can be used as a clue to differentiate between benign and malignant. Most normal cells do not release angiogenic substances except during embryogenesis, growth, wound repair or immune states. An important pre-condition for angiogenesis seems to be a certain amount of tumour cell mass. In an initial (avascular) tumour stage, micro metastases are fed by regular nodal vessels. It is estimated that it takes 1 billion malignant cells to produce a tissue mass of 1 cm$^3$. Only after the original vessel system becomes insufficient for the nutrition of micro metastases as a consequence of its destruction or the diffusion distance becoming too large, a spontaneous and distinct growth tendency of new blood vessels begins with the release of angiogenic stimulus from tumour cells called “tumour angiogenetic factor”. This neovascularisation penetrate the node from its periphery and consisted of thin-walled blood vessels that lacked a muscular layer and often shows chaotic anastomoses and shunts. Tumour growth appears to depend on this process. The architecture and the hemodynamic of nodal vessels would differ among various nodal diseases. This property of nodal disease provides the potential for diagnosis if vascular changes can be reliably detected. Thus color Doppler sonography, one of the advances in sonography can aid in differentiating benign from malignant lymph nodes.

The normal lymph nodes are hypo-echoic and homogeneous. When the lymph node is infiltrated by metastatic cells, the

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**Table 5: Blood flow vs FNAC finding**

| Blood flow | FNAC findings suggestive of malignant lymph node | Chi-square test | $P$ value |
|------------|-----------------------------------------------|----------------|----------|
| Nil        | Negative: 3, 60.0%  Positive: 2, 40.0%      | 8.74           | 0.0330   |
|            | Central: 24, 72.7%  9, 27.3%                 |                |          |
| Peripheral | 1, 14.3%          6, 85.7%                    |                |          |
| Mixed      | 5, 50.0%          5, 50.0%                     |                |          |

Significant at 5% level

**Table 6: Resistance index (Cut-off = 0.6) vs FNAC finding**

| Resistance index | FNAC findings suggestive of malignant lymph node | Fisher’s exact test | $P$ value |
|------------------|-----------------------------------------------|-------------------|----------|
| $<0.6$           | Negative: 31, 72.1%  Positive: 12, 27.9%       | 9.81              | 0.0008   |
| $\geq0.6$        | 2, 16.7%          10, 83.3%                     |                  |          |

Significant at 1% level
node echogenicity changes to heterogeneous having both hypo-echoic and hyper-echoic areas. In the present study, out of the 55 lymph nodes, 32 were homogenous and 23 were found to be heterogeneous. On FNAC examination, 78.1% of homogenous nodes were found to be non-metastatic, whereas 65.2% of heterogeneous nodes were found to be metastatic.

To our knowledge, in 1988, Morton et al., were the first to describe flow signals in the hilum of lymph nodes by using color Doppler ultrasound. Lymphatic vessels are not displayed at color Doppler sonography due to the low flow velocity and the lack of backscattering erythrocytes. Our assessment of vascular patterns with Doppler sonography revealed two categories of patterns in cervical lymphadenopathies. One was a benign pattern group characteristic of avascular and hilar types, and the other was a malignant pattern group showing spotted, peripheral and mixed types. In this study, 33 nodes showed central/hilar colour flow signals, suggestive of a benign nature, of which 24 nodes proved to be benign and 9 malignant according to FNAC examination. Nine malignant lymph nodes showed central flow in our study, which was comparable to the study by Sato et al., in which similar metastasis was confirmed in one lymph node with central colour flow signals. The reason for this could be the presence of micro metastasis at the early stage of lymph node involvement that could not be detected by color Doppler ultrasonography as intra-nodal vascular alterations take place at a relatively late stage of metastasis. In the early stage of microinfiltration, vascularity may be increased owing to local immune reaction.

Out of seven nodes showing peripheral perfusion, six were metastatic. In metastatic lymphadenopathy, destruction of hilar vascularity by tumour cells may result in the induction of vascular supply from the peripheral pre-existing vessels or from vessels in the peri-nodal soft tissue. Thus, they have peripheral flow. The findings of our study are comparable with a previous study, which suggested that the peripheral flow in malignant nodes is in aberrant arterioles or veins within the capsule, subcapsular area or surrounding connective tissue.

In our study, 10 lymph nodes showed mixed vascularity, the distribution of which was equal, that is 5 were metastatic and 5 were non-metastatic on FNAC examination. Mixed flow of the metastatic node might be explained by two pathogeneses. First, as the tumour nests replace the node, the pre-existing nodal vessels may proliferate and transform into feeding vessels by tumour angiogenesis, resulting in central aberrant nodal vessels. Second, advanced tumour infiltration of a node will destroy the hilar blood supply, resulting in induction of the vascular supply from the peripheral pre-existing vessel or vessels in peri-nodal connective tissue, which may be accelerated by extracapsular invasion.

This study showed an absence of flow in five lymph nodes, out of which three were non-metastatic nodes and two were metastatic nodes on FNAC examination. There can be different reasons for no flow. It may be because of the total replacement of the nodal tissue by necrosed and keratinised tumour tissue. The relatively low number of backscattering erythrocytes in the tiny peripheral vessels decreases the signal intensity, which may not surpass the noise level. Low flow velocities or high Doppler angles result in a low Doppler frequency shift, which may be suppressed by the high pass or wall filter. Post-processing functions to reduce motion artefacts may also suppress flow signals in the echogenic centre of the lymph node. Consequently, absent flow signals do not mean that perfusion is absent.

In the study of vascular resistance of lymph nodes, by comparing the highest RI within suspected lymph nodes, we could differentiate between benign and malignant lymphadenopathies, which showed high vascular resistance. Some workers have worked on the analysis of vascular resistance in cervical lymphadenopathies; however, their results were inconsistent and even contrary to each other. Chang et al. assumed that metastatic lymph nodes contain arteriovenous shunts and vessels that lack a muscle layer. They found that the lymph nodes involved by malignant processes typically had a low vascular resistance. The problem was that they selected and compared the lowest RI of each nodal flow sampling. Conversely, Steinkemp et al. and Choi et al. by analysing vessels showing the most vigorous flow, demonstrated the presence of higher resistance flow in malignant lymphadenopathy.

We found that the cut-off value of RI 0.6 was statistically significant in the assessment of metastatic node (P < 0.01) with a sensitivity of 45.5% and specificity of 93.9%. This finding was in accordance to the findings of Steinkemp et al. and Na DG et al., who found a sensitivity and specificity of 47% and 94%, respectively, with the cut-off value of RI 0.7. When a sampled cervical lymph node had a high RI, it would usually prove to be metastatic. A possible reason for this extraordinarily high resistance was that as tumour cells spread into the lymph node, they grow and replace a large portion of the lymph node. Ultimately, the lymph node is totally replaced by tumour cells. At this stage, tumour cells compress vessels in the lymph node. This vascular compression by tumour cells would increase vascular resistance, causing an increase in RI.

On comparison of the clinical features (TNM staging) with Doppler sonographic features, we found that the characteristic features suggestive of malignant lymph nodes on Doppler sonography such as peripheral blood flow and high RI were more consistently and frequently associated with the higher sub stages of T3 and T4 and N2b and N2c of TNM staging system. All the lymph nodes
showing the peripheral vascularity belonged to T3 and T4 stage group, whereas six out of seven lymph nodes showing the peripheral flow belonged to N2b and N2c stage group. Similarly 75% of lymph nodes (9 out of 12 lymph nodes) with RI more than 0.6, which is suggestive of malignant lymph node, belonged to T3 and T4 stage group. Thus, our study supports the fact that T stage is reflective of tumour burden and the risk of nodal metastasis increases with increasing T stage of primary tumour.

The usefulness of color Doppler ultrasonography is often doubted due to inconsistent results and disagreement on different methodologies and vessel sampling.\textsuperscript{6,10,12} There are previous studies and in which colour doppler ultrasound CDUS was used as a method of differentiating benign from malignant lymphadenopathy. However, there is controversy regarding its reliability. Giovagnorio et al.\textsuperscript{13} reported that CDUS is promising because it is easily applicable and does not require calculations. Na et al. stated that tissue characterisation is not possible by ultrasound and it cannot detect early stage malignant lymphadenopathy, however, the use of high frequency transducers has improved the ability to detect and interrogate the vascular signals.

In this study, all the findings suggested superiority of the color Doppler ultrasonography examination. One of the goals of this study was to differentiate between benign and malignant cervical lymph nodes using the color Doppler sonography, and the present study appreciates the important role of color Doppler sonography in the diagnostic approach to cervical lymphadenopathy.

Further in this study, we have used non-invasive ultrasonography with minimally invasive FNAC test to correlate the features of ultrasonography of enlarged cervicofacial lymph nodes in patients with oral cancer causing minimum discomfort to the patient. This may validate the role of Doppler sonography as a non-invasive diagnostic tool for the detection of the metastatic nodes.

One limitation of this study is that the changes in internal architecture of the lymph nodes cannot be recognised in deeper nodes. The possible explanations for this can be due to decreasing contrast resolution because of signal attenuation with increasing distance of the object of interest from the ultrasound probe and the poorer spatial resolution of ultrasound probes used for analysing deeper structures.

**ACKNOWLEDGEMENT**

We would like to thanks Dr. Charles P. Sourguname, DMRD Consultant Radiologist, MPGI Puducherry.

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**How to cite this article:** Aggarwal A, Daniel MJ, Singh S, Patil P, Hindustanwala F, Kaushik SV. Nodal vascularity as an indicator of cervicofacial metastasis in oral cancer: A Doppler sonographic study. Niger Med J 2014;55:299-305.

**Source of Support:** Nil, Conflict of Interest: None declared.