Ultrasonographic and histopathological features of cervical lymph node metastases

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Abstract

Objectives: Different approaches have been made to differentiate benign from malignant cervical lymphadenopathy using ultrasound examination. Assessment of nodal status is essential in patients with head and neck carcinomas as it predicts prognosis and helps in the selection of treatment options. The present study was designed to evaluate the role of ultrasound in the assessment of malignant cervical lymph nodes using the histological gold standard results. Gray-scale ultrasound assesses the nodal size, shape, border, internal architecture and color Doppler ultrasound evaluate the vascular pattern of lymph nodes. Materials and Methods: 158 cervical lymphadenopathies evaluated by ultrasound in 100 patients over a period of 36 months (between January 2010 and December 2012) were evaluated for the presence of intranodal vascular pattern, which was considered benign when it traversed through the node without disruption. Results: Of the 158 cervical tumors evaluated, 114 (72.2%) were found to be malignant on pathologic review. Malignant vascular markings were present in 133/158 lymph nodes evaluated. The presence of malignant vascular pattern had a sensitivity of 97.37% and a positive predictive value of 82.84%. Malignant gray-scale ultrasound markings had a sensitivity of 23.3% and a positive predictive value of 100%. Conclusions: The presence of normal intranodal blood flow was associated with a benign diagnosis in 87.5% of the masses evaluated. The addition of this color Doppler ultrasound finding improves the ability of ultrasound exam to predict the likelihood of malignant involvement.

Keywords: lymph nodes, ultrasound examination, positive predictive value, malignant tumors.

Introduction

Assessment of nodal status is essential in patients with head and neck carcinomas as it predicts prognosis and helps in the selection of treatment options [1–10]. In patients with proven head and neck carcinomas, the presence of a unilateral metastatic node reduces the 5-year survival rate by 50%, whereas the presence of bilateral metastatic nodes reduces the 5-year survival rate to 25% [11–13].

Metastatic cervical lymph nodes from head and neck carcinomas are usually site specific with respect to the location of the primary tumor [14, 15]. Besides metastases, lymphoma is also a common malignant disease and head and neck involvement is relatively common [11, 16–18]. Clinically, lymphomatous cervical lymph nodes are difficult to differentiate from other causes of lymphadenopathy including metastatic nodes. As the treatment options differ, accurate identification of the nature of the diseases is essential.

Ultrasound (US) is sensitive compared to clinical examination (96.8% and 73.3% respectively) in patients with head and neck cancer [11].

Color Doppler ultrasound (CDUS) is a valuable tool in differentiation of benign from malignant lesions within parenchymal organs [19–23]. Evaluation of enlarged lymph nodes is another application of CDUS. CDUS is a sensitive non-invasive imaging technique capable of detecting vessels as small as those found in lymph nodes.

The present study was designed to evaluate the role of ultrasonography in the assessment of malignant cervical lymph nodes. Gray-scale ultrasound assesses the nodal size, shape, border, internal architecture (echogenicity and necrosis) [24]. The vascular pattern of lymph nodes is evaluated with CDUS.

Materials and Methods

In this prospective study, ultrasound patterns of neck masses were evaluated. The neck was divided into 12 levels (six bilaterally) [25] and into eight regions according to their location in the neck established by Hajek et al. [26]. A number of 100 patients were included in the study with ages ranging from 19 and 78 years. The male to female ratio was 4:1. On histopathological exam (HPE), 75 patients were diagnosed with malignant tumors and 25 with benign lesions. At those patients, we analyzed 158 neck masses. On these 158 cervical tumors, 114 were malignant and 44 benign masses. Malignant masses consisted of the following number (N) of diagnoses: lymphoma (N=8), metastasis of laryngeal carcinoma (N=79), metastasis of undifferentiating carcinoma (N=11), metastasis of malignant melanoma (N=6), metastasis of thyroid neoplasm (N=8) and metastasis of lung cancer (N=2).

Several cases of cervical lymph node metastases are described in Figures 1–12.
Ultrasound was done using a 10 mHz linear transducer (Philips HD-11XE). Scans were obtained with the transducer placed transversely and longitudinally and measurements were made in a section plane that showed a maximum cross sectional area. The ultrasound findings documented were nodal site, number, internal architecture, relation to surrounding structures and vessels.

The gray-scale US features included in this study were (1) echogenicity, (2) border, (3) size, (4) necrosis and (5) shape. The sixth ultrasound character was the evaluation of vascular pattern of the lesion. Nodal blood flow was considered benign when it passes through the center of the lymph node without disruption. Nodes were classified for each of the six features as either malignant or benign in nature. The malignant features were hypoechoic echogenicity, sharply demarcated border, size >10 mm, round contour, presence of necrosis and abnormal vascular pattern. Benign features were considered to be the opposite of these findings.

Initial confirmation of neck masses was done by biopsy or surgical resection.

The postoperative harvested biological material that were send for morphopathological examination were treated with 4% formalin, included in paraffin, then sectioned and stained by Hematoxylin and Eosin (HE). Afterwards, they were examined by optic microscopy, scanned using Mirax, photographed and viewed using MiraxViewer.
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Figure 5 – Case No. 3. Patient B.F., 63-year-old male. Lymph node metastasis of squamous cell carcinoma without primary tumor (CUDS result): hypoechoic lymph node tumor with irregular border, necrosis and abnormal vascular pattern.

Figure 6 – Case No. 3. Lymph node metastasis of squamous cell carcinoma without primary tumor. HE staining, 100× (MiraxScan/Viewer). Lymph node with tumoral plaques composed of atypical polygonal squamous cells with eosinophilic cytoplasm, hyperchromatic large nuclei with numerous atypical mitotic areas without keratinization phenomena.

Figure 7 – Case No. 4. Patient M.P., 21-year-old male. Lymph node metastasis of malignant melanoma without primary tumor (CUDS result): hypoechoic lymph node tumor with regular border and central vascular pattern.

Figure 8 – Case No. 4. Lymph node metastasis of malignant melanoma without primary tumor. HE staining, 100× (MiraxScan/Viewer). Lymph node with a tumoral tissue composed of atypical melanocytic cells arranged in nodules of various sizes. Some of cells have accumulation of pigment with epithelioid appearance and atypical mitoses.

The study protocol was approved by our institutional review board, and all patients gave written informed consent.

An Excel table was used for the centralization and data analysis.

The Ultrasound results were correlated using the GraphPad InStat 3 statistics software (version 3.06), by chi-square or Fisher tests.

The obtained values were considered statistically significant in case of $p<0.05$ and a 95% confidence level.

Negative and positive predictive values were used to assess the performance of sonographic examinations in the detection of metastatic nodes.

The negative predictive value (NPV) is the percentage of nodes interpreted on sonograms as negative for malignancy that were histopathologically proved not to be malignant.

The positive predictive value (PPV) is the percentage of nodes interpreted at sonography as positive for malignancy that were histopathologically proved to be malignant.

We also obtained the sensitivity (true-positive results/[true-positive results + false-negative results]) and specificity (true-negative results/[true-negative results + false-positive results]).

The accuracy was calculated by the following formula: (true-positive results + true-negative results)/total number of nodes.
Figure 9 – Case No. 5. Patient S.P., 60-year-old male. Lymph node metastasis of sarcomatoid carcinoma without primary tumor (CUDS result): hypoechoic lymph node tumor with irregular border and peripheral vascular pattern.

Figure 10 – Case No. 5. Lymph node metastasis of sarcomatoid carcinoma without primary tumor. HE staining, 100× (MiraxScan/Viewer). Residual lymph node with proliferation of tumoral elongated spindle cells, arranged in bundles and vortices with oval hyperchromatic nuclei with rounded ends and numerous atypical mitotic figures.

Figure 11 – Case No. 6. Patient G.I., 51-year-old male. Metastasis of papillary thyroid carcinoma (gray-scale and CUDS result): lymph node tumor without vascular pattern.

Figure 12 – Case No. 6. Metastasis of papillary thyroid carcinoma. HE staining, 100× (MiraxScan/Viewer): branched follicular and papillary structures bounded by epithelium with altered polarity, abundant and eosinophilic cytoplasm, central nuclei showing a papillary tumoral architecture.

Results

The individual criteria for detection of malignancy on US were compared with the histopathological findings.

Size

On US, size of the nodes detected ranged from 0.7×0.3 cm to 5.7×4 cm (longitudinal diameter × axial diameter). All nodes considered positive for malignancy on US had an axial diameter of >10 mm while those negative for malignancy were <0.5 cm. On histopathological exam (HPE) all nodes positive for malignancy had an axial diameter of >1 cm while those negative were <0.4 cm. A diameter >10 mm was present in 98 of the 158 lymphadenopathies. Of the 98 tumors found to have a diameter >10 mm, 84 (85.73%) were found to have malignant pathologic results. Of the 60 nodes that did not demonstrate a diameter >10 mm, 0 (50%) was found to be benign on pathologic review. Thus, using univariate analysis, the size criteria had a sensitivity of 73.68% and a specificity of 68.88% with a PPV of 85.71% a NPV of 50% and an accuracy of 72.15% (p<0.0001).

Shape

Of the 117 nodes detected on US with round shape, 96 (82.05%) were found positive for malignancy on HPE and 41 masses were found negative on HPE. Of these 41 masses, 18 (43.9%) were round and 23 (56.1%) were oval. The shape of the lymph node was assessed by the L/S (long axis/short axis) ratio [Solbiati-(L/T-) indices].
Normal lymph nodes are usually elliptical with an L/T ratio of >2 whereas metastatic nodes tend to be rounder and L/T is below 2. Thus, using univariate analysis, contour recorded a sensitivity of 84.21% and a specificity of 52.47% with a PPV of 82.05%, a NPV of 56.1% and an accuracy of 75.31% (p<0.0001).

**Echogenicity**

Hypoechoic echogenicity was present in 99 of the 158 neck masses. Of these, 89 (89.89%) were found to have malignant pathologic results. Of the 59 masses that did not demonstrate hypoechoic features, 25 (42.37%) were found to be malignant on pathologic review. Thus, using univariate analysis, echogenicity features demonstrated a sensitivity of 78.07% and a specificity of 77.27% with a PPV of 89.9%, a NPV of 57.63% and an accuracy of 77.84% (p<0.0001).

**Necrosis**

Of the 41 nodes detected on US with necrosis, all were found positive on HPE. Thus, using univariate analysis, the necrosis criterion had a sensitivity of 35.96% and a specificity of 100% with a PPV of 100% a NPV of 37.61% and an accuracy of 53.79% (p<0.0001).

**Extra-capsular spread (ECS)**

A sharply demarcated border was present in 48 of the 158 tumors. Of the 48 nodes found to have a sharply demarcated border, 45 (93.75%) were found to have malignant pathologic results. Of the 110 tumors that did not demonstrate a sharply demarcated border, 69 (62.72%) were found to be malignant on pathologic review. Thus, using univariate analysis, border features proved a sensitivity of 39.47% and a specificity of 52.47% with a PPV of 82.05% and a NPV of 56.1%. P-value was 0.0001 (considered significant) and accuracy was 75.31%.

In our patient population, benign vascular markings were present in 25 of the 158 cervical masses evaluated. Of the 25 nodes found to have benign vascular pattern, 21 (87.5%) were found to have benign histopathological results (Table 1).

<table>
<thead>
<tr>
<th>%</th>
<th>Echogenicity</th>
<th>Border</th>
<th>Shape</th>
<th>Size</th>
<th>Necrosis</th>
<th>Vascular pattern</th>
<th>Six features</th>
</tr>
</thead>
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<tr>
<td>Sensitivity</td>
<td>78.07</td>
<td>39.47</td>
<td>64.21</td>
<td>73.68</td>
<td>35.96</td>
<td>97.37</td>
<td>95.24</td>
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<tr>
<td>Specificity</td>
<td>77.27</td>
<td>54.47</td>
<td>52.47</td>
<td>68.88</td>
<td>100</td>
<td>47.73</td>
<td>100</td>
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<tr>
<td>PPV</td>
<td>89.9</td>
<td>82.05</td>
<td>82.05</td>
<td>85.71</td>
<td>100</td>
<td>82.84</td>
<td>100</td>
</tr>
<tr>
<td>NPV</td>
<td>57.63</td>
<td>56.1</td>
<td>56.1</td>
<td>50</td>
<td>37.61</td>
<td>87.5</td>
<td>95.24</td>
</tr>
</tbody>
</table>

PPV – Positive predictive value; NPV – Negative predictive value.

Of the 133 nodes that did not demonstrate benign vascular markings, 111 (83.45%) were found to be malignant on pathologic review (p<0.0001). Thus, using univariate analysis, lack of benign vascular pattern demonstrated a sensitivity of 97.37% and a specificity of 47.73%. Lack of benign vascular markings was found to have a positive predictive value of 82.84%, whereas the presence of benign pattern had a negative predictive value of 87.5%. The accuracy in this case was 83.5%, p<0.0001.

A combination of these six malignant features was present in 24.05% (38) of the nodes evaluated. This combination demonstrated a sensitivity of 95.24%, a specificity of 100%, a PPV of 100%, NPV of 95.24%, and an accuracy of 87.5% (p<0.0001).

**Discussion**

Various approaches have been made to differentiate benign from malignant cervical lymphadenopathy by ultrasound examination. The lymph node status is essential in patients with cancer in cervical area [14]. In gray-scale sonography, assessment of L/S ratio has proven to be a major advance in the sonographic differentiation of enlarged nodes [27, 28], achieving an accuracy of up to 95% [29].

Color Doppler is the modality of choice for the assessment of vascular pattern (VP) [19, 30]. By comparison, hilar and non-hilar patterns appear highly specific for benign and metastatic nodes respectively [31–33]. Tumor infiltration of a node distorts the normal vascular pattern, which is composed by an artery and vein that enters through the node at the hilum [34, 35].

In our study, we found that the lack of benign vascular markings had a sensitivity of 97.37% and a NPV of 84.5%. Thus, when malignant vascular pattern was seen, 82.84% of lesions were associated with a malignant lymph node. Unfortunately, malignant vasculature was found in only 133 of lymph nodes that were evaluated. This means that the lack of benign pattern flow has a relatively poor PPV (82.84%) as a single marker. Danegore-Khasbage et al. in a prospective study evaluated 70 cervical lymph nodes in 30 known primary oral cancer patients with CDUS during a period of eight months and the CDUS evaluation was found to be highly significant with a sensitivity of 92.9% and a specificity of 84.21%, after comparing the CDUS findings with HPE results [36]. The overall accuracy of VP improves further when combined with size, shape and other gray-scale features. Tschammler et al. in their study found a specificity of 77% and a sensitivity of 96% of CDUS [22] examination.

In our study, other features such as echogenicity, shape, necrosis and vascular pattern demonstrated sensitivities of 78.07%, 84.21%, 35.96% and 97.37% and PPV values of 89.9%, 82.05%, 100% and 82.84% respectively. Among these features, necrosis has highest PPV value. Other studies have shown varying levels of accuracy for the US features of echogenicity, border, necrosis and size. In their paper, Zhang et al. [37] reported a sensitivity of 59.8%, specificity of 76.5% and accuracy of 67.1% for the round shape, values close to our results. Extracapsular spread is characterized by irregular nodal borders on US [38, 39]. Steinke et al. examined 110 patients with N-all HNSCC for ECS with US and reported a sensitivity of 79% with a specificity of 82%, which was comparable to CT and MRI [40].
Ahuja and Ying looked at VP and gray-scale features in 101 metastatic nodes from a mixed population of tumors and 72 non-metastatic nodes. Using a minimum of three features to denote malignancy (abnormal internal echogenicity, deranged internal architecture and an L/T of <2.0), gray-scale alone had a sensitivity of 95% and specificity 83%. By comparison, VP had a sensitivity of 90% and specificity of 100%. However, when VP and gray-scale parameters were combined (four features of malignancy), both sensitivity and specificity reached 100%.

We found that, by using six features of malignancy, we could achieve a PPV of 100%, which means that 100% of lymph nodes with all six malignant features are true malignant at histological results. In our study, p-values obtained by chi-square test are <0.05, which means that malignant features/pathologic results association is statistically significant.

US was useful in diagnosing malignancy using axial diameter or size only if the size was <0.5 cm or >1 cm. Nodes ranging in size between these two figures were not accurately assessed. All nodes showing necrosis on US were positive for malignancy. No reactive nodes showed necrosis.

**Conclusions**

Sonography is a useful imaging tool in the assessment of cervical lymph nodes. Although color Doppler ultrasound is a reliable and reproducible method, which can provide a useful adjunct to conventional ultrasound, increasing diagnostic accuracy in cervical masses the final diagnosis is made only by histopathological exam. The identification of metastases in lymph nodes of the neck has a major effect on the prognosis and treatment of head and neck cancer. We conclude that ultrasonographic examination of cervical lymph nodes can yield important information regarding the diagnosis.

**Contribution Note**

All the authors have equal contribution to the paper.

**References**


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