# The Role of Ultrasonography for Differentiating and Management of Malignant Cervical Lymph Nodes

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#### ABSTRACT

Objective: To investigate the value of grey scale and Doppler ultrasonography in the assessment of metastatic and lymphomatous cervical lymph nodes. Methods: One hundred and nineteen malignant cervical lymph nodes in 119 patients diagnosed as malignant according to grey scale, color Doppler and spectral Doppler ultrasonography features were included in this study. The sizes, shape, echo pattern, echogenic hilus, nodal border, cystic necrosis and coagulation necrosis, vascular distribution pattern, resistivity and pulsatility index values of lymph nodes were noted. All patients had histopathological diagnosis. Results: The final diagnosis of the 42 lymph nodes was lymphoma, and of the 77 lymph nodes was carcinoma metastasis (33 thyroid carcinoma metastasis and 44 squamous cell carcinoma metastasis). While a hyperechoic pattern and calcification were detected in the lymph nodes originating from thyroid carcinoma as 39% and 33%, respectively, a reticular pattern (26%) and low resistive and pulsatility indices were detected in lymph nodes originating from lymphoma. These criteria were statistically significant for the differential diagnosis (p<0.05). Size, shape, hypoechoic echo pattern, absence of echogenic hilus, nodal border, cystic necrosis, coagulation necrosis and vascular distribution pattern were not found to be significant for the detection of a primary tumour. **Conclusion**: Hyperechoic echo pattern, reticular pattern, calcification, low resistivity and pulsatility indices are useful parameters for the differential diagnosis of malignant cervical lymph nodes. These ultrasonography critaria can be used for assesment and management of unknown primary malign neck nodes.

Key words: Lymphoma, lymph node, metastasis, ultrasound

## Malign Servikal Lenf Nodlarının Ayırımında ve Yönetiminde Ultrasonografinin Rolü

#### ÖZET

Amac: Metastatik ve lenfomatöz servikal lenf nodlarının değerlendirilmesinde gri skala ve Doppler ultrasonografinin değerini araştırmak. Yöntem: Gri skala, renkli Doppler ve spectral Doppler ultrasonografi özelliklerine göre malign tanı alan 119 hastaya ait 119 malign servikal lenf nodu bu calısmaya dahil edildi. Lenf nodlarının boyut, sekil, eko paterni, ekojenik hilus, nodal sınır, kistik nekroz ve koagülasyon nekrozu, vasküler dağılım paterni, rezidivite ve pulsatilite indeks değerleri kaydedildi. Bütün hastalar histopatolojik tanı aldı. Bulgular: Kırkiki lenf nodu lenfoma, 77 lenf nodu karsinom metastazı (33 tiroid karsinom metastazı, 44 squamöz hücreli karsinom metastazı) tanısı aldı. Tiroid karsinom metastazlarında hiperekoik patern ve kalsifikasyon sırasıyla %39 ve %33 oranında bulundu. Lenfomatöz lenf nodlarında retiküler patern (%26) ve düşük rezidivite ve pulsatilite indeks değerleri saptandı. Bu kriterler ayırıcı tanıda istatistiksel olarak anlamlı bulundu (p<0.05). Boyut, sekil, hipoekoik patern, ekojenik hilus yokluğu, nodal sınır, kistik nekroz, koagülasyon nekrozu ve vasküler dağılım paterni primer tumor saptanmasında anlamlı bulunmadı. Sonuç: Hiperekoik patern, retiküler patern, kalsifikasyon, düşük rezidivite ve pulsatilite indeks değerleri, malign servikal lenf nodlarının ayırıcı tanısında faydalı parametrelerdir. Bu ultrasonografi kriterleri primeri bilinmeyen malign servikal lenf nodlarının değerlendirilmesinde ve yönetiminde kullanılabilir.

Anahtar kelimeler: Lenfoma, lenf nodu, metastaz, ultrasonografi

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# INTRODUCTION

Malignant lymph nodes of the neck mainly consist of metastasis and lymphoma. Metastatic cervical lymph nodes whose primaries are unknown constitute 3-5% of all headneck cancers (1). Nodal metastases are common and generally related with both skin and mucosal carcinomas of the head and neck region. Cervical lymph nodes are also common site for both Hodgkin's and non Hodgkin's lymphoma. For appropriate treatment, an accurate diagnosis is essential as the treatment modalities of these two pathologies are quietly different.

Clinically, it is difficult to make a differential diagnosis for cervical lymph nodes. Ultrasonography (US) can be used as the first-line imaging tool without ionizing radiation in the diagnostic evaluation of cervical lymphadenopathy, due to its ease, noninvasiveness, reproducibility, and cost effectiveness. There are numerous published reports on the usage of grey scale US, color and spectral Doppler US to distinguish between benign and malignant cervical lymph nodes (2-4). The role of US in the differentiation of benign nodes from malignant ones is well established. However, limited studies are available for differentiating of the nature of malignant disease by means of these examinations (5, 6).

The purpose of this study was to investigate the role of grey scale and Doppler US findings in the assessment of metastatic and lymphomatous cervical lymph nodes and patient management.

# MATERIAL AND METHODS

This study was conducted as a prospective study and included 119 patients (49 female, 70 male, the mean age was  $52.03\pm17.42$  years) with unknown primary neck nodes between the years 2007-2010. The patients initially had a grey scale US examination for the presence of lymph node. In cases with more than one lymph node, the largest lymph node was analysed. This study was approved by the ethical commity of our university. The US examinations of all the patients were performed using a 7.5 MHz linear transducer (XU Applio, Toshiba, Tokyo, Japan).

Criteria including size, shape, echo pattern, presence of echogenic hilus, border and internal structure of the lymph nodes used for the assessment of malignant cervical lymph nodes by grey scale US. The size of the lymph node: A measurement of 5mm in the short axis was chosen as the cut-off point for inclusion. The shape of the lymph node was determined by the short: long axis ratio (S/L) on a transverse plane. Lymph nodes with a S/L ratio of less than 0.5 were accepted as long or oval nodes, whereas those with a S/L ratio of 0.5 or more were accepted as round nodes. The echo pattern of the lymph node was classified as hypo, iso, or hyperechoic compared with the surrounding musculature. The reticular pattern was described as a micro-nodular echo mould. The echogenic hilus was defined as presence or absence of hilar echogenity that is continuous with the surrounding fat. The border of the lymph node was classified as sharp or unsharp (irregular) according to the boundary between the lymph nodes and the surrounding soft tissues. The internal structure of the lymph node was evaluated for the presence of calcification, cystic (liquefaction necrosis) and coagulation necrosis. Coagulation necrosis is usually echogenic, irregularly demarcated, and is not continuous with the surrounding fat.

Following grey scale US examination, color Doppler US and spectral Doppler US examinations were performed. The vascular distribution of the lymph node (hilar, peripheral, and mixed pattern) and the vascular resistance parameters (Resistivity index: RI; pulsatility index: PI) were determined during the scanning.

All the scans were performed employing the standardized parameters. The adjustment of color Doppler US was regulated for high sensitivity with a low wall filters and pulse repetitions frequency 700 Hz to detect the vessels with low blood flow. Vascular resistance (RI and PI) was measured in at least three vessels. Each of the RI and PI measurements were obtained from 3 successive spectral Doppler wave forms and an average value of RI and PI was scored in the analyses. In all examinations, the sample volume was standardized to 1mm and the Doppler angle was set to 60 degree or lower.

Patients with benign cervical lymph nodes according to sonographic characteristics (oval shaped, isoechoic, with an echogenic hilus) and purely cystic lymph nodes were excluded. Patients with malignant cervical lymph nodes according to sonographic characteristics underwent fineneedle aspiration cytology (FNAC). If the FNAC of the lymph nodes was non-diagnostic, an excisional biopsy was obtained. Patients with malignant lymph nodes according to histopathological diagnosis were included in the study. Four patients who had malignant characteristics according to sonographical criteria were found to be benign on

	Lymphoma (n:42) (%)	Carcinoma metastasis (n:77) (%)	p value
Shape			p>0.05
Oval	1 (2.4%)	2 (2.6%)	
Round	41 (97.6%)	75 (97.4%)	
Echogenicity			
Hypoechoic	29 (69%)	52 (67.5%)	p>0.05
İsoechoic	1 (2.4%)	12 (15.6%)	
Hyperechoic	1 (2.4%)	13 (16.9%)	
Reticular echogenicity	11 (26.2%)	0 (0%)	p<0.05
Hilus			p>0.05
Present	4 (9.5%)	6 (7.8%)	
Absent	38 (90.5%)	71 (92.2%)	
Nodal border			p>0.05
Sharp Unsharp	42 (100%) 0 (0%)	74 (96.1%) 3 (3.9%)	
Cystic necrosis	7 (16.7%)	25 (32.5%)	p>0.05
Coagulation necrosis	3 (7.1%)	10 (13%)	p>0.05
Calcification	0 (0%)	12 (15.6%)	p<0.05
Vascularity			p>0.05
Hilar	1 (2.4%)	4 (5.2%)	
Peripheral	20 (47.6%)	48(62.3%)	
Mixed	21 (50%)	25 (32.5%)	
RI	0.739±0.093	0.807±0.126	p<0.05
PI	1.505±0.405	2.014±0.699	p<0.05

 Table 1. Grey scale, color Doppler and spectral Doppler US features of lymphoma and carcinoma metastasis.

US, ultrasonography; RI, Resistivity index; PI, Pulsatility index.

histopathological examination. Three patients (1 malignant neuroendocrine tumor metastasis and 2 malignant melanoma metastasis) were excluded since their number was inadequate for statistical analysis.

### Statistical Analysis

The comparison of qualitative variables was made through the exact method of chi-square (x2) analysis. For cases in which the variables were found to be dependent in the chi-square analysis, the significant cells were determined with the help of the standard residual (SR). The actual p values of the assessed parameters were given and the value p<0.05 was accepted to be statistically significant. Diagnostic measures were calculated using easyROC software.

## RESULTS

The study included 119 patients (42 lymphoma, 77 carcinoma metastasis (CM) ). Of the 42 patients with lymphoma, 14 were Hodgkin lymphoma and 28 were non-Hodgkin lymphoma. Thirty-three of 77 patients with CM, had thyroid carcinoma metastasis (TCM). Other 44 patients had squamous cell carcinoma metastasis (SCCM). The grey scale US, color Doppler US and spectral Doppler US findings of the malignant lymph nodes are summarized in Table 1 and 2.

The mean short axis of the lymph nodes was  $18.81\pm8.05$ mm,  $17.20\pm8.78$ mm and the mean long axis of the lymph nodes was  $26.09\pm9.97$ mm,  $23.05\pm11.10$ mm for lymphoma and CM cases, respectively. In this study, the size of lymph node was not found to be statistically significant to help in differentiating the primary tumour.

	Thyroid carcinoma metastasis (n:33) (%)	Squamous cell carcinoma metastasis (n:44) (%)	p value
Shape			p>0.05
Oval	1 (3%)	1 (2.3%)	
Round	32 (97%)	43 (97.7%)	
Echogenicity			
Hypoechoic	14 (42.4%)	38 (86.4%)	p>0.05
İsoechoic	6 (18.2%)	6 (13.6%)	
Hyperechoic	13 (39.4%)	0 (0%)	p<0.05
Reticular echogenicity	0 (0%)	0 (0%)	
Hilus			p>0.05
Present	1 (3%)	5 (11.4%)	
Absent	32 (97%)	39 (88.6%)	
Nodal border			p>0.05
Sharp Unsharp	32 (97%) 1 (3%)	42 (95.5%) 2 (4.5%)	
Cystic necrosis	13 (39.4%)	12 (27.3%)	p>0.05
Coagulation necrosis	3 (9.1%)	7 (15.9%)	p>0.05
Calcification	11 (33.3%)	1 (2.3%)	p<0.05
Vascularity			p>0.05
Hilar	0 (0%)	4 (9.1%)	
Peripheral	21 (63.6%)	27 (61.4%)	
Mixed	12 (36.4%)	13 (29.5%)	
RI	0.786±0.132	0.823±0.121	p>0.05
PI	1.858±0.578	2.130±0.763	p>0.05

**Table 2.** Grey scale, color Doppler and spectral Doppler US features of thyroid and squamous cell carcinoma metastasis.

US, ultrasonography; RI, Resistivity index; PI, Pulsatility index.

The shape of the majority of the lymphomatous and metastatic lymph nodes (98%), was found to be round (S/  $L \ge 0,5$ ). There was no dependency between the groups in terms of lymph node shape and the differences between them were statistically not significant. A hypoechoic pattern was detected in 69% of the lymphomas, 67% of the CM cases. There was no dependency between the groups in terms of hypoechoic pattern and the differences between them were statistically not significant. In order to determine the level of statistical significance of the echo pattern in TCM patients, SR analysis was employed. According to this analysis, it was accepted statistically significant for 13 cases (39%) displaying hyperechoic pat-



**Figure 1.** Grey-scale US image shows hyperechoic echo pattern (arrow head) and punctat calcifications (arrows) in a metastatic lymph node from thyroid carcinoma metastasis.



**Figure 2.** Color Doppler US image shows peripheral flow pattern, also note reticular pattern (arrows) in a lymphomatous lymph node.

tern in TCM (|SR|>1.96) (Figure 1). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of hyperechoic pattern in the diagnosis of TCM were 39%, 100%, 100%, 68%, respectively. In order to determine the level of statistical significance of the echo pattern in lymphoma patients SR analysis was employed. According to this analysis, it was accepted statistically significant for 11 of the cases (26%) displaying a reticular pattern in lymphomatous lymph nodes (|SR|>1.96) (Figure 2). Sensitivity, specificity, PPV and NPV of reticular pattern in the diagnosis of lymphomatous lymph nodes were 26%, 100%, 100%, 71%, respectively. Absense of echogenic hilus was observed in 90% of the lymphoma patients and 92% of the CM patients and the difference was not accepted as statistically significant. The majority of the cervical lymph nodes (97%) had a sharp border and



**Figure 3.** Grey-scale US shows hyperechoic coagulation necrosis (arrow heads) in carcinoma metastasis.

no dependence was found between the groups, and the difference was not accepted as statistically significant. Calcification was found in 11 TCM cases (33%), and 1 SCCM case (2%) (Figure 1). No calcification was found in the lymphoma cases. It was seen that diagnosis between the groups and calcification were dependent on each other and the difference between them was statistically significant. Sensitivity, specificity, PPV and negative predictive value NPV of calcification in the diagnosis of TCM were 66%, 2%, 33%, 8%, respectively. Cystic necrosis was found in 16% of lymphoma, 32% of CM cases. The difference was not accepted as statistically significant. Coagulation necrosis was detected in 7% of the lymphoma, and 13% of the CM cases. No dependence was found between the groups, and the difference was not accepted as statistically significant (Figure 3).



Figure 4. Spectral Doppler and power Doppler US images shows peripheral and hilar flow pattern (mixed) in carcinom metastasis. RI: 1.00, PI: 3.41.



**Figure 5**. Spectral Doppler US image shows low RI value (0.68) in lymphomatous lymph node.

There was no dependency between the Hodgkin and non-Hodgkin lymphoma patients in terms of shape, echo pattern, hilus, nodal border, calcification, cystic necrosis, coagulation necrosis and vascular flow pattern and the differences between them were statistically not significant (p>0.05). The grey scale US, color Doppler US and spectral Doppler US findings of the Hodgkin and non-Hodgkin lymphoma lymph nodes are summarized in Table 3.

The flow pattern in lymphoma was 47% peripheral, and 50% mixed flow pattern; in CM it was 62% peripheral, and 32% mixed flow. Hilar flow pattern was 4% in all cases. No statistical relation was observed between the diagnosis and vascular pattern. The RI average  $\pm$  standard deviation value was 0.739 $\pm$ 0.093, and 0.807 $\pm$ 0.126, for

Table 3. Grey scale, color Doppler and spectral Doppler US features of Hodgkin and non-Hodgkin
lymphoma lymph nodes.

	Hodgkin lymphoma (n:14) (%)	Non-Hodgkin lymphoma (n:28) (%)	p value
Shape			p>0.05
Oval	0 (0%)	1 (3.6%)	
Round	14 (100%)	27 (96.4%)	
Echogenicity			p>0.05
Hypoechoic	11 (78.6%)	18 (64.3%)	
İsoechoic	0 (0%)	1 (3.6%)	
Hyperechoic	0 (0%)	1 (3.6%)	
Reticular echogenicity	3 (21.4%)	8 (28.6%)	
Hilus			p>0.05
Present	3 (21.4%)	1 (3.6%)	
Absent	11 (78.6%)	27 (96.4%)	
Nodal border			p>0.05
Sharp Unsharp	14 (100%) 0 (0%)	28 (100%) 0 (0%)	
Cystic necrosis	2 (14.3%)	5 (17.9%)	p>0.05
Coagulation necrosis	0 (0%)	3 (10.7%)	p>0.05
Vascularity			p>0.05
Hilar	1 (7.1%)	0 (0%)	
Peripheral	6 (42.9%)	14 (50%)	
Mixed	7 (50%)	14 (50%)	
RI	0.732±0.084	0.743±0.099	p>0.05
PI	1.495±0.291	1.511±0.456	p>0.05

US, ultrasonography; RI, Resistivity index; PI, Pulsatility index.

the lymphoma, and CM cases, respectively. It was found be that the lymphoma group had the lowest RI value among 4). the disease groups included in the study. In lymphoma cases, RI values were found significantly lower than CM lyr cases (Figures 4, and 5). The PI average ± standard deviation value was 1.505±0.405, and 2.014±0.699 for the lymphoma and CM cases, respectively. It was found that the lymphoma group had the lowest PI value of all the

There was no dependency between the Hodgkin and non-Hodgkin lymphoma patients in terms of RI and PI values and the differences between them were statistically not significant (p>0.05).

disease groups included in this study and the difference

was accepted as statistically significant.

#### DISCUSSION

The most common causes of malignant cervical lymphadenopathy are lymphoma and metastatic squamous cell carcinoma of the head and neck region. The presence of lymph node metastasis is important as it affects treatment planning and prognosis. Accurate diagnosis is essential as the treatment modalities of these two pathologies are quietly different.

US is the first choice imaging tool for diagnostic evaluation of cervical lymphadenopathy. The role of US in the differentiation of benign nodes from malignant ones is well established. Grey scale US has a sensitivity of 95% and a specificity of 83% in differentiating metastatic and reactive nodes (7). The findings of this study are in accordance with the literature as the round shape, hypoechoic pattern, absence of echogenic hilus, sharp border, peripheal and mixed type flow pattern, high RI and PI values were critaria that support malignant lymph node (8). But these findings were not accepted to be significant for the differential diagnosis of the primary tumour. Cystic necrosis is frequently seen in tuberculosis lymphadenitis, metastatic nodes from squamous cell carcinomas and in thyroid papillary carcinomas (9). In this study cystic necrosis was more common in TCM and SCCM cases. However, cystic necrosis has no contribution for the detection of the primary tumour as in our study. In line with the literature (6), a low rate of coagulation necrosis was observed in our study. It is not significant for detecting the primary tumour (p>0.05).

There are a great many published reports in the literature on the usage of grey scale and Doppler US to distinguish between benign and malignant cervical lymph nodes (2-4). However limited studies are available for the differential diagnosis of the primaries of malignant cervical lymph nodes by means of grey scale, color Doppler, and spectral Doppler US examinations (5, 6). In this study reticular pattern was only found in lymphomatous lymph nodes and it was a useful finding for the detection of the primary tumour (p<0.05). According to Ahuja et al. (9) reticular pattern is frequently seen (64%) in non-Hodgkin's lymphoma. Our rate of reticular pattern (26%) was lower than the reported rates in the literature. Since we did not subgroup our lymphoma cases we think that this is the cause for our low rates.

Hyperechoic pattern is frequently found in TCM lymph nodes. Hyperechoic pattern was detected to be 77% in the lymph nodes resulting from papillary TCM in a study by Ahuja et al. (6). It is stated that the hyperechoic pattern results from accumulation of colloid (thyroglobulin) produced by thyroid carcinoma. In this study hyperechoic pattern was detected in 39% of TCM cases and it was found to be statistically significant for predicting TCM as the primary tumour (p<0.05). We think that lower value of hyperechoic pattern in our study may be related with not performing a histopathological subgroup analysis such as papillary, medullary, and follicular. Calcification is also a rare finding in the lymph nodes. It was reported that calcification within metastatic lymph nodes highly suggests metastatic nodes from medullary and papillary thyroid carcinoma. Calcification is reported to result from psammoma bodies. Ahuja et al. (6) reported the calcification rate in papillary carcinoma as 51%. In the present study we found the calcification rate as 33% in TCM cases and 2% in SCCM cases. No calcification was found in the lymphoma cases. We think that calcification is a significant criterion for detecting the primary tumour. Hyperechoic pattern and calcification suggest TCM according to this study and literature. It was reported that, thyroglobulin and calcitonin measurement in washout fluid from fine needle aspiration (FNA) of neck lymph nodes is highly reliable diagnostic procedure for TCM (10, 11, 12). If the calcification and hyperechoic pattern are seen in metastatic lymph node, this procedure may be added to FNA.

It has been reported that RI and PI values are higher in malignant lymph nodes due to suppression by surrounding tumour cells (4). However, other studies reported the RI and PI values for malignant lymph nodes were low because of lack of muscular elements in tumour vessels and presence of arteriovenous shunts (2, 13). In another study, it was suggested that intranodal vessels with low and high resistance may be observed due to both the suppression of a tumour and angiogenesis inside a lymph node (14). The RI and PI values for the lymphomatous lymph nodes are believed to often be higher than those for the reactive and tuberculosis lymph nodes and lower than those for metastatic lymph nodes (4, 15). Gupta et al. (16) found that mean RI value in lymphomatous lymph nodes to be 0.66, while they found 0.81 as the mean RI value for metastatic lymph nodes. Ying et al. (5) reported that RI with a cut-off value of 0.8 was more accurate in distinguishing metastases (RI>0.8) from lymphoma (RI<0.8), with an accuracy of 65% and 75%, respectively. In our study, RI and PI values were low in lymphomatous lymph nodes and high in metastatic lymph nodes which were in concordance with the reported studies. In cases with malignant cervical lymph nodes with unknown primaries, RI and PI parameters may be used for differential diagnosis for lymphomatous and CM lymph nodes.

US guided FNAC is widely used for evaluation of patients with malignant cervical lymph nodes. It is a safe, simple, guick and cost effective outpatient procedure with a reported diagnostic accuracy in malignant lymphadenopathy that 95% (17). In squamous cell carcinoma of the head and neck, cervical metastases have prognostic and therapeutic importance. In such a case FNAC provide adequate sample for diagnosis without compromising oncological outcome. Core needle biopsy or surgical lymph node resection might be a good alternative. But both procedures are invasive and may lead extracapsular spreading of the tumor. It was reported that in squamous cell carcinoma of the head and neck, surgical biopsy prior to definitive surgery may adversely affect prognosis and increase local complications, incidence of distant metastasis (18). On the other hand surgical lymph node resection requires general anesthesia and hospitalization. The usage of FNAC in lymphoma is controversial. Additional examination techniques such as immunocytochemistry, flow cytometry, cytogenetics, and molecular genetics are necessary for full classification of lymphoma. The accuracy of FNAC in the assessment of lymphoma is approximately 20% less than its accuracy in carcinoma (19). Surgical excision biopsy has been applied for lymphoma diagnosis in many institutions. Screaton et al. (20), reported that in 80% of their patients classification of lymphoma on the basis of core biopsy results was sufficient to commence therapy. The accuracy of core biopsy in differentiating lymphoma from reactive lymphadenopathy, given an adequate sample, was 98.5%. If the core biopsy is applied with the sonography guidance and larger size of biopsy needle, adequate sample can be achievable for diagnosis and classification.

In conclusion; US is an effective method for the evaluation of malignant cervical lymph nodes. Moreover it aids to narrow the disease to be considered in the differential diagnosis. Hyperechoic pattern, reticular pattern, calcification, low RI and PI values are the findings that may direct the clinicians and radiologist to choice of the biopsy method and patient management. If US findings (such as reticular pattern, low RI and PI values) suggest lymphomatous lymph node, core needle biopsy or open surgical biopsy can be used for definitive diagnosis. On the other hand if US findings suggest CM, FNAC can be used for diagnosis. If the calcification and hyperechoic pattern are seen in metastatic lymph node, thyroglobulin and calcitonin measurement in washout fluid from FNA will be very useful in diagnosis of a thyroid carcinoma.

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