Importance of Sonoelastography in Assessing Non-Thyroid Neck Masses

Objective: To evaluate the feasibility and value of sonoelastography in assessing non-thyroid neck masses.

Methods: Non-thyroid neck masses requiring surgical interventions were evaluated using conventional B-mode ultrasonography (US) (size, short/long axis rate, shape, hilum, echogenicity, calcification, necrosis, and peripheral edema) and sonoelastography (SE) with strain ratio (SR) and elasticity score (ES) before surgery. These parameters were compared with the histopathological examination.

Results: In total, 116 non-thyroid neck masses (66 lymph node, 35 parotid gland, eight submandibular gland, and seven cervical mass) of 89 patients (51 men, 38 women) with a mean age of 50.3±15.1 (19-79) years were evaluated. Thirty-seven malignant lymph nodes (23 metastatic and 14 lymphoma), seven malignant parotid tumors, two malignant submandibular tumors, 29 benign lymph nodes, 28 benign parotid lesions, and six benign submandibular lesions were evaluated. Mean SR and ES values of malignant masses were 6.3/3.2 for lymph nodes, 5.5/3.3 for the parotid gland, and 4.2/3 for the submandibular gland. Mean SR and ES values of benign lesions were 2.0/2.1 for lymph nodes, 4.4/3.2 for the parotid gland, and 3.2/3 for the submandibular gland. SR and ES were significantly higher for malignant masses compared with those for benign ones. SR was more predictive than ES in evaluating malignant lymph nodes. The area under the curve was 0.917(0.827-1.00) (p<0.05) for SR in differentiating benign-malignant lymph nodes, and the upper cut-off value was two. SR and ES were higher in the malign parotid and submandibular gland lesions than the benign ones, but the difference was not statistically significant.

Conclusion: Strain ratio value could be a useful parameter in differentiating benign-malignant lymph nodes. More studies are necessary for differentiating benign-malignant parotid and submandibular lesions using SE.

Keywords: Elastography, differential diagnosis, head and neck neoplasms, lymph nodes, salivary glands
In patients with head and neck cancer, noninvasive, cheap, fast, and easy evaluation of the cervical lymph nodes, which are the most important factors affecting the prognosis, may be possible through SE. In addition, the increase in preoperative knowledge about the structure of the neck masses is very important because it affects the surgical procedure and the morbidity of the patient (such as facial nerve paralysis in parotid masses). The data on elastographic features of large salivary gland lesions are still inadequate, and a contribution is needed in this regard (6).

The purpose of this study is to contribute to rapid and reliable diagnosis and prevention of unnecessary biopsies by evaluating superficial cervical lymph nodes and large salivary gland lesions through SE.

Methods
This prospective clinical study, approved by the Ethics Committee of Clinical Investigations (decision date: March 17, 2014; decision no. 14/28), was conducted at the Dışkapı Yıldırım Beyazıt Training and Research Hospital between April 2014 and August 2016 at the ENT and Radiology clinics.

Patient selection
Patients included in the study were selected among those carrying one of five different characteristics:

Type 1 patients: Patients with suspicious cervical lymphadenopathy who were not diagnosed with previous examinations and in whom excision of the surgical lymph nodes was indicated for the diagnosis.

Type 2 patients: Patients with previously known head and neck malignancy who were previously diagnosed and whose neck dissection should be performed as part of treatment. The lymph nodes of these patients, which can be assessed through US-SE, were evaluated separately from the neck dissection specimen.

Type 3 patients: Patients with a malignancy (other than the head and neck region) in whom cervical lymph node excision is planned in terms of distant metastasis.

Type 4 patients: Patients with parotid masses for which surgical excision was indicated for histopathological diagnosis.

Type 5 patients: Patients with a submandibular gland lesion for which surgical excision was indicated for histopathological diagnosis.

Detailed backgrounds and anamneses of all patients were received and the patients’ demographic information was recorded. If there was a primary tumor disease/focus associated with the mass in the neck, histopathological diagnoses were recorded. A detailed ENT examination was performed in all patients. The elastographic properties of the mass were examined during conventional B-mode US using the elastographic property of the same device in all patients over 18 years of age before the surgery. Patients who previously had sharp object injuries in the neck region where the surgery would be performed, who had a history of deep neck infection, who previously underwent surgical intervention in the neck region, or who had radiotherapy in the head and neck region were not included in the study. All phases of the study were explained to the patients in detail by the experts, and all patients signed the informed consent form prepared for this study.

Ultrasonography and sonoelastography methods
First, conventional B-mode US and then US-SE (linear transducer, 8–13 MHz Toshiba Aplio 500, Tokyo, Japan) were applied to all the patients in supine position prior to surgery. Light and intermittent pressures were applied on the tissue for elastographic evaluation until a sustainable, optimal, and standardized pressure was achieved. Sonogram and elastogram were displayed side by side on the screen. The lesion and the surrounding subcutaneous fatty tissue were evaluated. An elastogram based on the color scale was displayed on the B-mode image. This scale ranged from red (soft zone) to blue (rigid zone). While the red color represented a high elasticity tissue with many soft components, the blue color represented a tissue with many hard components. Different scoring systems can be used to determine the elasticity scores. In this study, the 5-point scoring system defined by Alam et al. (7) (the pattern ranging from 1 [soft] to 5 [rigid]) was used. According to this system, the lesions that scored between 1 and 3 were considered benign, and those that scored between 4 and 5 were regarded as malignant. Afterwards, an adjustable area of interest covering the majority of the target lesion was displayed. By using the average strain value (strain T) and the reference average strain value (strain RA) of the surrounding and subcutaneous fat tissue that is at the same depth and size, SR (strain RA/strain T) value was recorded. The SR value reflects the rigidity of the lesion, and as the value increases, the likelihood that the lesion is malignant increases (6).

The main features of US and SE that were evaluated and recorded were the horizontal diameter, vertical diameter, long/short axis ratio, shape (regular/irregular), boundaries (clear/not clear), hilum (yes/no), echogenicity (homogenous/heterogeneous), calcification (yes/no), necrosis (yes/no), surrounding edema (yes/no), strain value in reference to the muscle (strain ratio: SR), and elasticity score (ES) of the mass. Afterwards, the type of surgery that was performed in the patient and the result of the histopathologic examination of the mass/lymph node that was excised were recorded. These data were compared with reference to histopathologic features of the lymph node/parotid/submandibular gland excised for diagnostic and/or therapeutic purposes and the diagnostic usability of the US-SE examination was analyzed. In order to reduce possible bias in the evaluation of elastograms, the images were numbered anonymously and were scored three months after the last evaluation.

Statistics
Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was
used in the analysis of quantitative data. The chi-square test was used to analyze qualitative data, and Fischer's exact test was used when chi-square test conditions were not met. The effect level and cut-off value were investigated with ROC curve. The confidence interval (CI) for those under the ROC curve was 95%. The effect level was investigated with univariate and multivariate logistic regression. Statistical analyses were performed using the Statistical Package for the Social Sciences 22.0 program (SPSS Inc.; version 22.0, Armonk, NY, USA).

Results

One hundred sixteen non-thyroid neck masses (66 superficial cervical lymph nodes and anterior cervical masses, 35 parotid lesions, and eight submandibular gland lesions) from 89 patients (51 men and 38 women) with a mean age of 50.3±15.1 (19-79) were analyzed. It was found in the histopathological examination that 29 of the lymph nodes were benign and 37 were malignant. Twenty-eight of the parotid lesions were benign and seven were malignant. Six of the submandibular gland lesions were benign and two were malignant. The detailed distribution of the masses according to the histopathological diagnosis is shown in Table 1. Both in the evaluation of all cases and in the evaluation of the cases in two separate groups as lymph nodes (66 cases) and large salivary glands (43 cases); the age and gender distribution of patients with benign and malignant diagnosis did not show a significant difference (in all cases; p=0.143 for age and p=0.856 for gender).

The data of the US and SE evaluation parameters of the lymph nodes and the relationship between these data and whether the excised lesion was benign or malignant in the histopathological evaluation are shown in Table 2. The age and gender distribution of the patients did not differ significantly between the benign and malignant group (p=0.149 for age and p=0.871 for gender).

As seen in this table, horizontal diameter, vertical diameter, SR, and ES values were significantly higher in the malignant group (p<0.05). The long/short (L/S) axis ratio was significantly lower (p<0.05) in the malignant group than in the benign group. In the malignant group, the lack of clear borders, amorphousness, hilum abnormalities, and heterogeneous echogenicity were significantly higher (p<0.05). Between the benign and malignant groups, calcification, presence of necrosis, and the ratios of surrounding edema were not statistically significant (p>0.05).

As for the gradual univariate and multivariate logistic regression analyses of US and ES evaluations of the lymph nodes; in the univariate model, the vertical diameter, L/S axis ratio, SR, ES, border clarity, shape, hilum, and echogenicity evaluation parameters were observed to be significantly effective (p<0.05) in distinguishing benign and malign lymph nodes. In the multivariate model, vertical diameter and SR were observed to be significantly and independently effective (p<0.05) in distinguishing benign and malign lymph nodes (Table 3).

In the ROC curve of SR value whose significant effectiveness was observed on the prediction of malignant and benign lymph nodes, the value of the area under the curve was 0.917 (0.827-1.00) (p<0.05). The highest value of SR under the curve for the prediction of malignant and benign lymph node was 0.932 (0.856-1.00) (p<0.05), and the cut-off value for this area was two (Table 4 and Figure 1).

The data of the US and SE evaluation parameters of the parotid and submandibular gland, the relationship between these data and the histopathological evaluation are shown in Table 5. The age and gender distribution of the patients did not differ sig-
significantly in the benign and malignant groups (p=0.139 for age and p=0.742 for gender). As seen in this table, there were higher values of SR, ES, horizontal and vertical diameter, border uncertainty, shape irregularity, heterogeneity, presence of calcification, presence of necrosis, and peripheral edema in malignant lesions, but these high values were not statistically significant (p>0.05).

No significant effect of US and ES parameters was observed in the univariate and multivariate logistic regression analyses of US and ES evaluations of parotid and submandibular gland lesions (Table 6).

According to the histopathological evaluation, the average value of SR was found to be 2.3 and the average value of ES was found to be 1.9 in the SE evaluation of six patients with thyroglossal duct cysts (two cases), branchial cleft cysts (two cases), and lipoma (two cases).

In the analysis of the data of all 116 cases, it was observed in the SE evaluation of the masses that the value of SR was significant in distinguishing between malignant and benign histology. In the ROC curve of the SR, the value of the area under the curve was 0.816 (0.722-0.910) (p<0.05). In distinguishing between malignant and benign non-thyroid neck mass, the highest value of SR under the curve was 0.842 (0.756-0.928) (p<0.05), and the cut-off value for this area was two (Table 7 and Figure 2).

**Discussion**

Conventional B-mode US is the most common and the first-step imaging method in the evaluation of cervical masses in clinical practice. Although many studies have been published regarding the evaluation of cervical lymph nodes with B-mode sonography, specific criteria that can be used to distinguish metastatic and reactive nodes are still unclear (8). In the interpretation of cervical lymph nodes as malignant, the evaluation of a number of morphological features such as roundness, presence of necrosis, and obliteration of fatty hilum may be helpful, but these findings do not always give definite results and there is no single specific criterion for malignancy (9). For example, in the evaluation of lymph nodes, border irregularity is a datum that can be interpreted in favor of the metastatic lymph node, but sensitivity and specificity are not high (8).

### Table 3. Univariate and multivariate logistic regression analysis of lymph nodes in US and ES evaluation

<table>
<thead>
<tr>
<th></th>
<th>Univariate model</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>SR</td>
<td>94.7</td>
<td>11.8 -</td>
</tr>
<tr>
<td>ES</td>
<td>4.4</td>
<td>1.6 -</td>
</tr>
<tr>
<td>Vertical diameter</td>
<td>9.6</td>
<td>2.6 -</td>
</tr>
<tr>
<td>L/S axis ratio</td>
<td>0.2</td>
<td>0.1 -</td>
</tr>
<tr>
<td>Margin clearness</td>
<td>5.7</td>
<td>1.9 -</td>
</tr>
<tr>
<td>Shape</td>
<td>2.7</td>
<td>1.1 -</td>
</tr>
<tr>
<td>Hilum</td>
<td>6.1</td>
<td>1.8 -</td>
</tr>
<tr>
<td>Echogenity</td>
<td>2.8</td>
<td>1.2 -</td>
</tr>
<tr>
<td>Calcification</td>
<td>2.6</td>
<td>0.6 -</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1.5</td>
<td>0.5 -</td>
</tr>
<tr>
<td>Surrounding edema</td>
<td>3.2</td>
<td>0.8 -</td>
</tr>
</tbody>
</table>

SR: strain ratio; ES: elasticity score; L/S: long/short; CI: confidence interval; OR: odds ratio

p-value of parameters that have a significant effect in the univariate model for differentiation of benign-malignant is bold-faced

### Table 4. In the evaluation of lymph node, AUC and significance values for SR and SR threshold value of two

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>AUC 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>0.917</td>
<td>0.827 -</td>
<td>1.000</td>
</tr>
<tr>
<td>SR threshold value (2)</td>
<td>0.932</td>
<td>0.856 -</td>
<td>1.000</td>
</tr>
</tbody>
</table>

SR: strain ratio; AUC: area under curve value; CI: confidence interval

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In our study, it was also found that the clarity of the borders in the malignant lymph nodes decreased. Metastatic lymph nodes take a more spherical shape, and thus, it is considered that L/S axis ratio decreases. For example, Alam et al. (7) reported that the lymph node short/long axial diameter ratio that is greater than 0.6 may be in favor of metastasis. We also found in our study that the long/short axis ratio was significantly reduced in malignant lymph nodes compared with the benign ones and that the vertical diameter measurement was the most valuable among the B-mode parameters in terms of malignancy. We also found the absence/
abnormality of hilum, which was shown in some studies to be a valuable parameter for malignancy in lymph node evaluation, similarly significant in our study (8). While the absence of hilum was shown to be the most important US criterion for the lymph node malignancy with an accuracy of 86% in the study of Alam et al. (7), it was reported that hyperechogenic hilum was found in 51% of metastatic lymph nodes in the study of Vassallo et al. (10). In our study, lymph node hilum abnormality had an accuracy of 69% in the determination of malignancy. We also found that peripheral edema, necrosis, and calcification were not useful parameters to be used in benign-malignant differentiation of the lymph nodes. This may be due to the fact that these parameters have not been determined in adequate numbers for statistical evaluation.

In the study of Lyshchik et al. (4), which was one of the first studies in which US and SE were evaluated together in the evaluation of lymph nodes, it was reported that among all evaluation parameters, a value of SR higher than 1.5 is the most useful parameter in favor of the metastatic lymph node. In their studies comparing lymph nodes in different features with histopathological and follow-up results, Zhang et al. (11) reported the threshold SR value over 2.3. The disadvantage of this study is the lack of histopathological diagnosis in some cases. In our study, we found that a SR value higher than two was the most significant sonographic parameter in favor of malignant lymph node. In comparison to the study of Lyshchik et al. (4), in which only metastatic lymph nodes were evaluated, the reason of determining a higher threshold value could be that we evaluated a smaller number of lymph nodes (66 versus 141).

In previous studies on the evaluation of lymph nodes with SE, Alam et al. (7) reported an accuracy of 89% for SE. Hefeda et al. (12) reported this rate as 89.9%. In our study, we found this rate as 83%. The reason for this lower rate in our study was considered as the inclusion of lymphomas in our study, while only metastatic lymph nodes were evaluated in other studies. Since some malignancies such as lymphoma may be soft, whereas benign lesions with focal deposits may cause partial hard areas, they may be considered as false positives in ES. There is little information about elastographic findings of lymph nodes lesions dominated by fibrosis and calcification (13). Despite all these possible errors, the high specificity and accuracy of SE is an indication that it could be useful in identifying the suspicious nodes and in preventing unnecessary biopsies.

In a meta-analysis in which the studies in the literature were compiled, it was reported that SR had a higher accuracy than ES in detecting lymph node malignancy (14). In the study of Teng et al. (15), a threshold value of 1.78 SR was found to be more significant in detecting malignant lymph nodes than ES. The results of our study were similar to the literature in this respect. In the regression analysis, the accuracy rates for SR and ES were 83% and 62.5%, respectively.

As in lymph nodes, in the evaluation of large salivary gland lesions, the first step is usually US, but alone, it is limited in distinguishing malignant-benign lesions (16). There is insufficient data on sonoelastographic features of large salivary gland lesions. Dumitriu et al. (17) reported that salivary gland tumors did not exhibit a specific elastographic pattern and therefore would not provide a significant contribution to differential diagnosis because Wharton tumors and pleomorphic adenomas were reported to contain heterogeneous areas of different elasticity. Bhatia et al. (18) reported that pleomorphic adenomas and malignant lesions in SE could have a higher ES score than Wharton tumors, but they reported that benign and malignant lesions could not be safely distinguished with SE. This may be caused by the reflection of the cell diversity in the inner structure of pleomorphic adenoma. Pleomorphic adenoma is well circumscribed and shows lobulation, and SE does not have these known sonographic features. Therefore, it is thought that SE will not provide additional contribution when the classical US is inadequate (17, 18).

In their studies evaluating pleomorphic adenomas and Wharton tumors of parotid gland by ultrasonographic methods, Yerli and Eski (19) reported that ES may be helpful in diagnosis when used with B-mode and color Doppler US, but not when used alone. In the study in which they evaluated parotid masses with SE, Wierzbicka et al. (20) reported that SE alone was not sufficient to exclude malignancy. Similar to these studies, we found the SR values of malignant large salivary gland tumors to be higher, but this difference was not significant. Nevertheless, high SR values may raise doubts in terms of malignancy. This prediction needs further evidence, and further studies are needed for the use of SE in this regard. In our study, the analysis of a small number of salivary gland malignancies made the analysis weak.

The main disadvantage of SE is the difficulty in controlling tissue compression. Excessive pressure can cause misinterpretations. This error rate can be reduced by acoustic imaging. The new SE method known as shear wave is promising to reduce this problem. Another limiting factor is the difficulty of applying uniform pressure throughout the entire ultrasonic region of interest in the tissues adjacent to the bone structures. We did not include the patients who previously received radiotherapy and who previously had neck surgery. Sonoelastography evaluation before and after such treatments may be the subject of another study.

**Conclusion**

With high sensitivity in the lymph nodes, SE improves the diagnostic value of B-mode sonography in the differential diagnosis of benign and malignant non-thyroid neck masses. The promising results of SE in the head and neck region suggest that it may be part of routine diagnostic ultrasonographic evaluation in the near future. Its benefit in evaluating salivary gland tumors is limited. Further studies are necessary to determine and standardize sonoelastographic properties of different diseases.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Clinical Investigations Ethics Committee (Decision date: 17/03/2014, Decision no: 14/28).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.
Peer-review: Externally peer-reviewed.


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