Differentiating benign from malignant superficial lymph nodes with sonoelastography

Sorin M. Dudea, Carolina Botar-Jid, Dana Dumitriu, Dan Vasilescu, Simona Manole, Manuela Lavinia Lenghel

Radiology Department, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

The aim of the paper is to provide a comprehensive overview on the applications of real time sonoelastography (SE) in the diagnosis of superficial lymphadenopathy. Some technical aspects of performing SE are presented as a preamble. The typical appearance of benign and malignant nodes is illustrated. The paper discusses and depicts the various elastographic scores in use. It also provides a critical appraisal of the relative strain ratio (SR) or stiffness index. Shear wave elastography, as a novel technique, is mentioned. In conclusion, hardness on more than 50% of the node surface or $SR > 1.5$ is fair to good indicators of malignancy. Work is still needed both to fully understand the various appearance of disease and to standardize the application.

Keywords: sonoelastography, lymph nodes, neoplasm

Accurate assessment of the superficial lymph node status is of paramount importance in the treatment planning, follow-up and prognosis of malignancies originating in the head and neck, breast, superficial tissues or in lymphoma. Ultrasonography (US) is extensively used as a first line diagnostic means, due to its cost-effectiveness, ease of use and high resolution of provided information. However, grey-scale and Doppler information are limited either in sensitivity or specificity and no single US criterion has sufficient diagnostic accuracy [1-5].

Sonoelastography (SE) depicts the relative stiffness of tissues. Beyond breast, prostate and thyroid applications, over the last five years, the method was also used as a complimentary imaging technique to conventional US for the assessment of superficial lymph nodes [6-9]. Assessment of nodal SE information is done either by grading the appearance on a score system (elasticity score – ES) or by calculating a relative stiffness or strain ratio (SR) [10].

The aim of this paper is to review the current status of the knowledge on the applications of SE in the diagnosis of the character of superficial lymphadenopathy.

Technical aspects

Real-time sonoelastography is, essentially, an elaborate speckle tracking technique with autocorrelation for out-of-plane displacement of the target [11,12]. It provides information about the relative stiffness of the structures within the scan plane, inside a region of interest (ROI). It is, therefore, important to encompass in the scan area not only the target lesion but also surrounding „normal” reference soft tissues. There are no standard recommendations on how to achieve this. In our experience [13,14], the upper limit of the ROI should always be placed as close to the transducer as possible. When aiming to use ES, the ROI should exceed the target boundaries at least 5 mm on each side. When the purpose is to calculate SR, the ROI should be as wide as possible, to encompass both the target lesion and the surrounding, reference tissue, at the same depth with the lesion. Transducer stabilizer, although desirable, is difficult to use of curved surfaces such as neck or axilla. During compression the transducer should be perpendicular to the skin surface and the compression quality factor, whenever

Received 10.03.2013 Accepted 30.03.2013

Med Ultrason

2013, Vol. 15, No 2, 132-139

Corresponding author: Sorin M. Dudea

Dept. Radiology

Str. Clinicilor 1-3

400006 Cluj-Napoca, Cluj, Romania

Email: dudea@clicknet.ro

available, should be comprised within the optimal range (our group only uses quality factor 3 or 4) [15]. The most representative image obtained with optimal compression factor is stored for further assessment.

Some groups [7,16] suggest encompassing the target area and peripheral reference tissue in the approximate same proportion within the ROI. Other authors [17,18] suggest that the lymph node should occupy no more than 30% of the ROI and neighboring tissue at least 70%. It is, however, important to avoid the presence of bone or blood vessels in the scan area, as it may alter the overall image interpretation.

Debate is on its way on how to represent stiffness in real time sonoelastography. The first commercially available machines depicted hard areas in blue and soft areas in red. However, nowadays more and more manufacturers choose the opposite.

Benign lymph nodes

Inflammatory or reactive lymph nodes, not containing metastatic deposits, have the same SE appearance as the soft tissues of the neck and are scarcely visible as distinct entities on SE images [6]. They contain almost no hard, blue areas or, when present, sparse blue areas occupy less than 45% of the node surface [7]. Benign nodes are mostly displayed in colors of yellow, green and turquoise, color red being never encountered and blue of sparse and inconstant occurrence. On the color scale, nodal cortex appears harder than the medulla [17] (fig 1).

Unfortunately, not all non-malignant nodes comply with this appearance. Tuberculous nodes, with scarring, calcification or necrosis may display hard areas [18] or a mixture of colors. Little is still known about the SE appearance of relapsing or chronic lymphadenitis and there are no reports on the SE aspect in rare benign disease such as Kikuchi or Kimura disease.

Malignant lymph nodes

On SE images, malignant nodes stand out from neighboring tissues, due to their increased stiffness [6]. Blue areas, depicting rigid, hard tissue, occupy more than 45% of the lymph node area [7]. Red, yellow and green are not encountered in malignant deposit areas, where stiff tissue is depicted only in turquoise and blue [17]. The cortex is stiffer than the medulla or the node is uniformly hard (fig 2).

The assumption that malignant tissue is harder than surrounding normal tissue is only true for the majority of cases but not for every patient. Focal deposits within a lymph node may produce a small, hard area, occupying

Fig 1. Gray scale (right) and sonoelastogram (left) of a typical benign hypoechoic lymph node (arrow), displaying almost exclusively hues of orange, yellow, green and turquoise.

Fig 2. Gray scale (right) and sonoelastogram (left) of a typical malignant hypoechoic inhomogeneous lymph node (arrow), displaying almost exclusively blue hues.

Fig 3. Focal metastatic deposits (arrow) that occupy less than 50% of the node surface.

less than 45% of the node surface (fig 3). Some malignancies, especially lymphomas, produce „softer” appearing nodes, with less blue [15] (fig 4). Necrotic nodes with liquefaction will display an evocative blue-green-red pattern (fig 5).

All the above mentioned technical and interpretation-al issues lead to the need of using either a scoring system or a numerical value, in the attempt to better differentiate benign nodes from malignancy.

Fig 4. Malignant lymphoma: node with sizeable strain and little stiff, blue areas.

Fig 5. Malignant necrotic lymph node displaying the typical blue-green-red pattern (arrow).

Elasticity scores and diagnostic value

The SE appearance of the nodes is classified into scores. Several types of scoring are currently in use.

In an early work, using offline processing and no color coding, Lyschik et al [6] classified the nodes according to their visualization, brightness compared to neighboring muscle and regularity of the outline (table I).

According to these criteria, malignancy is suggested by partial or intense visibility of the nodes, which are substantially darker or very dark compared to the surrounding muscles. On the other hand, margin regularity or definition does not allow differentiation of benign from malignant nodes.

Alam et al [7] suggested a five pattern classification system, presented in table II.

All reactive nodes displayed pattern 1 or 2. Most of the metastatic nodes, but not all, displayed patterns 3, 4 or 5. The cutoff value of 45% was obtained by planimetry and statistical analysis.

Another classification, using ES from 1 (entirely soft) to 4 (completely stiff), proposed by Bhatia et al [8], with $ES > 2$ as a cutoff for malignancy, achieved suboptimal discrimination and fair to good interobserver variability.

Similarly, the classification proposed by Furukawa et al [16,19,20] uses four patterns (table III). Patterns 3 and

Table I. Lymph node appearance on SE and diagnostic value, according to Lyschik [6]

Criterion	Score	1	2	3	4
Node visualization		none	Barely	Partially	intense
Brightness compared to surrounding neck muscles		Same or brighter	Slightly darker	Substantially darker	Very dark
Margin irregularity		regular	slight	moderate	Very
Definition of node margin		Distinct, > 50%		Indistinct, < 50%	

Table II. Classification of SE appearance of lymph nodes according to Alam [7].

Pattern				
1	2	3	4	5
Absent or very small hard area	Hard area < 45% of lymph node	Hard area > 45% of lymph node	Peripheral hard and central soft area	Hard area over the entire node, with or without soft rim

Table III. Classification of SE appearance of lymph nodes proposed by Furukawa [19,20]

Pattern			
1	2	3	4
> 80% of the cross sectional area is soft (red or green)	50 – 80% of the node area is soft (green or red)	50 – 80 % of the area is blue	> 80% of the node area is blue

Table IV. SE scoring system of lymph nodes proposed by Ishibashi [21]

Score (% of blue area on cross section)				
1	2	3	4	5
0	<50%	50%	>50%	Central necrosis

4 are only observed in malignant nodes. Pattern 1 and 2 are encountered both in benign and malignant nodes.

More recently, Ishibashi et al [21] proposed another five level scoring system, presented in table IV. Scores 3 to 5 are independent indicators of malignancy.

Table V. SE scoring system [15].

Score	Description
1	the whole nodule is soft (similar to the surrounding tissues)
2	<50% of the nodule surface is blue and no individualized hypoechoic nodules are seen in the lymph node structure
3	<50% of the nodule surface is blue and individualized soft hypoechoic nodules are seen in the lymph node structure
4	<50% of the nodule surface is blue and individualized hard hypoechoic nodules are seen in the lymph node structure
5	50% - 100% of the nodule surface is blue and no individualized hypoechoic nodules are seen in the lymph node structure
6	50% - 100% of the nodule surface is blue and individualized hard hypoechoic nodules are seen in the lymph node structure
7	the blue area covers the whole nodules and extends in the soft tissues
8	blue (hard) nodule containing fluid areas (necrosis)

Fig 6. Appearance of lymph node types on sonoelastography: a. benign, soft node, type 1 in all scores; b. node with less than 50% hard surface, type 2 in most scores, type 1 by Furukawa [19]; c. Node with central stiff area, occupying more than 50% of the surface, type 3 according to Alam [7] and [19], type 4 according to Ishibashi [21] and type 5 by Lenghel [15]; d. node with central elastic core and hard peripheral rim, more than 50% blue, type 4 by [7] and [21], type 3 by [19], type 5 by [15]; e. the node surface is entirely blue, type 5 by [7], type 4 by [19] and [21], type 7 by [15]; f. Node with central necrosis displaying the blue-green-red pattern, type 5 by [21], type 8 by [15], unclassified by other authors.

Our group proposed a scoring system that takes into account both the SE and the grey scale appearance of the node [15] (table V). Scores 4 to 8 were highly indicative of malignancy. This scoring system takes into account the occurrence of focal metastatic deposits that occupy less than 50% of the node sectional area but may still be depicted as hard foci (score 4).

The various appearances of lymph nodes on sonoelastography, according to the suggested scores, are depicted in figure 6.

The diagnostic value of the different scoring systems is summarized in table VI.

The possible reasons for the variance in the above results are related to the equipment used, the pathology of the explored lesions, the scoring system applied and the reference standard for diagnosis.

In certain studies, the equipment was experimental. Commercially available equipment came from at least three different manufacturers, each of them with a proprietary implementation of the technology.

Table VI. Diagnostic value of different scoring systems for the SE diagnosis of malignancy in superficial lymph nodes.

Author Reference Year	Criterion	SE	SP	VVP	NPV	OA	AUROC	Reference standard	Obs.
Lyshchik [6] 2007	Node visualization $\geq$ score 3	67	93	87	79	82	–	histology	– experimental setting, commercially unavailable – only thyroid and hypopharyngeal metastases
	Node darker than surrounding tissues ($\geq$ score 3)	63	95	91	78	82	–		
	Regular or moderately irregular margins (Score < 3)	35	95	84	66	70	–		
	$> 50\%$ of border distinct (score < 3)	48	73	57	66	62	–		
Alam [7] 2008	Hard area $> 45\%$ of lymph node (Score ≥ 3)	83	100	100	78	89	0,873	Histology or imaging, follow-up	– commercially available equipment – metastatic nodes, mixed origin
Zhang [16] 2009	More than 50% of nodal surface blue (Score > 2)	74,4	97,1	–	–	84,5	–	FNAB, imaging, follow-up	– using the Furukawa score – mixture of metastatic sources, and lymphoma
Bhatia [8] 2010	Score > 2	62,2	83,8			73	0,68–0,74		
Taylor [22] 2011	Score > 2	90	86	83	93				
Choi [23] 2011	Score > 2	80,7	66,7			73,4			
Teng [18] 2012	More than 50% of nodal surface blue (Score > 2)	88,4	35,1	–	–	66,3	–	Histology and follow-up	using the Furukawa score mixture of metastasis of various sources and lymphoma
Ying [10] 2012	Meta-analysis	74	90				0,88		
Lenghel [15] 2012	Score ≥ 4	66,67	96,67	–	–	–	0,846	Histology and follow-up	Benign vs. malignant, lymphoma included
		71,43	96,67	–	–	–	0,855		Benign vs. metastatic, lymphoma excluded

The studied groups were also very different. In some studies only metastases with a specific origin were assessed, while other studies evaluated malignancies with different origin, both metastatic and primary. As shown in more studies, including ours [15], lymphomas show more strain and may alter the overall outcome.

The scoring systems are also very different in layout. Some use planimetry, which may be tedious or may necessitate specialized software and/or offline processing. Most of the scores define more than 50% of the node surface blue (i.e. hard) as cutoff criterion for malignancy. This approach does not take into account the fact that elastography may detect small (less than 50%) metastatic deposits into an otherwise normal node [24].

Finally, the reference method used for diagnosing malignancy varied from histology to cytology (FNAB), imaging methods or clinical outcome and follow-up.

Relative stiffness index or strain ratio: calculation and diagnostic value.

Most of real-time elastography scanners provide a means to compare the relative stiffness of two neighboring areas (fig 7).

Lyshchik et al [6] calculated the muscle – to-lymph node strain ratio. The ROIs were placed on the same image, over the lymph node and over the surrounding neck

Fig 7. Calculating lymph node to muscle strain ratio.

muscles. The ROI sizes ranged from 5 – 10 mm. The depth difference of the two ROIs never exceeded 10 mm, in order to avoid the effect of stress decay with depth.

Zhang et al [16] measured the strain ration between the surrounding tissue and the lymph node. However, there was no specification on what surrounding tissue referred to. ROI area and position were also not quantified. Other groups [9,18] calculated the muscle-to-lymph node strain ratio without referring to ROI size or relative position.

Taylor et al [22] compared the lymph node and the (non-specified) background tissue while Choi et al [23] calculated the strain ratio of the lymph node and subcutaneous fat tissue.

The cutoff values and diagnostic benefit of the strain ration is summarized in table VII.

Table VII. Diagnostic value of strain ratio for the SE diagnosis of malignancy in superficial lymph nodes.

Author Reference Year	Strain index	SE	SP	VVP	NPV	OA	AUROC	Reference standard	Obs.
Lyshchik [6] 2007	> 1,5	85	98	96	90	92	–	histology	– experimental setting, commercially unavailable – only thyroid and hypopharyngeal metastases
Zhang [16] 2009	> 2,395	78,41	98,51				0,915	FNAB, imaging, follow-up	– mixture of metastatic sources, and lymphoma
Tan [9] 2010	>1,5	92,8	53,4	70,7	86,1	75		histology	Mixture of nonmalignant conditions, including tuberculosis and primary and secondary malignancies.
Taylor [22] 2011	< 0,65	100	48	58	100				Axilla, breast cancer
Choi [23] 2011	>2,3	82,8	56,3						Axilla, breast cancer
Ying [10] 2012	Meta-analysis	88	81				0,91		

The fluctuation in the data has many explanations. Some of them are common to the already discussed sources of variation encountered in ES nodal assessment (technological implementation, sources of metastases, reference standard for diagnosis). Others are due to the still nonstandardized measurement technique of SR.

Most machines compute strain ratio as B/A where B is the strain of normal, reference tissue and A is the strain of the investigated lymph node. This implies that nodal strain should be measured first (A) and reference tissue strain, second (B). As malignant nodes display little or almost no strain as compared to surrounding reference tissues, as expected, the ratio is greater than one. However, if for any reason, such as measuring reference tissue strain first, the ratio is computed as A/B , the value will be subunitary, as in the paper of Taylor et al [22]. In effect, if A/B is less than 0, 65 then B/A will be greater than 1.53, which is in accordance with some of the other papers.

Another explanation of the variation lies in the tissue used for reference. Intuitively, fat displays more strain than muscle, therefore it is to be expected that, with the same malignant node to be explored, strain ratio using fat for reference (as in the paper of Choi et al [23]) will have a greater value than strain ratio computed with muscle as the reference tissue, as in the papers of Lyshchik et al [6] or Tan et al [9].

There are still nonquantified issues concerning strain ratio in most papers. Box size, shape and distance from the transducer may represent factors that induce variation. Intra- and interobserver variability are poorly studied and so is inter-image variability for the same case. Variation associated with manufacturer implementation of the technique is not really known. There is no clear answer to how to measure strain ratio in a partially involved node. Different cellularity of the malignant nodes may also induce different elastic behavior [16].

Shear-wave elastography is a rather novel technique that allows for absolute measurement of stiffness in kilopascal units. Bhatia et al [25] found that, in the diagnosis benign versus malignant nodes, the value of 30.1 kPa has the accuracy 61.8%, with 41.9% sensitivity, and 100% specificity. Another group [26] found that mean and maximal stiffness measurement allows for differentiation of malignant lymph nodes in breast cancer patients assessed for sentinel nodes. With only few papers published on this topic yet, it is not clear what underlies malignant nodal heterogeneity as observed in this technique. Shear wave elastography seems to be rather suited for the diagnosis of a subset of nodes and not for screening purposes [25].

In conclusion, elastography with its various technical implementations seems to be a promising tool that complements standard ultrasonography for the diagnosis

of malignant superficial lymph nodes. Hardness on more than 50% of the node surface or $SR > 1.5$ are fair to good indicators of malignancy. Much work is still needed both to fully understand the various appearance of disease and to standardize the application.

References

1. Ahuja AT, Ying M, Ho SY, et al. Ultrasound of malignant cervical lymph nodes. *Cancer Imaging* 2008; 8: 48-56.
2. Neal CH, Daly CP, Nees AV, Helvie MA. Can preoperative axillary US help exclude N2 and N3 metastatic breast cancer? *Radiology* 2010; 257: 335-341.
3. Landry CS, Grubbs EG, Busaidy NL, et al. Cystic lymph nodes in the lateral neck as indicators of metastatic papillary thyroid cancer. *Endocr Pract* 2011; 17: 240-244.
4. Choi JS, Kim J, Kwak JY, Kim MJ, Chang HS, Kim EK. Preoperative staging of papillary thyroid carcinoma: comparison of ultrasound imaging and CT. *AJR Am J Roentgenol* 2009; 193:871-878.
5. Dudea SM, Lenghel M, Botar-Jid C, Vasilescu D, Duma M. Ultrasonography of superficial lymph nodes: benign vs. malignant. *Med Ultrason* 2012; 14: 294-306.
6. Lyshchik A, Higashi T, Asato R, et al. Cervical lymph node metastases: diagnosis at sonoelastography - initial experience. *Radiology* 2007; 243: 258-267.
7. Alam F, Naito K, Horiguchi J, Fukuda H, Tachikake T, Ito K. Accuracy of sonographic elastography in the differential diagnosis of enlarged cervical lymph nodes: comparison with conventional B-mode sonography. *AJR Am J Roentgenol* 2008; 191: 604-610.
8. Bhatia KS, Cho CC, Yuen YH, Rasalkar DD, King AD, Ahuja AT. Real-time qualitative ultrasound elastography of cervical lymph nodes in routine clinical practice: interobserver agreement and correlation with malignancy. *Ultrasound Med Biol* 2010; 36: 1990-1997.
9. Tan R, Xiao Y, He Q. Ultrasound elastography: Its potential role in assessment of cervical lymphadenopathy. *Acad Radiol* 2010; 17: 849-855.
10. Ying L, Hou Y, Zheng HM, Lin X, Xie ZL, Hu YP. Real-time elastography for the differentiation of benign and malignant superficial lymph nodes: a meta-analysis. *Eur J Radiol* 2012;81:2576-2584.
11. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrason Imaging* 1991; 13: 111-134.
12. Shiina T, Nitta N, Ueno E, Bamber JC. Real time tissue elasticity imaging using the combined autocorrelation method. *J Med Ultrason* 2002; 29: 119-128.
13. Ciurea AI, Bolboacă SD, Ciortea CA, Botar-Jid C, Dudea SM. The influence of technical factors on sonoelastographic assessment of solid breast nodules. *Ultraschall Med* 2011; 32: S27-34.
14. Chiorean AR, Duma MM, Dudea SM, et al. Typical and unusual sonoelastographic patterns of breast cystic lesions:

- impact on BI-RADS classification. *Ultraschall Med* 2012; 33: E138–E144.
15. Lenghel LM, Bolboacă SD, Botar-Jid C, Băciuț G, Dudea SM. The value of a new score for sonoelastographic differentiation between benign and malignant cervical lymph nodes. *Med Ultrason* 2012; 14: 271-277.
  16. Zhang Y, Lv Q, Yin Y, et al. The value of ultrasound elastography in differential diagnosis of superficial lymph nodes. *Front Med China* 2009; 3: 368–374.
  17. Wojcinski S, Dupont J, Schmidt W, Cassel M, Hillemanns P. Real-time ultrasound elastography in 180 axillary lymph nodes: elasticity distribution in healthy lymph nodes and prediction of breast cancer metastases. *BMC Med Imaging* 2012; 12 :35.
  18. Teng DK, Wang H, Lin YQ, Sui GQ, Guo F, Sun LN. Value of ultrasound elastography in assessment of enlarged cervical lymph nodes. *Asian Pac J Cancer Prev* 2012; 13: 2081–2085.
  19. Furukawa MK, Fujita Y, Kubota A, Furukawa M, Hanamura H. Diagnosis of cervical lymph node metastasis of head and neck squamous cell carcinoma - usefulness of Power Doppler ultrasonography and elastography. *Medix* 2007; Suppl: 20-23.
  20. Furukawa MK, Kubota A, Hanamura H, Furukawa M. Clinical application of real-time tissue elastography to head and neck cancer—evaluation of cervical lymph node metastasis with realtime tissue elastography. [abstract] *Nippon Jibiinkoka Gakkai Kaiho* 2007; 110: 503-505.
  21. Ishibashi N, Yamagata K, Sasaki H, et al. Real-time tissue elastography for the diagnosis of lymph node metastasis in oral squamous cell carcinoma. *Ultrasound Med Biol* 2012; 38: 389-395.
  22. Taylor K, O’Keeffe S, Britton PD, et al. Ultrasound elastography as an adjuvant to conventional ultrasound in the pre-operative assessment of axillary lymph nodes in suspected breast cancer: a pilot study. *Clin Radiol* 2011; 66: 1064-1071.
  23. Choi JJ, Kang BJ, Kim SH, et al. Role of sonographic elastography in the differential diagnosis of axillary lymph nodes in breast cancer. *J Ultrasound Med* 2011; 30: 429-436.
  24. Aoyagi S, Izumi K, Hata H, Kawasaki H, Shimizu H. Usefulness of real-time tissue elastography for detecting lymph-node metastases in squamous cell carcinoma. *Clin Exp Dermatol* 2009; 34: e744-747.
  25. Bhatia KS, Cho CC, Tong CS, Yuen EH, Ahuja AT. Shear wave elasticity imaging of cervical lymph nodes. *Ultrasound Med Biol* 2012; 38: 195-201.
  26. Tourasse C, Dénier JF, Awada A, Gratadour AC, Nessah-Bousquet K, Gay J. Elastography in the assessment of sentinel lymph nodes prior to dissection. *Eur J Radiol* 2012; 81: 3154-3159.