CONTINUING EDUCATION PROGRAM: FOCUS...

Elastography of the thyroid

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KEYWORDS
Thyroid; Quasi-static elastography; Shear wave elastography; Cancer

Abstract Thyroid nodules are very common, while thyroid cancer is rare and has a very good prognosis. Thyroid nodule ultrasound characterization performed by experienced clinicians allows the selection of the tumours to be punctured and guiding fine needle aspiration (FNA). FNA provide cytology information able to differentiate benign tumours from cancer in approximately 80% of cases. However, it remains difficult to identify thyroid cancers with ultrasound imaging, as demonstrated by the very low rate of cancers detected in all of the carried out FNA (approximately 5%). As a majority of thyroid cancers are hard, the stiffness evaluation has become part of nodular characterization. Since 2005, elastography has been used for the evaluation of thyroid nodules; quasi-static elastography was the first technique available and used, at first, an external pressure induced by the probe, which was then replaced by carotid internal excitation allowing improvement in sensitivity. Semi-quantitative analysis allows comparison of tissue elasticities between tissue with elasticity anomalies and normal tissue and provides therefore useful analytic information. Shear wave elastography (SWE) provides a map of the elasticity in a region and allows stiffness quantification of lesions in kilopascals in order to reinforce the predictive value of malignancy. A tumour whose stiffness is greater than 65 kPa or for which the stiffness ratio is greater than 3.7 compared to surrounding healthy tissue is highly suspicious. SWE may enable the detection of malignant follicular tumours that currently escape detection by the ultrasound-guided ultrasound/aspiration cytology couple. Lymph node metastasis of papillary thyroid cancer can also be detected by elastography due to its increased stiffness.

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The frequency of thyroid nodules contrasts singularly with the frequency of thyroid cancer. In France, one in two women has at least one thyroid nodule, while in 2011, 6600 cancers were diagnosed, almost half of which were sub-centimetric cancers and 25% were demonstrated during histology (Source INCA 09 2012).

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The diagnosis of cancer is most often established during the ultrasound-guided cytological fine needle aspiration (FNA). It is therefore important that ultrasound be as precise as possible and the most capable of selecting the nodules to be punctured.

Thyroid nodule ultrasound imaging semiology has been enriched with time, thanks to technological evolutions and in particular thanks to the changes in practices. We know that the signs described in B-mode and Doppler imaging have low contributiveness when taken alone but increase in specificity and significance when they are combined [1]. The Thyroid Imaging Reporting and Data System classification (TI-RADS) inspired by the breast BI-RADS classification recently started allowing us to classify nodules according to ultrasound criteria and to determine a risk of malignancy (Table 1) [2].

However, ultrasound imaging criteria do not make it possible to formally identify thyroid cancers, as clearly shown by the incidence of malignant lesions identified by FNA (approximately 5%) [3].

The interpretation of FNA depends first on the quality of the sample(s) and then on the training of the pathologist. Even in experienced hands, 10% of smears are not contributory [1].

There is therefore a place for new diagnostic techniques. In view of the major role of ultrasound in thyroid exploration, ultrasound elastography should naturally take an increasingly large place to improve the characterization of nodules. Moreover, it has been integrated in the nodular classification, TI-RADS, as the eighth item.

Table 1  TI-RADS score (according to Dr Gilles Russ).

<table>
<thead>
<tr>
<th>TI-RADS score</th>
<th>Meaning</th>
<th>Risk of malignancy (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Normal exam</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Benign</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Very probably benign</td>
<td>0.25</td>
</tr>
<tr>
<td>4A</td>
<td>Low suspicion of malignancy</td>
<td>6</td>
</tr>
<tr>
<td>4B</td>
<td>High suspicion of malignancy</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>Practically certain malignancy</td>
<td>100</td>
</tr>
</tbody>
</table>

Advantages and limitations of the different techniques for the study of the thyroid

The discovery in the soft tissue of a stiffer zone has always been a source of suspicion. An increase of tissue stiffness is linked to a loss of its elasticity, i.e. its ability to deform then recover its initial form.

Elastography, by studying the deformability-stiffness couple, has the objective of representing this feeling of stiffness, or palpation. Generally, nodules appearing stiff when palpated or on elastography are suspicious.

Most malignant tumours are characterised by the composition of their abnormally firm stroma due to the presence of collagen and myo-fibroblasts. This is the desmoplastic transformation. This tumour stroma promotes the proliferation of malignant cells (and could even initiate them) [4]. However, certain benign fibrous tumours can be very stiff as well (histiocytio-fibromas, for example).

Thyroid ultrasound elastography could therefore make it possible to identify cancers with increased stiffness, such as papillary cancers. On the other hand, cancers with non-modified elasticities will not be detected, as is the case in most follicular cancers.

Quasi-static elastography was the first to be used. Initially, the compression was generated by the pressure applied on the ultrasound probe on the skin by the operator. Currently, the improvement in the sensitivity of very small tissue movement detection makes it possible to use the carotid pulsation to induce tissue deformation [5]. Colorimetric analysis is not always easy (Fig. 1). Semi-quantitative analysis provides numerical values that correspond to the deformation ratios. The machine calculates a ratio between the zones of interest (Regions Of Interest [ROI]) placed by the operator on the nodule and on the healthy tissue (Figs. 2 and 3). The calculation can thus be made using the rates of deformation of the structure ("strain rate") (Fig. 4).

Quasi-static elastography is available in linear transducers used for thyroid ultrasound examination in most companies with different acronyms ("Real-Time Elastography or RTE" for Hitachi, "ElaXto" for Esaote, "Real-time Elastography" for Toshiba, "strain-based elastography" for Philips US, "Ultrasound Elastography Imaging" for General
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Figure 2. Strain elastography. 2D colour map of stiffness. Right upper third nodule. Nodule is softer than the parenchyma.

Electric, etc.). However, quasi-static thyroid elastography remains subject to several limitations:
• an area of healthy tissue must be placed in the elastography ROI, even if we do not use the ratio calculation. In fact, the repartition scale for “stiffness” is divided up from the lowest value to the highest value in an arbitrary manner in this ROI. If all of the tissue in the ROI is abnormal, the nodule stiffness varies with the obtained data. This is a challenge especially in the case of a nodule developed as part of an autoimmune thyroid disease [6];
• the impossibility of evaluating stiffness or performing semi-quantitative analysis in certain cases (toto-lobar nodule, nodule in residual tissue in the central compartment);
• the difficulties in evaluating the intensity of the strain constraint in the studied region.

To overcome these limitations, a new technique elastography, technique based on shear wave has been developed; Shear wave elastography (Aixplorer®, Supersonic Imagine and SWV ARFI, Siemens) provides a great deal of precision and is perfectly suited to the study of this superficial gland [7] as it displays a map that represents the local elasticity values of tissues in real-time (for Supersonic Imagine only) and in a quantitative manner without any compression of the organ.

Figure 4. Strain elastography. Semi-quantitative technique. Medio-lobar nodule. Nodule twice as hard as the parenchyma (Toshiba).

However, certain difficulties remain for the study of pre-tracheal nodules (pressure artefacts on the isthmus, standardization of ROIs, visco-elastic properties of tissues).

The practical examination of the thyroid with elastography

Elastography can be integrated into the conventional ultrasound examination. Each characterized (and described on the dedicated diagram) nodule receives two acquisitions of elastographic data. The examination is completely painless for the patient. The patient may be asked to hold his breath for a very short period. No additional French health care codification is provided for to date, unlike the codification provided for in the evaluation of hepatic fibrosis.

Quasi-static elastography

The ultrasound probe is placed in front of the nodule with interposition gel (or water if FNA is being carried out during the same act). The beating of the carotid artery generates a sufficient deformation to create a qualitative map image in the region of interest. The duration of the examination is increased in a minimal manner for this additional elastographic acquisition (a few minutes).

In case of a semi-quantitative study, the examination of image loops thanks to quantification software increases the operator time significantly. It can be carried out using the ultrasound machine or on an off-line quantification station. This study can be deferred.

Shear wave elastography (Aixplorer)

The elastography image is overlaid on the B-Mode image. The elastography acquisition box is positioned on the thyroid, with care being taken not to expert pressure on the probe. It provides a real-time map of elasticity. The ROIs are positioned in the nodule and in the healthy surrounding tissue (Fig. 5). For each of these ROIs, the software instantly calculates the mean, minimum and maximum stiffness as well as the standard deviation, which increases with increasing tissue elasticity heterogeneity. When two ROIs
are positioned, the system also provides an elasticity ratio between the two ROIs (Fig. 5). It is important to move a small ROI in the nodule in order to detect the stiffer zones and to position, if possible, the comparative ROI at the same depth. The observation of a very low value (around 0) points to a liquid lesion (sometimes with a misleading eechostructure in B-mode) (Fig. 6).

Setting principles:
• the setting of the elastography scale is fundamental. On the thyroid pre-setting, the maximum value is set at 180 kPa, which is too high. Under these conditions, the thyroid or lymph node tissue (generally 20 to 40 kPa) appears coded in a perfectly homogeneous manner with a colour code corresponding to a soft tissue (blue colour code), even in the presence of a nodule with increased stiffness [7]. The maximum value of the elastography scale must absolutely be lowered to around 80 kPa (Fig. 7);
• it is important to check that the intensity of the signal is sufficient to conduct the examination. In case of a weak signal, there is either a coding defect (absence of coloured pixels) or a deep signal that is uniformly low (Fig. 8). The elasticity values are less than 2 kPa. In this case, the “pen” pre-setting must be used for penetration or the transducer changed by opting for a linear probe with lower frequencies (SL10-2);
• the gain can be increased until the elastographic noise appears (Fig. 9);
• the trachea can generate an artefact that makes the analysis of isthmic nodules delicate (Fig. 10);
• the pressure on the probe must be minimized in order to avoid generating a superficial artefact of increased stiffness and variations in stiffness in homogeneous tissues (Fig. 11);
• the ROIs can be large in diameter as long as the standard deviation remains low (Fig. 12).
The study of peri-tumoural stiffness is not a determining criterion (unlike in breast pathology).

Inter- and intra-operator reproducibility in quasi-static elastography is acceptable, with a correlation coefficient ranging from 0.73 to 0.79 for inter-observer variability and between 0.73 and 0.84 for intra-observer variability [8]. Shear wave elastography appears more reproducible in our experience, but there are no publications evaluating this parameter in thyroid pathology to our knowledge.

The basics of interpretation

In quasi-static elastography

We visually compare the differences in colour between the nodular zones and the surrounding healthy tissue. To do this, we use scores established by Rago [9] or Astéria [10]. The lesions appearing with low stiffness in a complete or predominantly homogeneous manner are considered to be benign, while stiff lesions are considered to be malignant.
Figure 13. Semi-quantitative strain technique: thyroid cancer: high stiffness ratio between the nodule and the healthy tissue.

Figure 14. Shear wave elastography. Thyroid cancer. Maximum stiffness of 162 kPa.

Summary of the literature

In 2005, Lyshchik studied ex vivo the stiffness of the thyroid and the different thyroid tumours and found a very significant difference between papillary cancer (63.3 ± 36.8 kPa) and healthy tissue (10 ± 4.2 kPa) [17]. The ratio for benign tumours was less than 2.4 and was well above 5 for papillary cancers [8,9]. It was the first of a long series of studies carried out in quasi-static elastography with manual compression, then carotid strain. All of these studies showed a high prevalence of cancer in tumours deemed to be stiff and a high prevalence of benign tumours in those deemed to be soft [9,10,18–20]. We found similar results in quasi-static elastography by studying deformations in a semi-quantitative manner using the Q-Lab software (Philips US, Bothell, WA, USA) [21]. The calculation of the ratio of the deformation slope between the nodule and the adjacent healthy thyroid shows significant differences depending on the nature of the lesion (Fig. 17). All cancers diagnosed in cytology with histological confirmation (three papillary cancers, one medullar cancer) had a stiffness index significantly higher than that of benign tumours (Fig. 5).

In 2010, the meta-analysis carried out by Bojunga et al. concerned 639 studied nodules. Quasi-static elastography has a sensitivity of 92% and a specificity of 90% for the diagnosis of thyroid cancer (Fig. 18) [22]. However, there was an important selection bias, since the prevalence of cancer was 24%, which is very different from that of a normal ultrasound practice.
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Two more recent studies also used semi-quantitative parameters. The study by Cantisani et al. concerned 97 patients referred for thyroid surgery [11]. An elasticity ratio greater than 2 made it possible to obtain the following performances: sensitivity of 97.3%, specificity of 91.7%, positive predictive value (PPV) of 87.8%, negative predictive value (NPV) of 98.2%. Elastography was more sensitive and specific than all of the other ultrasound signs. The study by Vorlander et al. concerned a larger number of patients (309), and found a NPV of 100% for a ratio of 3.2 and a PPV of 42% for a ratio of 6.7 [23].

Shear wave elastography finds similar results with an increase in shear wave speed within malignant lesions, which reflects an increase in their stiffness. The number of publications using this technique is limited and likely explains the still discordant character of its performance and the difficulty in reporting a threshold for the diagnosis of thyroid cancer. Two articles report shear wave elastography performances. The study by Sebag et al. involved 93 patients and 39 controlled subjects (i.e. 146 nodules, 21 of which were cancers) [24]. A threshold value of 65 kPa determined to maximize the PPV yielded a sensitivity of 85.2% and a specificity of 93.9%. The ultrasound alone score had mediocre sensibility of 51.9% (with a specificity of 97%), while the combination ultrasound score + elastography had a sensibility of 81.5% and a specificity of 97%. These results were confirmed by the second study carried out in 148 patients by this group and published in 2012 [13] with a threshold of 66 kPa and a sensitivity of 97% with a NPV of 99% in 297 nodules (35 of which were cancers). The article by Bhatia et al. concerned 74 patients with 17 cancers, 13 of which were papillary [25]. With a threshold of 34.5 kPa, the sensibility and specificity for the detection of cancer were 76.9% and 71.1%, respectively. For benign lesions, the size was correlated with stiffness (P < 0.01).

Thyroid elastography using the ARFI technique was also reported by two recent publications. The Bojunga et al. study concerned 158 nodules of more than 5 mm in 138 patients (21 of which were cancers), studies that used both quasi-static elastography and the ARFI method [15]. The median shear wave speed was 1.76 m/s, 1.90 m/s, and 2.69 m/s for healthy thyroid tissue, benign nodules and cancers, respectively. There was a statistically significant difference between cancers and healthy tissue or benign nodules. On the other hand, diagnostic precision was not significantly different between the two elastography techniques, and the combination of the two did not make it possible to improve the results. The Friedrich-Rust study concerned 66 nodules in 55 patients, including three papillary carcinomas, and used quasi-static elastography and ARFI [26]. The median shear wave speed in the normal thyroid parenchyma was 1.98 m/s (varying between 1.2 and 3.6 m/s) and was not different from that of benign nodular lesions, which was 2.02 m/s (varying between 0.92 and 3.97 m/s). For the three cancers, the median value was 4.3 m/s with a minimum of 2.4 m/s and a maximum of 4.5 m/s.

The true difficulty of thyroid elastography comes from follicular carcinomas, which can be of low stiffness and not different from that of benign lesions [15]. The study by Lippolis et al. concerned follicular lesions studied pre-operatively in quasi-static elastography (102 patients with

Figure 17. Semi-quantitative study [15]. The cancers are significantly harder than the other nodules.

Figure 18. Meta-analysis by Bojunga [15]. Sensibility and specificity in eight studies taking histology as the gold standard.
undetermined cytology, with 64 follicular adenomas, 32 papillary cancers, four follicular carcinomas and two hyperplastic nodules upon postoperative histology [27]. The lesions were classified according to a scale in four scores, and the information provided by quasi-static elastography was negligible, since the PPV was 34% and the NPV was 50%.

Information provided by elastography for the study of thyroid pathology

Thyroid elastography makes it possible to improve the positive predictive value (PPV) and the negative predictive value (NPV) of malignancy obtained from conventional ultrasound studies [11,28]. Elastography must therefore be integrated as a parameter of the ultrasound classification of the nodule, as the French Endocrinology Society specified in its recent “Consensus on the treatment of thyroid nodules”. It cannot replace it in any case. In view of recent publications, it seems that the increase in PPV and NPV would be a great asset in particular for teams that do not have much expertise in nodular characterisation. When the two scores are high with the conventional imaging nodular characterisation parameters, the information provided by elastography is less important [29,30].

Shear wave elastography makes it possible to objectively quantify tissue stiffness by providing a numerical value that varies between 10 and 40 kPa for healthy thyroid tissue. Several studies proposed this measurement for the characterisation of non-nodular thyroid diseases (Fig. 19) [31,32].

Elastography helps characterising of certain structures, like post-thyroidectomy residual tissue in the central compartment, thyroiditis pseudo-nodules or cysts with thick contents that appear to be a hypoechoicenic solid nodule.

Elastography can also be useful for in the investigation of cervical adenopathy. In quasi-static elastography, metastatic thyroid adenopathy has a very different appearance from that of a normal lymph node [33] (Fig. 20). In the absence of comparative tissue, measurement of the ratio is impossible. Shear wave elastography seems to be easier to interpret, as it does not require comparative healthy tissue. The first observations clearly show an increased stiffness for secondary lesions, which could of course improve the selection of targets and guidance for the realisation of

FNA (Fig. 21) [34]. In addition, the detection of liquid areas, which are very suggestive of papillary cancers, is improved, as they have very low stiffness close to 0.

Possibilities for the future and conclusion

With regard to ultrasound imaging, elastography is undoubtedly a major technological advance, probably the most important since the colour Doppler ultrasound was made available (1982). The anatomical characteristics of the thyroid (superficial organ) and the frequency of nodular pathology make it an ideal organ for this technique.

Static elastography has been proven its diagnostic relevance and is currently available from many constructors. The availability of semi-quantitative data (deformation ratio) could be an additional judgment criterion.

Shear wave elastography is becoming the reference technique. Prospective studies (on-going) will probably confirm it (as this was the case in the breast). Its use in conjunction with other imaging techniques is very promising, like 3D

Figure 19. Shear wave elastography. Riedel’s thyroiditis. Very high stiffness index. Stiffness ratio with the healthy tissue greater than 30.

Figure 20. Strain elastography. Normal lymph node and metastatic adenopathy.
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Disclosure of interest

Dr
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References


Figure 21. Shear wave elastography: metastatic lymph node. Stiffness index max over 180 kPa.

Figure 22. Shear wave elastography. Follicular tumour (indeterminate at Bethesda). Stiffness index max below 65 kPa and stiffness ratio with surrounding tissue of 1.


