Can Elastography Stretch Our Understanding of Thyroid Histomorphology?

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Understanding the etiology of nodular thyroid disease is a fundamental prerequisite for its subsequent eradication (1–3). For this complex disorder, where the phenotypic presentation is based on an ill-defined interplay between genetic and environmental factors (3, 4), overwhelming evidence points at the amount of tobacco smoking (positively correlated) and decreasing iodine intake (negatively correlated) being the most important modifiable environmental triggers (3, 5, 6). Based on this, it is no surprise that the epidemiology and the phenotypic presentation vary with the population in focus. In a very simplified manner, at least at the level of the individual seeking medical care, the relative risk of harboring thyroid malignancy in a thyroid nodule, although still much lower than the likelihood of a benign disorder, is highest in an iodine-replete, nonsmoking individual. This is so because such individuals have a lower risk of having colloid goiter. It follows that the physician’s individualized risk assessment is probably a major determinant for the huge variation in the expert opinion regarding the diagnostic and therapeutic management of nodular thyroid disease, whether uni- or multinodular (1, 3).

For diagnostic purposes, guidelines generally recommend the use of functional and morphological characterization using serum TSH for the former and a combination of clinical examination, diagnostic imaging, and fine-needle aspiration cytology (FNAC) for the latter (7). Using such a strategy combined with serum calcitonin to rule out the approximately 1% risk of medullary thyroid cancer, it is generally believed that the chance of overlooking thyroid malignancy can be reduced to less than 1% in the 60–70% of individuals who have a benign FNAC (7). The remaining 30–40% have thyroid malignancy or insufficient or indeterminate FNAC. These figures are based on a number of criteria for obtaining and analyzing the cytology material, as well as on the obvious disregard of a benign FNAC in the face of certain clinical (e.g. family history of thyroid malignancy, hard and/or rapidly growing nodule, signs of invasive growth, and regional lymphadenopathy, to mention but a few) or serological (elevated calcitonin) markers (7, 8).

It is generally believed that ultrasound (US) criteria such as hypoechogenicity, the lack of a complete halo surrounding the nodule, microcalcifications, and marked intranodular and absent or slight perinodular vascularization using Doppler-flow (type III flow) are helpful in targeting nodules at the highest risk of harboring thyroid malignancy (7, 8). Used in a number of combinations, each characteristic increases the sensitivity but lacks adequate specificity for reliably diagnosing thyroid malignancy. During the last few years, a novel technology based on the elastic property of the tissue, US elastography (USE), has been added to the diagnostic armamentarium. The technology involves placing the probe and applying a uniform and slight pressure on the neck. A box, covering the target nodule and the immediate surrounding normal tissue, is highlighted on the scan image. Two US images, before and after tissue compression, are obtained. A dedicated software tracks the tissue displacement and displays this using a color scale ranging from red (highest elasticity corresponding to lowest risk of malignancy) over green (intermediate elasticity) to blue (lowest elasticity and correspondingly highest risk of malignancy).

Although available for about two decades, USE was first evaluated in the context of the thyroid by Lyshchik et al. (9) in 2005. Since then, a number of studies have evaluated this technique (10–16). They uniformly suggest that USE increases the ability to discriminate between benign and malignant nodules. Based on these eight studies (9–

Abbreviations: FNAC, Fine-needle aspiration cytology; SWE, shear wave elastography; US, ultrasound; USE, US elastography.
16), including a total of 639 thyroid nodules, Bojunga et al. (17) recently published a meta-analysis. Some background information is valuable before attempting to interpret this meta-analysis. On average, the studies were small, with less than 100 patients in each (530 in all). These patients had a total of 655 nodules, of which 639 could be analyzed with USE, suggesting that the vast majority of patients had a solitary nodule. We do not know exactly which patients were disqualified from participation, but the fact that nearly all studies were performed in European patients, where the majority of patients who have thyroid nodules have multinodular thyroid disease (1), gives an indication of considerable preselection. In general, most patients with coarse calcifications also seem to have been excluded. The fact that at least 153 (those with surgical confirmation) of 639 nodules (24%) were malignant again indicates preselection because in unselected consecutive nodule patients this would at most be 5–10%. In fact, in our own material it is less than 3% (18).

Another shortcoming is the availability of a “gold standard” (surgical diagnosis) in only 381 of the 639 (59.6%) nodules, whereas the rest had a surrogate definitive diagnosis based on FNAC. The fact that all nodules (98, 100, and 100%, respectively) in three of the eight studies were operated (9, 10, 15) must be interpreted as another indication of preselection of individuals for USE. Any opinion on the extent to which these factors potentially influence the interpretation of the data on which the meta-analysis is based would be speculative. However, the results cast a shadow over the degree to which generalization to a broader thyroid nodule population is permissible. Having said this, the authors (17) report a sensitivity of 92% [95% confidence interval (CI), 88–96%] and a specificity of 90% (95% CI, 85–95%) for the diagnosis of thyroid malignancy. Although a significant heterogeneity was reported for the specificities of the studies, this was not the case for the sensitivities. Overall, of the 153 final thyroid malignancies, 16 were overlooked by USE. Subdividing these according to phenotype, they accounted for four of the nine follicular carcinomas (44%), 10 of the 135 papillary carcinomas (7%), and both of the poorly differentiated metastatic adenocarcinomas (17).

The optimistic tone of the above meta-analysis could well lead to a decreased likelihood of having less favorable USE data published in the future. In this light, the recent study by experienced investigators (19) demonstrating a sensitivity of 90% (95% CI, 59–100%) but a specificity of only 50% (95% CI, 33–67%) for predicting malignancy deserves attention. Additionally, this study focused on the impact of the USE pattern cutoff (scores 1–5) for the subsequent variation in sensitivity and specificity data. Following up on this, Park et al. (20), while finding significant concordance among observers (not surprising since they were looking at the same variable) for a number of the usual US thyroid nodule characteristics, determined that this could be demonstrated neither for echogenicity nor for elastography. Because the latter two characteristics are suggested to be major determinants in the selection of which nodules to biopsy, their findings are worrying.

In this issue of JCEM, two papers offer novel and valuable extension of the use of USE (21, 22). The assessment of tissue elasticity can be derived from shear wave propagation speed, available with the newest generation of US machines. A color-coded image is displayed, showing softer tissue in blue and stiffer tissue in red. The quantitative information is expressed as an elasticity index and expressed in kilo-Pascals on a continuous scale and without applying pressure (22). Applying this so-called shear wave elastography (SWE), Sebag et al. (22) in 93 patients (146 nodules, of which 29 corresponding to 17.7% were malignant) and 39 controls compared the predictive value of SWE and the well-known US parameters with histology. The SWE technology offers a quantitative measure of elasticity and not the semiquantitative three to five elasticity classes reported previously (10–16). It is, therefore, considered less user-dependent, although the authors provide no clear-cut data substantiating this, such as observer variation. The fact that sensitivity for detecting malignancy, compared with US alone, rose from 51.9% (95% CI, 33.1–70.7%) to 81.5% (95% CI, 66.9–96.1%) with an unaltered high specificity of 97% when using SWE is intriguing (22).

Whether one uses one or the other algorithm, all thyroid nodule guidelines recommend the use of FNAC in thyroid nodule patients. There is also universal agreement on recommending diagnostic operation in the majority of patients with thyroid nodules and nondiagnostic or indeterminate FNAC on repeat aspiration (7). Almost independent of organization, with just small variations, on average around 30% of FNACs are either nondiagnostic or indeterminate. In view of this, despite the shortcomings mentioned earlier and the lack of a randomized design, the study of Rago et al. (21) merits attention. In this very group of patients (176 patients with a total of 195 nodules, of which 142 were indeterminate and 53 nondiagnostic), the value of USE was evaluated. Elasticity was scored semiquantitatively from 1–3, according to decreasing elasticity and increasing risk of malignancy. In indeterminate lesions, combining the scores 2 and 3, USE had a sensitivity of 96.8% and a specificity of 91.8% for predicting malignancy. A score of 1 (high elasticity) was only assigned to one of 31 carcinomas. In nondiagnostic lesions, again combining scores 2 and 3, USE had a sensitivity of 87.5% and a specificity of 86.7% for predicting malignancy. A score of 1 was only assigned to one of eight carcinomas.
Thus, overall, two patients were assigned a score potentially leading to a false-negative benign diagnosis.

None of the studies on USE adequately discuss some issues that hamper calculation of “true” sensitivities and specificities for diagnosing thyroid malignancy. Small sample sizes, inadequate account of selection criteria, unclear definition of what constitutes a consecutive group of patients, focus on patients with solitary nodules, and lack of surgical confirmation in the majority hinder to some extent wider ranging conclusions at present. The use of USE in multinodular goiter or in patients with previous surgery or radiiodine therapy merits attention. What is the role of USE in the management of micropapillary carcinomas? Can the technology aid us in the management of postion emission tomography/computed tomography-positive incidental thyroid tumors? Ideally, studies are needed that clarify the added cost, the psychosocial burden, and whether the information leads to improved quality of life. Most likely, these and other relevant questions are already under study.

Accepting that a definitive answer to the question posed in the title cannot yet be answered, the data offered (17, 21, 22) hold promise for a further narrowing of the diagnostic gray zone and consequently a broadening of the therapeutic arsenal for patients with indeterminate or nondiagnostic thyroid cytology. Were this to lead to a broader acceptance of offering nonsurgical therapy—such as radioiodine or percutaneous thermal ablation—to patients with benign thyroid nodules (1, 7, 8) and a higher degree of adherence with guidelines for thyroid nodule management (7), this would by no means be a trivial achievement. Finally, letting our ambitions be guided by what is on the horizon, it is my hope, on behalf of our patients, that the advent of a personal FNAC or sonographic molecular signature will render much of what we presently doing diagnostically, including USE, redundant in the near future.

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