EDITORIAL

Management of cytologically indeterminate thyroid nodules: *primum non nocere*

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by Kotecka-Blicharz et al

In the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Kotecka-Blicharz et al[1] explore the potential tools to refine the malignancy risk estimates of nodules with an indeterminate cytopathology in order to reduce the number of unnecessary "diagnostic" thyroid surgeries.

After the initial sonographic detection and risk stratification of thyroid nodules, fine-needle aspiration biopsy is the next step in the triage of such lesions. It offers guidance on subsequent management of most patients. Nevertheless, the decision-making process continues to be challenging in cases of follicular-patterned lesions, which are usually reported as indeterminate and assigned to Bethesda category III (atypia of undetermined significance [AUS] or follicular lesions of undetermined significance [FLUS]) or IV (follicular neoplasm or suspicious for a follicular or Hürthle cell neoplasm).[2] The reported malignancy rate in Bethesda category III is between 6% and 30%, and in Bethesda IV, between 10% and 40%. Surgical removal is usually advocated as a step towards histological diagnosis.[3] In most patients, lobectomy alone may be sufficient, as recommended by the clinical practice guidelines.[2] Total thyroidectomy should be reserved for patients with indeterminate nodules larger than 3 to 4 cm displaying progressive growth or worrisome features on ultrasound, and / or patients with clinical risk factors.

In the described Polish cohort,[1] many patients were overtreated; namely, not only were they referred for surgery, but surgical removal was carried out to an undue extent (ie, total thyroidectomy instead of lobectomy). This resulted in a significant rate of surgical complications, such as hypoparathyroidism or recurrent laryngeal nerve palsy as well as hypothyroidism itself. This is particularly unfortunate, given the low malignancy rate reported (6.7% and 11.3% in Bethesda categories III and IV, respectively).

In recent years, several authors proposed potential solutions to avoid unnecessary "diagnostic" surgeries and move toward a patient-tailored therapeutic approach; these include a sonographic restratification,[4] use of ancillary ultrasound techniques such as elastosonography[5] and contrast-enhanced ultrasound,[6] a thorough clinical history–taking, repeat biopsy, and molecular analysis.[7]

As Kotecka-Blicharz et al[1] pointed out, the role of thyroid ultrasound when reused after an indeterminate cytopathology to fine-tune risk estimates and management is controversial.[4,8] In their study, the ultrasound-based risk stratification systems appeared to play a role in predicting the actual risk of malignancy in Bethesda III nodules (with EU-TIRADS 3 category having a risk of less than 5%).[1] Conversely, patients' symptoms or clinical risk factors turned out not to be predictive of final diagnosis in the Polish series. The study is probably underpowered to detect the role of such variables. It is worth noting that the range of clinical features that come into play in estimating the risk of malignancy is quite broad and may hardly be weighed, as it is part of clinical reasoning not easy to outsource. Risk estimates can be modulated by a variety of factors related to a patient's medical history (eg, childhood irradiation or exposure to ionizing radiation from fallout, family history of thyroid cancer, or hereditary syndromes that include a predisposition to thyroid cancer) or demographic data. Older age has been reported to decrease the risk of malignancy,[9,10] and this finding is consistent with what was observed in the Polish population. Recently, the location of the nodule within the gland has been labeled as a risk factor of malignancy.[11]

According to the Bethesda System for Reporting Thyroid Cytopathology, repeat biopsy is a key step in the management of thyroid nodules classified as AUS or FLUS. Based on the results of a recent meta-analysis, a repeated cytological examination enables to reclassify two-thirds of the AUS / FLUS specimens into a more definite cytological category, with a benign call rate of

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nearly 50% and a negative predictive value greater than 96%.[12]

Molecular testing of the cytological samples is a newer approach, more and more popular in the United States. Some new molecular assays are being developed in Europe,[13,14] so their availability is going to increase on our continent, too. The tests developed for indeterminate nodules are based on 3 main molecular approaches: testing for somatic mutations, gene expression evaluation, and microRNA-based classifiers. The currently available assays are quite expensive (USD 2000–USD 5000), which limits their widespread application in the clinical practice. Low-cost approaches include only a limited number of genes (or only the hotspots of selected genes), with a good specificity and positive predictive value, but inescapable drops in the negative predictive value.[13] These data make the latter tests unsuitable in the context of avoiding diagnostic surgery. Furthermore, real-world performance and clinical usefulness vary across different contexts and populations, according to the pretest probability of malignancy (ie, the cancer prevalence in each cohort). In fact, while the sensitivity and specificity are intrinsic properties of the test, predictive values vary with the prevalence of malignancy: the positive predictive value increases and the negative predictive value decreases when cancer rate increases. To use these tools wisely, clinicians should be aware of the malignancy rate at their home institution.

Overall, clinicians should use their judgment when drawing up the diagnostic-therapeutic pathways for thyroid nodules. As a basic condition, asymptomatic adults should not be referred for thyroid ultrasound screening, as not all malignant nodules deserve to be discovered[15] and treated. Once thyroid nodules come to light and demand our attention, the application of ultrasound-based risk stratifications systems should guide any shift toward fine-needle aspiration biopsy. When an indeterminate cytology report comes out, the actual risk of malignancy should be estimated according to the local, institutional rate of malignancy for each Bethesda category (ie, class III and IV), the sonographic appearance, and the clinical presentation. If available, molecular assays are promising tools for scaling up testing and ensuring that appropriate patient management can be implemented without delay. If the global risk estimate is low, active surveillance may be a viable option. If the risk is high, the patient should be referred for surgery: in most of these cases, however, a diagnostic lobectomy will suffice.

ARTICLE INFORMATION

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