EDITORIAL

The dilemma of non-palpable thyroid nodules

THE DILEMMA OF NON-PALPABLE THYROID NODULES

The management of clinically apparent thyroid lesions has been sharply improved by fine needle aspiration biopsy (FNA), a safe office procedure established as the initial step in most diagnostic algorithms. FNA, when utilized with experienced cytopathology support, provides an inexpensive tool for diagnosing suspicious and malignant lesions with an accuracy approaching 95% (1). However, a new diagnostic dilemma is facing the evaluation of thyroid nodular disease. An epidemic of clinically unapparent lesions is detected by high-resolution US of the cervical region (performed for diffuse thyroid diseases, for aspecific symptoms or for the imaging of parathyroid glands, lymph nodes, salivary glands and carotid arteries) and is referred to endocrinologists regarding concerns about malignancy.

Since clinically unapparent thyroid lesions are on average shown by US in half of the adult female population (2) and only a small fraction of them is malignant, the question of whether non-palpable thyroid nodules should be assessed by FNA biopsy is a matter of controversy. Several papers over the last few years have evaluated the clinical significance and the proper management of small thyroid lesions (3) and, in this issue of the *Journal of Endocrinological Investigation*, Nabriski *et al.* (4) provide additional data about the prevalence of malignancy, as assessed by cytological evaluation, in non-palpable nodules.

To define the cost-effective criteria for identifying which non-palpable thyroid lesions should undergo FNA evaluation it seems necessary to consider three factors: 1) The prevalence of malignancy in non-palpable nodules; 2) The aggressive behavior of incidentally discovered thyroid cancers 3) The predictive value of malignancy of clinical and US features.

Prevalence of malignancy

The prevalence of cancer in the prospective studies (5) in non-palpable thyroid lesions is over 5%. Therefore, the prevalence of cancer in incidentally discovered nodules appears to be similar (or slightly higher) to that reported in palpable lesions (1).

Aggressive behavior

Due to the discrepancy between the low incidence of clinically apparent thyroid cancer (1.5% of all new cancers) and the elevated prevalence of occult thyroid cancer in autopsy study (3.6 to 22% of cases), opinions still vary about the clinical significance of thyroid microcarcinomas. In our experience, extracapsular growth is present in 35% and nodal involvement in 19.4% of small cancers (<15 mm) diagnosed by FNA, with no dimensional cut-off for invasive growth (5). These data are in accordance with previous surgical series that have shown the extracapsular or metastatic growth of occult thyroid carcinomas in 15-64% of cases (6, 7) and confirm the heterogeneity of biologic behavior of thyroid microcarcinomas.

Prediction of malignancy

Clinical criteria are ineffective in determining the risk of malignancy in non-palpable lesions (5). The risk of cancer is not significantly increased in solitary nodules as opposed to multinodular goiters, confirming that observed in palpable nodules (8). Malignancy is not significantly more frequent in nodules greater than 10 mm and fixing a dimensional cut-off of 10 or 15 mm for cancer risk seems unhelpful. Malignant lesions present no significant correlation with local symptoms, previous surgery for thyroid cancer or a positive family history (5). On the contrary, US and color-flow doppler findings are important predictive features of malignancy in non-palpable lesions (5, 9). The specificity for cancer of microcalcifications (86-95%), irregular or microlobulated margins (83-85%) or chaotic arrangement of intranodular vascular images (49-81%) is elevated but their predictive value is partially blunted by their low sensitivity (29-59%, 55-77% and 66-74%, respectively) (5, 10). Although no single US sign taken by itself is fully predictive for malignancy, the combination of hypoechoic appearance (defined as a decreased echogenicity similar to strap muscles) with the US patterns associated with malignancy (punctate hyperechoic *foci* with scanty or no posterior shadowing, tortuosity of intralesional vessel course, presence of small lobules or irregularity of the margins) (9, 10) effectively points out the subset of non-palpable thyroid nodules that are at a high risk of cancer (5, 10). Additional US patterns that are suspicious for malignancy are a taller than wider shape of the nodule (defined as a nodule greater in its antero-posterior than in its transverse dimension) and the presence of suspicious cervical adenopathy (enlarged lymph nodes with rounded appearance and absence of the hilum) (9). Thus, in addition to its role in early diagnosis of thyroid autoimmune diseases (12), US plays a fundamental role in the definition of suspicious micronodules.

A strategy for the evaluation of non-palpable thyroid nodules

Most lesions in the present epidemic of thyroid nodules assessable only by US are devoid of clinical significance. To avoid the unsound use of US-FNA on a great part of the general population it is necessary to define which thyroid lesions are at a high risk of malignancy on the basis of US features. Therefore, cytological evaluation should not be performed on nodules that are definitely under 10 mm (unless

specific clinical risk factors are present) and should be guided more by sonographic than dimensional criteria. Hypoechoic appearance in conjunction with intranodular vascular images, blurred margins, microcalcifications and a more tall than wide shape is able to identify most neoplastic lesions (87–93% of cases) allowing the restriction of the number of FNA procedures to about one third of non-palpable nodules (5). As US findings become highly predictive for cancer only when more than one suspicious feature is present in the same lesion, the specificity for malignancy of US evaluation increases at the expense of its sensitivity (10). Using these criteria, endocrinologists will probably miss a small percentage (6-15%) of the microcarcinomas under investigation, but the sparing of the great number of additional biopsies necessary to detect the few remaining microcarcinomas seems to be cost-effective (5). In the near future, contrast enhanced sonography will probably improve the predictive value of US evaluation (9), further decreasing the small number of non-palpable malignancies escaping FNA assessment.

In conclusion, US-guided FNA should be performed on all hypoechoic nodules over or just under 10 mm with irregular margins, intranodular vascular spots, a taller than wider shape or microcalcifications. The optimal follow-up of incidentally discovered thyroid lesions that do not meet the criteria proposed for US-FNA has not yet been established. However, it seems reasonable to follow-up non-palpable nodules without sonographic features at risk for malignancy by repeating a US and clinical evaluation after six months followed by one every year thereafter.

REFERENCES

1. Gharib H. Diagnosis of thyroid nodules by fine needle aspiration biopsy. Curr. Opin. Endocrinol. Diabetes 1996, *3:* 433-438.
2. Rago T., Chiovato L., Aghini-Lombardi F. *et al.* Non-palpable thyroid nodules in a borderline iodine-sufficient area: Detection by ultrasonography and follow-up. J. Endocrinol. Invest. 2001, *24:* 770-776.
3. Ross D.S. Nonpalpable thyroid nodules-managing and epidemic. J. Clin. Endocrinol. Metab. 2002, *87:* 1938-1940.
4. Nabriski D., Ness-Abramof R, Brosh T., Konen O. Shapiro M.S. Shenkman L. Clinical relevance of nonpalpable thyroid nodules as assessed by ultrasound-guided fine needle aspiration biopsy. J. Endocrinol. Invest. 2003, *26*: 61-64.
5. Papini E., Guglielmi R., Bianchini A. *et al.* Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-doppler features. J. Clin. Endocrinol. Metab. 2002, *87:* 1941-1946.
6. Sugino K., Ito K. Jr., Ozaki O., Mimura T., Iwasaki H., Ito K. Papillary microcarcinoma of the thyroid. J. Endocrinol. Invest. 1998, *21:* 445-448.
7. Braga M., Graf H., Ogata A., Batista J., Hakim N.C. Aggressive behavior of papillary microcarcinoma in a patient with Graves' disease initially presenting as a cystic neck mass. J. Endocrinol. Invest. 2002, *25:* 250-3.
8. Belfiore A., La Rosa G.L., La Porta G.A. *et al.* Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. Am. J. Med. 1992, *93:* 363-369.
9. Solbiati L., Osti V., Cova L., Tonolini M. Ultrasound of thyroid, parathyroid glands and neck lymph nodes. Eur. Radiol. 2001, *11:* 2411-2424.
10. Rago T., Vitti P., Chiovato L. *et al.* Role of conventional ultrasonography and color flow-foppler sonography in predicting malignancy in "cold" thyroid nodules. Eur. J. Endocrinol. 1998, *138:* 41-46.
11. Kim E.K., Park C.S., Chunh W.Y., Oh K.K., Kim D.I., Lee J.T., Yoo H.S. New sonographic criteria for recommending fine-needle aspiration biopsy of non-palpable solid nodules of the thyroid. Am. J. Roentgenol. 2002, *178*: 687-691.
12. Rago T., Chiovato L., Grasso L., Pinchera A., Vitti P. Thyroid ultrasonography as a tool for detecting thyroid autoimmune diseases and predicting dysfunction in apparently healthy subjects. J. Endocrinol. Invest. 2001, *24:* 763-769.

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