INVITED COMMENTARY

Ultrasonography in the evaluation of cold thyroid nodules

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In our catchment area of roughly 1 million inhabitants (tertiary referral centre) a diagnosis of thyroid malignancy is made in 20 patients each year. Only about 50% of these patients have a solitary cold thyroid nodule revealed on scintiscan. The total number of patients evaluated for a solitary thyroid nodule is 200 each year and because usually only 10 of these patients proves to have thyroid malignancy, it is generally believed that the risk of thyroid malignancy in a solitary nodule referred for diagnostic examination is approximately 2–5%. However, correctly performed epidemiological studies to substantiate this have not been undertaken.

As diagnosing the few malignant lesions has often been compared to 'looking for a needle in a haystack', thyroid surgery has been the treatment of choice in most patients in a number of centres (including ours) for a number of years. This has mainly been based on scepticism as to the reliability of fine-needle biopsy as a diagnostic criterion and, considering that the majority of patients have few or no complaints, has led to superfluous surgery in the vast majority of patients. It is therefore in the interest of both patients and society, not least for economic reasons, to achieve better selection of candidates for surgery.

It has generally been believed that diagnostic imaging could assist this aim, and imaging of the thyroid (anterior neck) has increasingly been used in the primary evaluation of the thyroid nodule. For a number of reasons ultrasonography (US) has evolved as the imaging modality most often used in most centres. In addition to its low cost, rapid investigation, the acquisition of dynamic pictures, the possibility of performing guided biopsies and punctures, its non-ionizing nature and easy accessibility, the technique allows determination of thyroid and nodule size, echo structure (diffuse, uni- or multinodular), echogenicity (iso-, hyper- or hypoechoic structures) and evaluation of adjoining neck structures. Indeed, a number of centres use US-guided biopsy as the initial step in the evaluation of the thyroid nodule, although this remains a matter of debate (1, 2).

Fujimoto *et al.*, in 1967, were the first to diagnose thyroid nodules using the new diagnostic tool of ultrasound (3). The first studies were performed with static B-mode scanners, reproducing only larger thyroid lesions (greater than 1 cm in diameter) in a static 'black-and-white' image. The rapid development of US

equipment during the past two decades has now made it possible to use high-frequency transducers with frequencies of 7–13 MHz reproducing real-time grey-scale pictures of even very small (2–3 mm) thyroid lesions. Thus high frequency US has now become an established imaging technique for the evaluation of structures in the neck.

Several studies have been designed in order to evaluate whether high-frequency US can be used in the differentiation of benign and malignant thyroid nodules. Parameters such as echogenicity, cystic degeneration, calcifications and the appearance of the margins (halo sign) have been tested (2, 4). A general finding – as also seen in the study by Rago *et al.* in this issue of *European Journal of Endocrinology* (5) – has been that there is no US pattern, alone or in combination with other techniques, that may be considered specific for thyroid cancer. The only reliable indicators of malignancy are invasive growth into surrounding structures, metastases to cervical lymph nodes, or both.

The introduction of colour Doppler (CD) a decade ago opened new fields in medicine by displaying the speed and direction of blood flow. CD encodes the frequency of pulsed Doppler signals by colour that is overlaid to B-mode US with its two-dimensional spatial information. Detection of velocities less than 1 cm/s in combination with an enhanced spatial resolution (high-frequency US) allows visualisation of very small vessels in the tissue. Tissue vascularisation in small areas such as nodular thyroid lesions can be assessed. However, the differential diagnosis of solid lesions in the thyroid requires a more specific description of CD, because each lesion may have a different content of vessels with different flow velocities.

Classification of thyroid nodules into three or four different groups on the basis of the flow distribution has been suggested by several authors (5, 6). However, to date no study has been able to show a specific flow pattern for malignancy. In the present study by Rago *et al.* (5), intranodular blood flow was found in about 67% of malignant nodules and in about 50% of the benign neoplastic nodules. In addition non-neoplastic nodules (adenomatous goitre) may also show an intranodular flow pattern (6). Although intranodular blood flow can be detected in a greater percentage of malignant nodules, the specificity and sensitivity data

seem to imply that at present little is gained by using CD in the evaluation of cold thyroid nodules. In this setting, the question should be asked, 'Did CD add any information to that obtained by US-guided Fine needle aspiration biopsy of the nodules?' We would guess the answer to be, 'No'.

A major improvement for detection of flow in malignant neovascularisation has recently been achieved by introduction of power Doppler (PD) US and US contrast agents. PD displays the strength of the Doppler signals in colour, omitting the other parameters of speed and direction as displayed by standard CD. PD can increase the CD-gain by 10–15 dB, resulting in an improved sensitivity for detection of colour flow (7).

With the rapid development of techniques (CD and PD) for colour flow mapping, the need for ideal US contrast agents has increased. Several different types of US contrast media are under development at present, enabling application of the technique to functional studies and, in the near future, therapeutic applications (8). In principle, encapsulated microbubbles – less than 10 µm in diameter – pass through the lung capillaries after i.v. injection of a microcrystal suspension (e.g. galactose). Because of the difference in acoustic properties between the gas-containing bubbles and the surrounding blood and plasma, the B-mode CD, and especially the PD, signals can be enhanced up to 25 dB. Thus, theoretically, the most sensitive US method for detection of small tumour vessels within malignant thyroid nodules is a combination of the use of PD and US contrast. However, large clinical series are still needed to evaluate the use of these new techniques in the differentiation of malignant and benign thyroid lesions.

US is a body imaging technique that is very operator-dependent. It is solely the operator's decision to choose an optimal setting for the US scanner, to select the anatomical area to be examined and to interpret the findings. One problem when mapping the flow in and around the thyroid is to obtain an objective quantification of the information displayed. The reproducibility of the US findings, especially when dealing with multiple parameters, remains to be evaluated. Neither Rago *et al.* (5) nor others have provided this.

Because there are non-surgical alternatives, at least for the reduction of thyroid nodule size, if not for nodule ablation (1, 9), and these will be increasingly used in the future, it is mandatory to improve the diagnostic examination of cold thyroid nodules. In view of the

a priori low risk of malignancy in thyroid nodules, it will demand a very large number of participants to determine whether various characteristics of US can be used as reliable predictors of malignancy. Ideally, adequate data for specificity and accuracy would demand investigation of an enormous number of consecutive subjects, all of whom subsequently underwent surgery to get a 'final diagnosis'. For a number of reasons, among them ethical considerations, such a study will never be performed.

We and others (2, 9) are convinced that at least 60–70% of cold solitary thyroid nodules can be classified as benign colloid nodules with a minimal risk of overlooking malignancy (<1%) on the basis of US-guided fine-needle biopsies. Awaiting better diagnostic predictors of the nature of thyroid nodules, it would be amiable to reach a consensus regarding the elimination of superfluous surgery in minimal-risk thyroid nodules. Should this be achieved, much would be gained.

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