

Editorial: Nonpalpable Thyroid Nodules—Managing an Epidemic

Prevalence of thyroid nodules

Thyroid nodules are extraordinarily common. The prevalence of palpable thyroid nodules in two non-biased population-based studies—Framingham, Massachusetts, and Wickham, England—was 4.2 and 3.2%, respectively (1, 2). In the Framingham study, the prevalence was 6.4% in women and 1.5% in men (1). The true prevalence of thyroid nodules, however, requires autopsy data. A 1955 study at the Mayo Clinic found thyroid nodules in 50.5% of 821 consecutive autopsies of patients with clinically normal thyroid glands (3). Because 7.4% of autopsies were excluded from analysis because of premortem thyroid disease, the true prevalence is slightly higher than half the population. Even in an unlikely group of patients to have thyroid nodules, men in the military aged 18–39 yr, the prevalence of thyroid nodules at autopsy was 13% (4).

Nonpalpable thyroid nodules detected by ultrasound

High-resolution thyroid ultrasonography has emerged as the most useful imaging modality for the thyroid gland (5). Using high-frequency transducers of 10–13 million cycles per second (MHz), nodules as small as 2 mm are readily detected. As technology improves, the haunting prospect that thyroid nodules could be imaged in over half the population is becoming a clinical reality. Using a 7.5-MHz transducer, a non-biased population-based study in Hyvinkaa, Finland, detected nodules in 27% of women and 15% of men (6). Using a 10-MHz transducer, a small study from California detected nodules in 67% of subjects (72% of women and 41% of men) (7). Two studies of patients having neck ultrasonography using a 10-MHz transducer for evaluation of hyperparathyroidism found thyroid nodules in 40–46% of patients (8, 9). And 48% of patients who present with a palpable nodule have an additional nodule(s) detected by ultrasound (10).

Thyroid incidentalomas, an emerging epidemic

Referrals to endocrinologists for incidentally discovered thyroid nodules have become increasingly common. Thyroid nodules may be noted on chest or neck computed tomography or magnetic resonance imaging scans obtained for a myriad of reasons unrelated to thyroid pathology. Doppler assessment of the carotid arteries, and positron emission tomography imaging may also reveal nodular thyroid disease, as does neck ultrasonography obtained to image parathyroids, cervical lymph nodes, or salivary glands. Abnormal imaging studies suggesting thyroid pathology are

almost invariably followed by ultrasonography of the thyroid.

Endocrinologists themselves are using ultrasonography more frequently. A recent study suggested that ultrasonography would alter the clinical management of nodular thyroid disease in 63% of patients (11). A 1999 survey of members of the American Thyroid Association (ATA) found that only 34% would order an ultrasound to evaluate a patient with a solitary thyroid nodule compared with 80% of the members of the European Thyroid Association (12). A 2002 survey of ATA members found that 59% would order an ultrasound to evaluate a patient with nontoxic multinodular goiter compared with 84% of the members of the European Thyroid Association (13). One can speculate that the increased use of ultrasonography in the later study by ATA members reflects more than the difference in the clinical scenario (uninodular *vs.* multinodular goiter). As endocrine practices obtain ultrasound equipment for their own clinics, both for diagnosis and to perform ultrasound-guided needle aspirates, sonography is becoming an extension of the thyroid physical examination.

Incidence and prevalence of clinically apparent thyroid cancer

Unless a nonpalpable thyroid nodule is causing thyrotoxicosis or is large enough to be symptomatic, its significance is limited to the possibility that it represents a thyroid malignancy. Because many thyroid incidentalomas are discovered during metastatic evaluations of patients with other malignancies, the nature of nonpalpable thyroid nodules can be a source of considerable anxiety for individual patients. Thyroid cancer, however, is an uncommon malignancy. The American Cancer Society estimates that there were 19,500 new cases in 2001 (14,900 in women and 4,600 in men), representing only 1.5% of all new cancers. Death from thyroid cancer is even less common, with an estimated incidence of 1,300 deaths in 2001 representing only 0.23% of all cancer deaths. The Surveillance, Epidemiology, and End Results (SEER) program of The National Cancer Institute estimates the prevalence of thyroid cancer as 204,000 to 233,000 patients in the United States, which represents less than 0.1% of the population.

Occult thyroid cancer

Although clinically apparent thyroid cancer is relatively uncommon, clinically inapparent or occult thyroid cancer is quite common. Most define an occult thyroid cancer as a lesion under 10–15 mm that is an unexpected and incidental finding during surgery or autopsy. The prevalence of occult thyroid cancer at autopsy in the United States has varied from 0.45–13% and averages 3.6% (14). Rates as high as 36%

Abbreviations: ATA, American Thyroid Association; FNA, fine-needle aspiration.

have been reported from some countries. Variability in prevalence figures may partly reflect the methods used to detect occult cancers. In one Spanish autopsy study, the prevalence was 5.3% for visible lesions, but when the entire gland was submitted for histological examination the prevalence increased to 22%, including occult lesions measuring only 0.07–1.8 mm (15).

Because of the discrepancy between the prevalence of clinically apparent thyroid cancer and occult thyroid cancer, it is believed that most occult thyroid cancers have little biologic significance. Nonetheless, a Medline search of occult thyroid cancer will yield a plethora of case reports of occult thyroid cancers presenting with distant metastases.

Nonpalpable thyroid nodules: a conundrum

It has been suggested by several experts in the field that nonpalpable nodules under 15 mm should be followed clinically without fine-needle aspiration (FNA) (5, 16). With the widespread use of ultrasound-guided needle aspiration, the opportunity to assess rates of malignancy in nonpalpable nodules was irresistible. One study found seven thyroid cancers in 108 consecutive patients with nonpalpable nodules greater than 10 mm found on thyroid sonography (6.4%) (17). The rate was similar to that seen in palpable nodules in the same clinic. A second study examined the outcome of 450 ultrasound-guided needle biopsies of nonpalpable thyroid nodules (18). Three hundred twenty-eight nodules were less than 15 mm. Three hundred sixty-five nodules had diagnostic cytology. Twenty cancers (4.4%) were identified after surgery in 94 patients, but because many patients with suspicious cytology did not undergo surgery, the true prevalence of cancer in these nonpalpable nodules was likely underestimated and probably is similar to that observed in series of palpable thyroid nodules. The rate of malignancy was slightly higher in subcentimetric nodules (6.9%), however, diagnostic cytology was obtained in only 64% of lesions under 8 mm *vs.* 86% of those 10 mm or greater. The authors concluded that 75% of the cancers would have been identified if all nodules 10 mm or larger and all solid hypoechoic nodules were biopsied. This strategy would have avoided needle biopsy in only 16% of patients. As a result of these data, several experts suggested that nonpalpable thyroid nodules 1 cm or larger should have a needle biopsy (11, 19).

Does such a recommendation make sense? Although most nonpalpable thyroid nodules are less than 10 mm, 30% of those found in one study using screening sonography were over 1 cm (6), and 28% of additional nonpalpable nodules found by ultrasonography in patients with a palpable nodule were over 1 cm (10). Assuming a 40% prevalence of nonpalpable thyroid nodules, 28–30% of which are 10 mm or greater, 11–12% of the population, if screened, would require a thyroid biopsy, and the prevalence of thyroid cancer in the United States would increase 6- to 7-fold. Are we benefiting these additional patients by detecting their thyroid cancers, cancers that in many would possibly have remained occult? To what extent might we be detecting cancers earlier and reducing morbidity and mortality? Definitive answers to these questions may never be realized, because observing a nonpalpable or occult lesion with positive or suspicious cy-

tology is troublesome, whereas the true nature of nonbiopsied lesions chosen for observation is never certain.

However, it is indisputable that such a strategy is expensive and would require spending a significant fraction of the health care dollar on thyroid ultrasounds and needle aspirations. In addition to the economic costs, there is the significant morbidity of surgery and its complications, as well as adjuvant therapies and monitoring, both for patients who ultimately prove to have benign lesions and those whose surgery for occult malignancies may not be of true benefit. It would be useful to develop models that estimate these costs for a cancer that presently results in only 0.23% of cancer deaths in the United States.

A new strategy for management of nonpalpable thyroid nodules

The study by Papini *et al.* (20), in this issue of *JCEM*, provides important data and suggests new guidelines for managing nonpalpable thyroid nodules. They performed ultrasound-guided needle biopsies on 494 consecutive patients with nodules measuring 8–15 mm, obtained diagnostic cytology on 402 patients, and referred all patients with suspicious or malignant cytology for surgical excision. The results of surgery were compared to sonographic and color flow Doppler features obtained preoperatively. Three sonographic features were significant independent risk factors for malignancy: irregular margins, an intranodular vascular pattern, and microcalcifications. In addition, 87% of the cancers were hypoechoic solid nodules, however, this parameter had low specificity because 57% of benign lesions were also hypoechoic solid nodules.

Papini *et al.* (20) found that a combination of sonographic features was useful to predict malignancy: 87% of the cancers were hypoechoic and solid and, in addition, had irregular margins, an intranodular vascular pattern, or microcalcifications. Larger nodule size was not a risk factor for malignancy. Thus, using these criteria to select nodules for FNA, only 125 of the 402 nodules (31%) would have required a biopsy and 87% of the cancers would have been detected. This contrasts with a strategy of using only a 10-mm threshold for FNA, which would have required 271 biopsies (64%) but identified only 61% of the cancers. It also improves on criteria suggested by a recent study of 155 nodules (21). In that study, 94% of cancers had microcalcifications, irregular or microlobulated margins, marked hypoechoicogenicity, or a shape that was more tall than wide, but 82 of the 155 nodules (53%) had one or more of these characteristics and required a biopsy.

While the strategy of Papini *et al.* (20) is clearly more cost effective by reducing the number of needle aspirates by more than half compared with using a 10-mm threshold for FNA, and by increasing the yield of cancers identified, it could be criticized for missing 13% of the cancers. However, an additional 277 biopsies would be necessary to find the additional four cancers that comprised the remaining 13%, a yield of 1.4%.

The study also provides data that help address the more difficult question of the benefit of identifying these nonpalpable or occult cancers. Among the cancers detected, 36%

had extrathyroidal extension and 19% involved nodes; none were associated with distant metastases. These findings suggest, but do not prove, that at least some of these cancers demonstrated aggressive behavior and should, therefore, be considered biologically important.

Implementing this strategy will immediately reduce the number of FNAs for nonpalpable thyroid nodules, but it will not reduce the number of thyroid ultrasounds needed to monitor those nodules. Additional studies are needed to assess optimal follow-up of nodules that do not meet criteria for biopsy, as well as for nodules that are too small for biopsy. Equally important, studies are needed to establish the appropriate role of thyroid ultrasound as a screening tool in clinical practice. Finally, strategies such as these, which sensibly limit interventions and obtain reasonable yields, will only work if they are embraced by those groups that author clinical guidelines that are used to establish the “standard of care.”

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Acknowledgments

Received February 21, 2002. Accepted February 21, 2002.

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