I am pleased to have the opportunity to comment on the excellent article by Hoang et al in this issue of *RadioGraphics* (1). Over the past several years, there has been a dramatic increase in the number of thyroid nodules that have come to clinical attention because of the widespread use of high-resolution ultrasonography (US) to evaluate the thyroid gland (2). It is now recognized that the sonographic features of thyroid nodules are more predictive of thyroid cancer than is nodule size. Certain sonographic features play a key role in deciding which nodules should undergo fine-needle aspiration (FNA), and they have been incorporated into biopsy recommendations published by the Society of Radiologists in Ultrasound (SRU) (2) and the American Thyroid Association (ATA) (3). It is therefore incumbent on the sonologist to be able recognize these features so as to select appropriate nodules for biopsy. The authors review the sonographic features that carry a high predictive value for thyroid malignancy and discuss interpretative pitfalls, particularly those that make the detection of a malignancy more difficult.

FNA was introduced into this country approximately 2 decades ago and has been widely accepted as a safe and accurate procedure for the diagnosis of thyroid cancer. Prior to the incorporation of FNA into the management algorithm of palpable thyroid abnormalities, surgical excision was commonly performed to both diagnose and treat nodular thyroid disease. The use of FNA prior to surgical resection has led to an overall decrease in the number of thyroid surgeries, with a twofold increase in the diagnosis of carcinoma (4,5). The recommended first diagnostic test for a euthyroid patient with a palpable thyroid nodule more than 1.0–1.5 cm in diameter is palpation-guided FNA (6). This nodule size threshold was established on the basis of the knowledge that the size of a thyroid cancer is a predictor of outcome; the propensity of papillary cancers to cause adverse events increases above 1 cm, compared with 4 cm for follicular cancers (7). Although the prevalence of palpable nodules in the adult population in the United States is estimated to be 4%–6% (2), US of the thyroid gland allows detection of nonpalpable nodules in 17%–67% of asymptomatic adults (8,9). Even in patients with palpable nodules, the detection of unsuspected additional nodules at US approaches 50% (10,11). Nonpalpable nodules may come to clinical attention also as a result of other imaging examinations of the neck, such as carotid US, computed tomography (CT), and magnetic resonance (MR) imaging.

The clinical dilemma is how to manage the large number of nonpalpable nodules that are detected with US. Although nonpalpable nodules are as likely to be cancerous as are palpable nodules, most nodules detected with US are benign (5,10). The rationale behind avoiding biopsy of some nodules is not only that resources are limited but also that a nondiagnostic or an indeterminate biopsy results in indirect morbidity. Approximately 60%–70% of nodules biopsied with FNA are benign, and 10%–13% are malignant; however, approximately 15%–30% are characterized as indeterminate, a follicular lesion, or “suspicious” (2). Roughly 80% of the latter group of nodules are benign, including follicular adenomas, hyperplastic nodules, and foci of thyroiditis; the other 20% are malignant, representing mixed follicular and papillary cancer or pure follicular cancer (2,5). The current recommendation is to refer all patients with an indeterminate FNA result or persistent nondiagnostic FNA result (due to insufficient cellular material) for surgical excision (3,12). Therefore, the decision about whether to pursue FNA of a sonographically detected nonpalpable nodule involves balancing the need to identify clinically relevant cancers against the need to avoid unnecessary surgical excision to prove benignity in a large asymptomatic population of patients with inconclusive FNA results.

In a small percentage of patients, FNA of a nonpalpable sonographically detected nodule may be desirable regardless of the sonographic characteristics. The decision may be based on clinical factors, including an increased risk for thyroid cancer because of family history or a history of prior radiation exposure (3). For most patients who are at low risk for thyroid cancer, the goals of assessing the sonographic characteristics of detected nonpalpable nodules are (a) to determine the likelihood of malignancy so that patients with thyroid cancer can be diagnosed and treated
at an earlier stage, possibly with a resultant reduction of morbidity and mortality, and (b) to recognize sonographic features that have a high correlation with benign disease, so as to avoid unnecessary tests and surgery (2,12). As reviewed by the authors (1), the sonographic feature with the highest positive predictive value of cancer is the presence of calcifications within a nodule, particularly microcalcifications (2). Calcifications, including peripheral calcifications that occur in solitary nodules, hypoechoic nodules, and predominantly solid nodules, arouse concern about possible malignancy (13–15). For example, microcalcifications within a solid or predominantly solid nodule are associated with a risk of cancer that is three times that for a solid noncalcified nodule, and coarse calcifications are associated with twice the risk (2). It is important for the sonologist to be able to distinguish between microcalcifications and colloid reverberation artifact. Microcalcifications within a nodule signify a very high risk of malignancy (and therefore, the SRU strongly recommends FNA at a 1.0-cm size threshold), whereas colloid reverberation artifact is considered a strong predictor of benign disease (2,12). Lower-frequency transducers, slight angle adjustments in the scanning plane, and real-time examination often may make the comet-tail artifact of colloid within a nodule more apparent (16). The SRU guidelines recommend FNA of a colloid-containing nodule without suspicious features only if the nodule has a diameter of at least 2.0 cm, and they do not necessarily require it, given the very low likelihood of malignancy in such nodules (2). The ATA recommendations differ significantly in this regard: They recommend biopsy at the 1.0–1.5-cm size for all detected solitary nodules (3).

As described by the authors, other sonographic features with a relatively high predictive value for malignancy include a solid composition and marked hypoechoigenicity of a nodule (1). Some features that are relatively nonspecific individually are more predictive of malignancy when they appear in combination (eg, the combination of intranodular flow and hypoechoigenicity) (17,18). The presence of a thick or irregular halo in association with a solid consistency and iso- or hyperechogenicity often is correlated with a follicular tumor (12). At the opposite end of the spectrum, the sonographic features that are highly predictive of benign disease include entirely or nearly entirely cystic consistency without a calcified or vascular soft-tissue component; a honeycomblike or spongiform consistency; and a complete, thin, and regular halo. Many would argue that a biopsy could be avoided when these features are clearly apparent (12).

An analysis of the sonographic characteristics is particularly important in the evaluation of patients with multiple thyroid nodules. Based on the use of imaging to define nodularity, several reports have determined that an individual’s risk of thyroid cancer is the same whether one nodule or multiple nodules are present (19). Both the SRU and the ATA recommend analyzing the sonographic features of a multinodular gland to determine which nodule or nodules should be biopsied, instead of relying on the practice of selecting the largest nodule. When multiple nodules with different sonographic appearances are observed, each nodule can be evaluated by using the criteria established for solitary nodules (2). Our lab considers nodules that are sonographically similar to be histologically similar. For example, if a patient had one solid hypoechoic noncalcified 18-mm nodule and several partially cystic noncalcified sonographically similar nodules in the 10–25-mm size range, we would biopsy the solid nodule first. If the nodule was found benign at FNA, we would choose to biopsy the largest mixed cystic and solid nodule (25 mm), considering it representative of the remaining nodules. At present, there are many approaches to the patient with multiple nonsuspicious thyroid nodules. The approaches vary from no biopsy in a case where glandular tissue has been diffusely replaced by glandular tissue has been diffusely replaced by periluminal tissue (eg, lymphoma or abscess) (20,21). It is well known that there is a high prevalence of occult thyroid cancer, which is defined as a papillary cancer focus with a diameter of less than 1.0 cm. These occult cancers are detected at autopsy with frequencies ranging from 2.7% to 28.4% (7). In general, most of these are papillary thyroid microcarcinomas, small foci of cancer that are thought to pursue an indolent course. However, a small percentage of microcarcinomas are or become invasive or metastatic, with resultant morbidity (7). Others have argued that earlier detection of these lesions does little to affect mortality (22,23). The current recommendation of the ATA is to biopsy 8- and 9-mm nodules that are detected incidentally and that have one or more suspicious sonographic features, in-
Including microcalcifications, hypoechochogenicity, intranodular flow, and indistinct margins (3).

I fully concur with the authors that the results of scintigraphy generally are not useful for determining which nodules are more likely to be malignant in most euthyroid patients, since most benign nodules, like malignancies, do not demonstrate iodine uptake (5). However, iodine 123 scintigraphy is a worthwhile test in patients with indeterminate FNA results, since the demonstration of iodine uptake in a thyroid nodule virtually excludes a malignancy. Approximately 5% of nodules described at cytologic analysis as “follicular” show iodine uptake, which obviates surgical excision to determine their benignity. Patients with a cytologic result of “suspicious for papillary carcinoma” or “Hürthle cell lesion” should be referred for surgical excision (3).

As described in the article, one of the most specific findings in thyroid malignancy is the presence of metastatic lymphadenopathy or evidence of direct invasion of adjacent soft-tissue structures. I agree with the authors’ assertion that all patients should undergo an evaluation of the cervical lymph nodes as part of a routine thyroid US examination. This practice is particularly helpful when abnormal lymph nodes are identified ipsilateral to a suspicious thyroid nodule. FNA with cytopathologic analysis of an abnormal lymph node can be performed as the initial diagnostic procedure. If the results confirm the presence of metastatic thyroid carcinoma in the lymph node, the patient can be referred for thyroidectomy with resection of the affected lymph node chains. Thyroid cancer most commonly metastasizes to the ipsilateral cervical lymph nodes, but contralateral cervical metastases have been noted in as many as 20% of patients; for this reason, both lateral compartments of the neck should be examined with US (24,25). After a diagnosis of metastatic thyroid cancer is established, the identification of central compartment metastases is less important because the central compartment is typically explored at the time of thyroidectomy. In my opinion, the size of the lymph node is a less important feature than its morphologic characteristics at US. I commonly encounter metastatic lymph nodes that are normal in size or minimally enlarged but that show calcifications, cystic change, diffuse or focal increased vascularity, heterogeneous echotexture, and rounded shape, and I target these nodes rather than larger but otherwise normal-appearing lymph nodes for FNA (26,27). It is very common to see enlarged yet otherwise sonographically normal cervical lymph nodes because of benign inflammatory conditions of the nasopharynx, particularly in the upper portions of the cervical chains (levels 2 and 3) (27). Many patients with chronic lymphocytic thyroiditis (Hashimoto thyroiditis) have multiple enlarged but otherwise sonographically normal nodes in the central and lateral compartments.

The authors also draw attention to the potential misinterpretation of metastatic lymphadenopathy as benign thyroid disease. Cystic metastases to central compartment nodes, which are common with papillary cancers, are more likely to be mistaken for benign cystic thyroid nodules than correctly interpreted as abnormal lateral nodes. Misinterpretation is more likely to occur with cystic anterior prelaryngeal nodes, which are located just anterior to the isthmus, and less likely with paratracheal nodes, which lie just behind the thyroid; however, careful scanning usually demonstrates the extrathyroidal location of these cystic nodes. Fortunately, the coexisting cancerous thyroid lesion is often easily identifiable at US and can be targeted for FNA to establish the presence of thyroid cancer, even if central compartment metastases are overlooked (Fig 15). The presence of microcalcifications or coarse calcifications anywhere within the central compartment of the neck should prompt FNA even if the sonologist is uncertain about whether the lesion is a calcified thyroid nodule or a metastatic central compartment lymph node (Fig 16).

Palpable lymphadenopathy may be found in some patients in whom the primary thyroid cancer is clinically occult or (rarely) undetectable even with US (2). Consideration should be given to the possibility of metastatic thyroid cancer when a solitary cystic lesion is observed in the lateral part of the neck in either a child or an adult. Often the lymph node has been nearly entirely replaced by the cystic metastasis. An abnormal lymph node may be differentiated from a congenital cyst, exophytic thyroid cystic nodule, and parathyroid cyst by accurately identifying its location within either the anterior or the posterior cervical lymph node chain, and the diagnosis may be confirmed with FNA. When it is difficult to obtain cellular material from a predominantly cystic lymph node, a portion of the aspirate can be sent for thyroglobulin analysis. If thyroglobulin, a protein unique to follicular thyroid cells, is present in a cystic lesion in a lateral compartment, a diagnosis of metastatic thyroid cancer can be made (28).

Although many of the figures in the article consist of cross-sectional images of thyroid malignancies, I do not recommend cross-sectional imaging of the neck in most patients with a new diagnosis of differentiated thyroid cancer, since the vast majority will have only regional cervical metastases. US has the capacity to depict invasion of the...
thyroid capsule and extension into the adjacent soft tissues by some of the more aggressive differentiated thyroid cancers; however, it is of limited use in identifying the extent of invasion into the adjacent trachea and esophagus and detecting lymphadenopathy that extends into the upper mediastinum and retropharyngeal space. Therefore, I do recommend CT or MR imaging of the neck to help plan surgical resection in patients with undifferentiated thyroid cancer and for large, rapidly growing or invasive tumors (3,24).

The greatest departure of my views from those of the authors concerns their comments about diffuse thyroid disease and the coexistence of malignancy. It has been well established that chronic lymphocytic thyroiditis is a risk factor for the development of primary thyroid lymphoma, but, fortunately, that is a relatively rare occurrence (29). Although there are many reports of an increased occurrence of papillary cancers in thyroid glands affected by chronic lymphocytic thyroiditis, the degree to which the “increase” is related to an increased frequency of detection with US and surgical removal of the thyroid in these patients is not fully delineated. The diagnosis of coexistent malignancy with diffuse thyroid disease is often complicated by the heterogeneous background echotexture in affected glands, which has the effect of both masking true malignancies and creating a false impression of focal nodular disease. When confronted with a diffusely heterogeneous gland, I rely heavily on real-time examination to determine whether “true” nodules are present, rather than geographic, patchy areas of lymphocytic infiltration, and then I apply the SRU guidelines to target appropriate nodules for FNA. I also try to target focal clusters of calcifications, particularly microcalcifications, knowing that the delineation of a hypoechoic papillary cancer is difficult in a gland with overall decreased echogenicity. In addition, I consider it exceedingly rare for a thyroid cancer to produce thyrotoxicosis.

Although US of the thyroid has created “an epidemic of thyroid nodules” (22), it offers a partial solution, allowing targeted biopsy on the basis of an ability to recognize US findings that carry a high likelihood of malignancy. Yet even with this strategy, cancers without apparent suspicious sonographic features may remain undiagnosed (3,13). Thus, we are left with several uncertainties regarding the optimal management of thyroid nodules detected at US: Is it clinically relevant to diagnose all thyroid cancer, especially papillary cancers smaller than 1.0 cm? Does an early diagnosis of thyroid cancer truly affect the prognosis? What is the optimal biopsy strategy for a multinodular gland? Are there sonographic features indicative of such a low risk for malignancy that they obviate the need for FNA to exclude malignancy? Is it more cost effective to biopsy a nodule when it is first detected or to monitor it for growth with serial US examinations? Several of these questions are the focus of active research, and we can look forward to the formulation of future recommendations concerning the management of sonographically detected thyroid nodules.

References


Authors’ Response

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We thank Dr Langer for her comments.

We agree with Dr Langer’s observation that a thyroid carcinoma manifesting with diffuse infiltration and with thyrotoxicosis is very rare, and thyrotoxic carcinoma has been described in only isolated case reports (1–3). We have seen both situations, which became clear only after appreciation of lymph node metastasis.

Concerning diffuse autoimmune thyroid disease, we also agree that malignancy developing in long-standing disease is uncommon; nevertheless, thyroiditis is probably an independent risk factor for differentiated thyroid cancer as well as lymphoma. Thyroid nodules against a background of thyroiditis should be assessed just as an isolated thyroid nodule would be assessed, for the same sonographic features suggestive of malignancy.

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