ULTRASONOGRAPHY OF THE THYROID

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ABSTRACT

Thyroid ultrasonography (US) is the most common, extremely useful, safe, and cost-effective way to image the thyroid gland and its pathology. US has largely replaced the need for thyroid scintigraphy except to detect iodine-avid thyroid metastases after thyroidectomy and to identify hyper-functioning (toxic) thyroid nodules. This chapter reviews the literature; discusses the science and method of performing US; examines it's clinical utility to assess thyroid goiters, nodules, cancers, post-operative remnants, cervical lymph nodes, and metastases; presents it's practical value to enhance US-guided aspiration biopsy of thyroid lesions (FNA); and endorses it's importance in medical education. US reveals, with good sensitivity but only fair specificity very important and diagnostically useful clues to the clinician and surgeon about the likelihood that a thyroid nodule is malignant. Color flow Doppler enhancement of the US images, that delineates the vasculature, is essential. Comprehensive understanding of the local anatomy, the specific disease process, technical skill and experience are essential for proper interpretation of the US images. Features that favor the presence of a malignant nodule include decreased echogenicity, microcalcifications, central hypervascularity, irregular margins, an incomplete halo, a tall rather than wide shape (larger in the anteroposterior axis compared to the horizontal axis, the nodule is growing in one direction and not growing concentrically), documented enlargement of the solid portion of the nodule and associated lymphadenopathy. Several of these attributes enhance the diagnostic probability. The patient's history, physical examination, and comorbidities refine the diagnosis. FNA and cytological examination of thyroid nodules and adenopathy in adults, children, and adolescents has become a major, specific, and highly diagnostic tool that is safe and inexpensive. In addition, the aspirate may be analyzed by biochemical measurements and especially by evolving molecular genetic methods.

INTRODUCTION

Ultrasonography (US) is the most common and most useful way to image the thyroid gland and its pathology, as recognized in guidelines for managing thyroid disorders published by the American Thyroid Association (1) and other authoritative bodies. In addition to facilitating the diagnosis of clinically apparent nodules, the widespread use of US has resulted in uncovering a multitude of clinically imperceptible thyroid nodules, the overwhelming majority of which are benign. The high sensitivity for nodules but inadequate specificity for cancer has posed a management and economic problem. This chapter will address the method and utility of clinically effective thyroid US to assess the likelihood of cancer, to enhance fine needle aspiration biopsy and cytology (FNA), to facilitate other thyroid diagnoses, and to teach thyroidology.

Previously, imaging of the thyroid required scintiscanning to provide a map of those areas of the thyroid that accumulate and process radioactive iodine or other nucleotides. The major premise of thyroid scanning was that thyroid cancers concentrate less radioactive iodine than healthy tissue and therefore provided triage in the selection for thyroid surgery. Unfortunately, however, since benign nodules also concentrate radioactive iodine poorly, the selection process is too inefficient to be cost-effective. Although, scintiscanning remains of primary importance in patients who are hyperthyroid or for detection of iodine-avid tissue after thyroidectomy for thyroid cancer, US has largely replaced nuclear scanning for the majority of patients because of its higher resolution, superior correlation of true thyroid dimensions with the image, smaller expense, greater simplicity, and lack of need for radioisotope administration. The other imaging methods, computerized tomography (CT), magnetic resonance imaging (MRI), and 18F-FDG positron emission tomography (PET) are more costly than US, are not as efficient in detecting small lesions, and are best used selectively when US is inadequate to elucidate a clinical problem (2,3).

As with any test, US should be used to refine a differential diagnosis only when it is needed to answer a specific diagnostic question that has been raised by the clinical history and physical examination (4). Its use as a screening tool for thyroid nodules and lesions such as Hashimoto's disease is debatable. The US image must be integrated into patient management and correlated precisely with the other data. A technique has been reported that helps the clinician to interpret thyroid scintigrams of goiters and non-functioning nodules by assembling scintiscans and US side-by-side as one composite image (2). As an example of the utility of this protocol, sometimes it is difficult to correlate an ultrasound image and a scintigram. For instance, in a goiter, a small "cold" region may not be distinctive on the US examination. Thus, it may be unclear exactly where to insert a biopsy needle to obtain cytology of the nodule (that could be neoplastic) rather than sampling the rest of the goiter (that usually is benign). In such cases, it is useful to display the two different kinds of images side-by-side or superimposed.

Medical testing must be cost-effective. There is documentation that in a hospital or emergency department setting, the expense of thyroid ultrasound is quite low (5).

Although sonography can supply very important and clinically useful clues about the nature of a thyroid lesion, **it does not reliably differentiate benign lesions and cancer.** However, it can help significantly. US can:

1. Depict accurately the anatomy of the neck in the thyroid region,
2. Help the student and clinician to learn thyroid palpation,
3. Elucidate cryptic findings on physical examination,
4. Assess the comparative size of nodules, lymph nodes, or goiters in patients who are under observation or therapy,
5. Detect a non-palpable thyroid lesion in a patient who was exposed to therapeutic irradiation,
6. Give very important and clinically useful clues about the likelihood of malignancy,
7. Identify the solid component of a complex nodule,
8. Guide and facilitate fine needle aspiration biopsy of a nodule,
9. Evaluate for recurrence of a thyroid mass after surgery,
10. Monitor thyroid cancer patients for residual disease or early evidence of reappearance of malignancy in the thyroid bed or lymphadenopathy,
11. Identify patients who have ultrasonic thyroid patterns that suggest diagnoses such as thyroiditis.
12. Perhaps refine the management of patients on therapy such as antithyroid drugs,
13. Facilitate delivery of medication or physical high-energy therapy precisely into a lesion and spare the surrounding tissue,
14. Monitor *in utero* the fetal thyroid for size, ultrasonic texture, and vascularity,
15. Scrutinize the neonatal thyroid for size and location,
16. Screen the thyroid during epidemiologic investigation in the field.

TECHNICAL ASPECTS

Sonography depicts the internal structure of the thyroid gland and the regional anatomy and pathology without using ionizing radiation or iodine containing contrast medium (6,7). Rather, high frequency sound waves in the megahertz range (ultrasound), are used to produce an image. The procedure is safe, does not cause damage to tissue and is less costly than any other imaging procedure. The patient remains comfortable during the test, which typically takes only a few minutes unless there is a need to evaluate the lateral neck, does not require discontinuation of any medication, or preparation of the patient. The procedure is usually done with the patient reclining with the neck hyperextended but it can be done in the seated position. A probe that contains a piezoelectric crystal called a transducer is applied to the neck but since air does not transmit ultrasound, it must be coupled to the skin with a liquid medium or a gel. This instrument rapidly alternates as the generator of the ultrasound and the receiver of the signal that has been reflected by internal tissues. The signal is organized electronically into numerous shades of gray and is processed electronically to produce an image instantaneously (real-time). Although each image is a static picture, rapid sequential frames are processed electronically to depict motion. Two-dimensional images have been standard and 3-dimentional images are an improvement in certain circumstances (8). There is considerable potential for improving ultrasound images of the thyroid by using ultrasound contrast agents. These experimental materials include gas-filled micro-bubbles with a mean diameter less than that of a red blood corpuscle and Levovist, an agent consisting of granules that are composed of 99.9% galactose and 0.1% palmitic acid. They are injected intravenously, enhance the echogenicity of the blood, and increase the signal to noise ratio (9,10). Contrast-enhanced thyroid US features such as heterogeneous enhancement, slow "wash in", ill-defined enhancement of the border a the nodule, and fast "wash out" seem to be associated with increased association with malignancy (11).

Dynamic information such as blood flow can be added to the standard US signal by employing a physics principle called the Doppler effect. The frequency of a sound wave increases when it approaches a listener (the ear or, in the case of ultrasonography, a transducer) and decreases as it departs. The Doppler signals, which are superimposed on real time gray scale images, are extremely bright in black and white images and may be color coded to reveal the velocity (frequency shift) and direction of blood flow (phase shift) as well as the degree of vascularity of an organ (12,13). Flow in one direction is made red and in the opposite direction, blue. The shade and intensity of color can correlate with the velocity of flow. Thus, in general terms, venous and arterial flow can be depicted by assuming that flow in these two kinds of blood vessels is parallel, but in opposite directions. Since portions of blood vessels may be tortuous, modifying orientation to the probe, different colors are displayed within the same blood vessel even if the true direction of blood flow has not changed. Thus, an analysis of flow characteristics requires careful observations and cautious interpretations. The absence of flow in a fluid-filled structure can differentiate a cystic structure and a blood vessel.

Blood flow within anatomic structures can also be depicted by non-Doppler technology. This technique is called B-flow ultrasonic imaging (BFI). It is accomplished by transmitting precisely separated adjacent ultrasound beams and analyzing with a computer, the reflected echo pairs (14).

Various anatomic features and tissues result in different ultrasound characteristics (2,6). The air-filled trachea does not transmit the ultrasound. Calcified tissues such as bone and sometimes cartilage and calcific deposits in other anatomic structures block the passage of ultrasound resulting in a very bright signal and a linear echo-free shadow distally. Most tissues transmit the ultrasound to varying degrees and interfaces between tissues reflect portions of the sound waves. Fluid-filled structures have a uniform echo-free appearance whereas fleshy structures and organs have a ground glass appearance that may be uniform or heterogeneous depending on the characteristics of the structure.

The depth penetration and resolving power of ultrasound depends greatly on frequency (7). Depth penetration is inversely related and spatial resolution is directly related to the frequency of the ultrasound. For thyroid, a frequency of 7.5 to 10 - 15 megahertz is generally optimal for all but the largest goiters. Using these frequencies, nodules as small as two to three millimeters can be identified.

Performance and interpretation of thyroid sonograms are quite subjective and reflect probabilities, not certainty. Both overaggressive and excessively timid interpretation can be misleading. Routine protocols for sonography are not always optimal. Although some technologists become extremely proficient after specific training and experience, supervision and participation by a knowledgeable and interested physician-sonographer is usually required to obtain a precise and pertinent answer to a specific problem that has been posed by the clinician. For instance, one group has reported accurate, surgically proven preoperative identification of non-recurrent inferior laryngeal nerves (15). It is not that the ultrasound images depict an inferior laryngeal nerve. Rather, the diagnosis is suggested when, while performing the sonogram, the surgeon asks a specific, direct question about the anatomic region where the nerve should be located. Thereafter, a series of images are obtained with and without Doppler interrogation that reveal the presence of a small, linear structure that, on Doppler interrogation, is associated with blood vessels, allowing a probable answer to the inquiry. The surgeon is then in a position to operate, minimizing the risk of adverse consequences.

Standard sonographic reports may provide considerable information about major anatomic features, but are suboptimal unless the specific clinical concern is explored and answered. Indeed, because some radiologists may not address the clinical issue adequately, and for convenience, numerous thyroidologists and surgeons perform their own ultrasound examinations, in their office or clinic (point of service). However, it is essential that non-dedicated ultrasonographers have state-of-the-art equipment (might not be cost-effective) and that they are willing to expend a considerable amount of time for a complete study, in particular if there is a need to evaluate the lateral neck compartments. Technical ingenuity, electronic enhancements such as Doppler capability, and even artistry are frequently required. Special maneuvers, various degrees of hyperextension of the neck, swallowing to facilitate elevation of the lower portions of the thyroid gland above the clavicles, swallowing water to identify the esophagus, and a Valsalva maneuver to distend the jugular veins may enhance the value of the images. Nevertheless, sonography is rather difficult to interpret in the upper portion of the jugular region and in the areas adjacent to the trachea. Aiming the transducer obliquely may permit exploration of the region behind the trachea. Sonography is generally not useful below the clavicles.

To orient the imager, it can be useful to survey the entire neck and thyroid gland with a low-energy transducer before proceeding to 10-15 megahertz equipment. Protocols have been devised to assemble a montage of images to encompass an unusually large lobe or goiter. For an overview, panoramic ultrasound, which is a variation of conventional ultrasound allows one to produce images with a large anatomic field of view, displaying both lobes of the thyroid gland on a single image (16).

There may be considerable differences between sonographers in estimating the size of large goiters or nodules (17). One investigation has reported that curved-array transducers may avoid significant inter-observer variation that may occur when linear-array equipment is employed, especially when the gland is very large (18). The inter-observer variation may be almost 50% even among experienced ultrasonographers, because it is difficult to reproduce a two-dimensional image plane for multiple studies (19). Accuracy in volume estimation becomes most important when one uses ultrasound measurements to calculate an isotope dose or to compare changes over time in the size of a nodule or a goiter. Indeed, it has been suggested even for well-defined nodules, a change of less than 1 cm in size should not be accepted as a real change (17). The important aspect is that the clinician must be guided by the constellation of risk factors, local anatomy, and intervening events, when making a management decision. Stability of size is one factor, but not a major one.

Using planimetry from three-dimensional images reportedly has lower intra-observer variability (3.4%) and higher repeatability (96.5%) than the standard ellipsoid model for nodules and lobes, with 14.4% variability and 84.8% repeatability ($p < 0.001$) (20).

Importantly, for autonomous nodules, US-evidence of growth does not indicate a likelihood of malignancy. Rather, it usually reflects cystic or hemorrhagic degeneration, which correlates well with prior experience by pathologists and the literature. In contrast, growth of a non-functional follicular adenoma can be of concern and the lesion needs to be carefully evaluated for other suspicious signs (21). There may be imperfect concordance between the ultrasonic dimensions of large thyroid nodules compared with intraoperative findings (22).

SONOGRAPHY OF THE NORMAL THYROID AND ITS REGION

The anterior neck is depicted rather well with standard gray scale sonography (Figure 1). The thyroid gland is slightly more echo-dense than the adjacent structures because of its high iodine content. It has a homogenous ground glass appearance. Each lobe has a smooth globular-shaped contour and is no more than 3 - 4 centimeters in height, 1 - 1.5 cm in width, and 1 centimeter in depth. The isthmus is identified, anterior to the trachea as a uniform structure that is approximately 0.5 cm in height and 2 - 3 mm in depth. The pyramidal lobe is not seen unless it is significantly enlarged. In the female, the upper pole of each thyroid lobe may be seen at the level of the thyroid cartilage, whereas it is lower in the male. The surrounding muscles are of lower echogenicity than the thyroid and tissue planes between muscles are usually identifiable. The air-filled trachea does not transmit the ultrasound. Only the anterior portions of the cartilaginous rings are represented by dense, bright echoes. The carotid artery and other blood vessels are echo-free unless they are calcified. The jugular vein is usually in a collapsed condition and it distends with a Valsalva maneuver. There are frequently 1-2 mm echo-free zones on the surface and within the thyroid gland that represent blood vessels. The vascular nature of all of these echo-less areas can be demonstrated by color Doppler imaging to differentiate them from cystic structures (12,13). Lymph nodes may be observed. Nerves are generally not seen. However, a keen understanding of the local anatomy may permit critical interpretation of a series of gray scale US and Doppler images to gain useful insights into the probable presence or absence of an expected neurovascular bundle. Meticulous preoperative analysis that may include lymph node mapping can benefit surgical management (15). The parathyroid glands are observed only when they are enlarged and are less dense ultrasonically than thyroid tissue because of the absence of iodine. The esophagus may be demonstrated behind the medial part of the left thyroid lobe, especially if a sip of water distends it (Figure 2).

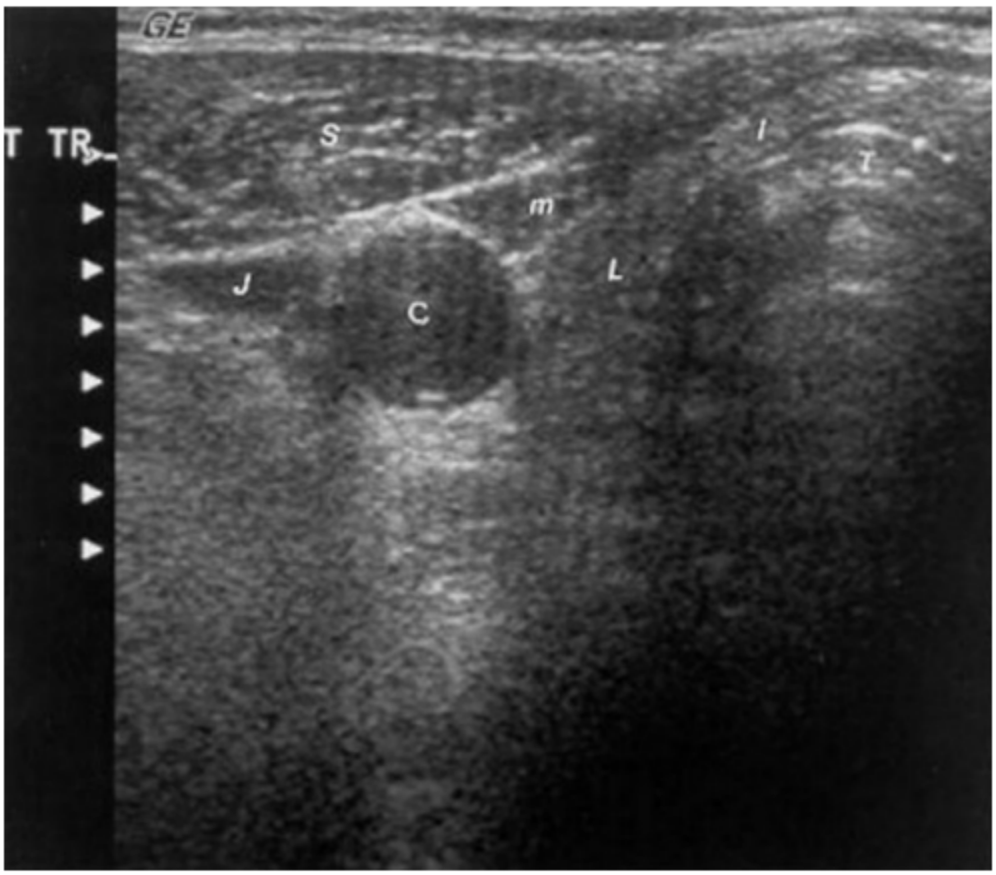

Figure 1. Sonogram of the neck in the transverse plane showing a normal right thyroid lobe and isthmus. L = small thyroid lobe in a patient who is taking suppressive amounts of L-thyroxine, I = isthmus, T = tracheal ring (the dense white arc represents calcification, distal to it reflects artifact), C = carotid artery (note the enhanced echoes deep to the fluid-filled blood vessel), J = jugular vein, S = sternocleidomastoid muscle, m = strap muscle.

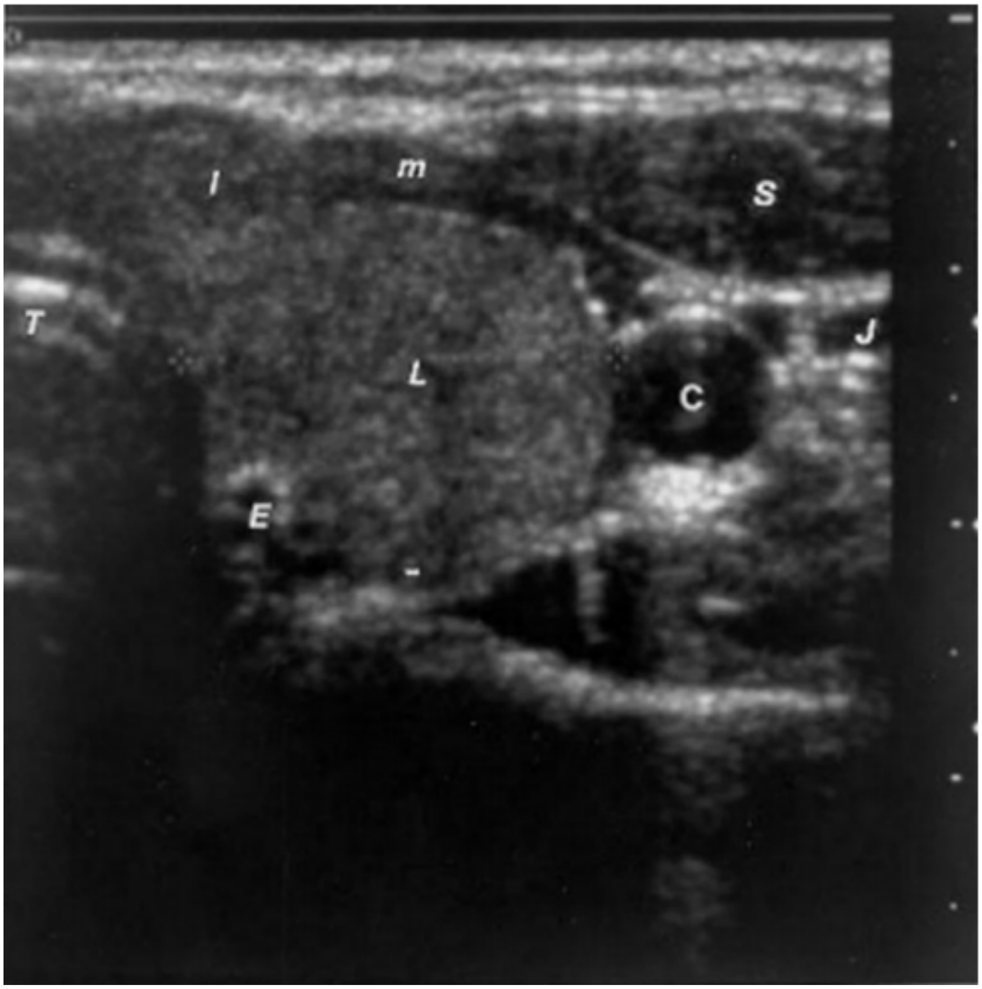

Figure 2. Sonogram of the left lobe of the thyroid gland in the transverse plane showing a rounded lobe of a goiter. L = enlarged lobe, I = widened isthmus, T = trachea, C = carotid artery (note the enhanced echoes deep to the fluid-filled blood vessel), J = jugular vein, S = sternocleidomastoid muscle, m = strap muscles, E = esophagus.

GENERAL THOUGHTS ABOUT SONOGRAPHY

Thyroid US may play a useful role in the management of patients even when the thyroid examination is normal but it is debatable if the procedure is cost-effective as a screening test (1). Many thyroidologists/endocrinologists advocate routine use of US at the time of physical examination to discover subclinical, non-palpable thyroid abnormalities, which will be discussed presently, and to enhance the sensitivity and accuracy of palpation. This practice is called “point of service” US.

Whether US is performed at the point of service or in an US laboratory by ultrasonographers/radiologists, it is important to employ thyroid sonography selectively to supplement or confirm a physical examination especially when clinical perception is confused by obesity, great muscularity, distortion by abnormal adjacent structures, tortuous regional blood vessels, a prominent thyroid cartilage, metastatic tumor, lymphadenopathy, or prior surgery.

In practice, US may be used to supplement an examination when there is uncertainty about the palpation. It is important, however, to comprehend that the optimal clinical value of US depends on the quality of the examination, including the experience of the examiner and the characteristics of the equipment. Grossly misleading results may occur with quick, incomplete studies, insensitive US machines or substandard interpretations. “Routine” sonography in a medical office, clinic or in a radiology facility by an incompletely trained clinician or general radiologist can be misleading. Without study, training and practice, there are likely to be unacceptable results and adverse outcomes. Furthermore, the efficacy of US when performed in sub-optimal conditions has yet to be critically examined.

In the academic situation, sonography is useful to teach palpation of the thyroid gland.

There are claims that US can offer insights into thyroid function. For instance, among 4649 randomly selected adult subjects one investigation found that there was correlation between thyroid hypoechogenicity and higher than average levels of serum TSH, even in subjects without overt thyroid disease (23). One group reported TSH elevations in 26 patients with autoimmune thyroiditis when there was a well-defined, approximately 10 mm triangular area of low echogenicity, between the lateral margin of one or both thyroid lobes, the medial wall of the carotid artery, and, posteriorly, the pre-vertebral muscles. Euthyroid patients (71) with thyroiditis and controls (154) did not demonstrate a hypoechoic "triangle" (24). In contrast, the question arises how accurately a normal thyroid sonogram will predict normal thyroid function? In one study of normal-appearing US, TSH was normal in 41/48 (85.4%) subjects but was elevated in 7 individuals (14.6%) ($p<0.001$) and anti-thyroid antibodies were detected in 5 patients (10.4%) (25). Therefore, a normal sonogram does not preclude hypothyroidism or Hashimoto's thyroiditis.

SONOGRAPHY USED TO FACILITATE AN UNCONVENTIONAL SURGICAL APPROACH TO THYROIDECTOMY OR REMOVAL OF METASTASES

US maybe used to guide a surgeon who performs a trans-axillary or sub-mammary approach to thyroidectomy, thereby avoiding a neck scar. Retro-pharyngeal thyroid metastases can be managed via trans-oral robotic and surgeon-performed US to localize and excise lymphadenopathy (26).

SONOGRAPHY IN THE PATIENT WITH AN ENLARGED THYROID GLAND (GOITER)

Thyroid sonography probably is not cost-effective in evaluating the average patient with thyroid enlargement. Since thyroid goiters are common and rarely associated with malignancy, there is little useful purpose to sonographic documentation of the size, shape, or uniformity of a goiter. However, US may be used in a goiter to identify non-palpable thyroid nodules for biopsy, or those that have enlarged or become harder. Importantly, US permits one to characterize nodules and estimate the risk of malignancy. The value of aspirating a selected nodule in a goiter is under current scrutiny. At this time, the data seems persuasive that the incidence of cancer in a particular nodule in a goiter is independent of the number of sonographically identified nodules, in distinction to prior belief. Therefore, this practice seems worthwhile (27,28).

At times, it will be useful to know the ultrasonic appearance of a dominant nodule in a goiter, a tender spot, a region of focal hardness because it might give a clue about pathology (Figure 2) (1). For example, sonography can identify one region in a goiter whose echo pattern is distinct from the rest of the goiter suggesting a second type of pathology, especially if the region is surrounded by an incomplete and irregular sonolucent rim, has punctate microcalcifications, or Doppler examination reveals internal vascularity. The significance of these ultrasonic features will be discussed below. Among the lesions that have been demonstrated in goiters using US are neoplasms and lymphoma. Other uses of sonography in goitrous patients include: differentiation of thyroid enlargement from adipose tissue or muscle, identifying a large unilateral mass in distinction to an asymmetric goiter, confirming substernal extension, providing the correct interpretation to varying clinical impressions among several examiners, and objectively documenting volume changes in response to suppressive therapy with thyroid hormone, which may be particularly useful information when patients change physicians.

An interesting public health use of US in underdeveloped countries has been to objectively identify goiter as a screen for iodine deficiency. Furthermore, in the epidemiological setting, with proper ultrasound equipment, assessment of thyroid volume and prevalence of thyroid nodules, but not echogenicity or echographic pattern, are comparable among different observers (29).

Sonography is useful to monitor patients undergoing long-term treatment with lithium for bipolar, major depressive, and schizoaffective disease. Their total thyroid volume in one investigation was significantly greater (23.7 ml vs. 13.6 ml) in the lithium-treated group (30) than among controls (96 sex- and age-matched control subjects). Furthermore, US detects thyroid enlargement with greater accuracy and sensitivity than palpation (31).

SONOGRAPHY WITH THYROIDITIS AUTONOMOUS NODULES, AND GRAVES' DISEASE

Routine sonography can be useful in distinguishing thyroiditis or Graves' disease, but it is uncertain whether this is cost-effective. Several publications have shown that the ultrasound pattern correlates with the presence of autoimmune thyroid disease and can predict thyroid dysfunction as will be discussed below (32). In subacute thyroiditis, the severely inflamed thyroid reflects very low intensity echoes, which is generally not seen with any other thyroid disorder (33). In the inflamed portions of the thyroid gland there is no increased vascular flow pattern on Doppler examination. The non-involved regions demonstrate normal vascularity and hemodynamics. In the recovery phase of subacute thyroiditis, the thyroid regains isoechogenicity and a Doppler study may show slightly increased vascularity (33-37). Hashimoto's thyroiditis and Graves' disease show moderately heterogeneous, reduced echogenicity (38-43). The diagnostic precision of this US pattern was compared to that of anti-thyroid peroxidase antibody (TPOAb) concentrations in 451 ambulatory patients with unknown thyroid status, excluding those with suspected hyperthyroidism or on drugs known to cause hypothyroidism. There was high intra-observer and inter-observer agreement on the abnormal thyroid ultrasound patterns, which were judged highly indicative of autoimmune thyroiditis and allowed the detection of thyroid dysfunction by other means with 96% probability (44). It has been reported that among 55 patients with hyperthyroidism (29 Graves' disease and 26 toxic nodules), color flow Doppler examination was useful to differentiate the etiology. Increased blood flow was successful in differentiating untreated Graves' disease from Hashimoto's thyroiditis, both of which had similar gray scale findings ($p < 0.001$), and from controls ($p < 0.001$). "Hot", autonomous nodules could also be differentiated from "cold" nodules because of more prominent vascular patterns and significantly higher peak systolic velocity values ($p < 0.001$) (45). The gray-scale US features of nontoxic autonomous nodules are similar to those of toxic autonomous nodules (46).

Investigation of patients with postpartum thyroiditis who had both high levels of antithyroid peroxidase antibody and a hypoechogenic thyroid gland also had a high risk of long-term thyroid dysfunction (47). In 119 patients with postpartum thyroiditis and 97 normal postpartum women as the control group, thyroid hypoechogenecity was present in 98.5% of patients and 7% of the control group ($p <0.001$). Initially, mean thyroid volume in the patients with thyroiditis was 77% greater than in the control group. After remission, mean thyroid volume decreased by 25% in the thyroiditis patients. Twelve months after delivery, hypoechogenicity persisted in 4 patients (48).

It has been reported that in children US findings of Hashimoto's thyroiditis are present in only a third at the time of diagnosis and half of the Hashimoto's children with normal initial thyroid sonography develop changes within 7 months. In some cases, characteristic Hashimoto's findings may not develop for over 4 years (49).

Especially in Graves' disease, color Doppler imaging of the thyroid can demonstrate diffuse hyperemia of the thyroid gland (50) that has been called a "thyroid inferno" (51). In patients with amiodarone-induced thyrotoxicosis, Doppler flow sonography has been reported to differentiate two types of disorder with implications for therapy (52-56). Patients with moderate to high vascular flow had underlying thyroid disease, such as latent Graves' disease or nodular goiter. The latter are at risk of amiodarone-induced thyrotoxicosis type I (AIT I), which is caused by the organification of the high amounts of iodine in amiodarone. In contrast, AIT II is caused by a destructive thyroiditis caused by the drug and there is typically no demonstrable vascular flow. The clinical value of this observation is that the Type II patients seem to respond to treatment with glucocorticoids. In contrast, AIT I patients tend to respond to a combined regimen with methimazole and potassium perchlorate (52). Although this conclusion was originally based on a small number of patients, the observations were confirmed in a retrospective case-note audit of 37 patients (53). Interestingly, in that study, euthyroid amiodarone-treated patients failed to show hyperactive flow (52). In another investigation, looking at the data from the perspective of patients who had been treated for amiodarone-induced thyrotoxicosis, in a retrospective study of 24 patients, responsiveness to prednisolone correlated poorly with the absence of enhanced blood flow in the thyroid glands, but the presence of enhanced flow appeared to correlate with non-response to prednisolone (55). Interleukin 6 (IL-6) levels correlated with the ultrasound classification in one study (52), but not in another (53).

A report has successfully validated excessive mean peak systolic velocity of the superior thyroidal artery in Graves' disease but not in patients with destructive thyroiditis (57).

An important application of standard US in patients with thyroiditis or Graves' disease is to assess those thyroid glands that have focal firm consistency or are enlarged or painful for coincidental tumor or lymphoma (1). In one report, patients with Hashimoto's thyroiditis had sonography to detect nodules and then had ultrasound-guided aspiration biopsy to elucidate the nature of the lesion. Two of 24 patients (8.3%) had papillary thyroid cancer (58).

In patients with thyrotoxicosis, US can assess the size of the thyroid gland to facilitate I-131 dosimetry. The size of each lobe is measured in the sagittal and transverse planes to provide the length (L), anterior-posterior depth (D), and transverse width (W), respectively. The volume of each lobe is calculated using the formula for a prolate ellipse: (volume = 0.5 {L x D x W}). 3D echography may improve the accuracy of assessment of thyroid volume (20).

Doppler sonography may become a useful tool for the clinical endocrinologist in the management of patients with Graves' disease if observations are confirmed in large populations. It has been suggested that color-flow mapping of the thyroid gland may have a role in the selection of an optimal dose of methimazole needed to maintain a euthyroid state in patients with Graves' disease (59). Another study has characterized Doppler ultrasound data from patients with Graves' disease, Hashimoto's disease, and goiter to obtain a "hemodynamic index" to ascertain when antithyroid drugs should be withdrawn or ablative therapy given in patients with Graves' disease. The hemodynamics in the thyroid was significantly different between untreated thyrotoxic and medically well-controlled patients but there were no significant differences between untreated or medically poorly controlled patients. It would be interesting to ascertain whether the hemodynamics permit an identification of a subset of well-controlled patients who will relapse after a course of therapy (60). Furthermore, Doppler sonography has provided data from 40 patients with Graves' disease showing significantly increased thyroid blood flow in euthyroid patients who presented early in relapse after withdrawal of antithyroid drug therapy when compared with 16 age-matched normal control subjects. Conversely, there were no significant differences in euthyroid patients who remained in remission when compared with normal controls (61). The value of quantifying thyroid blood flow at the time of diagnosis has been assessed in 24 patients with Graves' disease, using percutaneous spectral Doppler recordings from the thyroid arteries, in an attempt to predict the likelihood of remission following withdrawal of antithyroid drug therapy. The mean duration of treatment was 14 months and follow-up in 13 women was at least 18 months (range: 18 - 39 months) after antithyroid drug withdrawal. Mean peak systolic velocity and volume flow rate values as well as thyroid volume measured at the time of diagnosis were significantly higher (139 cm/s, SD 46; 195 ml/min, SD 170; 52 ml, SD 18) in patients who relapsed after drug treatment compared with patients in remission (71 cm/s, SD 27; 67 ml/min, SD 61; 25 ml, SD 13) (62). Thyroid hypoechogenicity at onset of Graves' disease is probably not a reliable prognostic index of relapse after medical treatment. However, the absence of thyroid hypoechogenicity after methimazole treatment seems to be a favorable prognosticator of remission (63). In another investigation, Doppler ultrasound determined increased peak systolic velocity in the inferior thyroid artery in untreated hyperthyroid patients with Graves' disease was significantly and positively associated with the maintenance dose of methimazole needed to keep TSH normal (64). Normoechoic Graves' hyperthyroid glands seem to be more resistant to therapy with I-131 than hypoechoic thyroids (65).

Another example of the value of Doppler ultrasound relates to the administration of iodide solutions that have been used traditionally prior to thyroid surgery for Graves' disease because it was thought that they reduce the vascularity of the thyroid gland. Doppler echography has demonstrated a significant decrease in thyroid vascularity in patients with Graves' disease after seven days of Lugol's solution, confirming the rationale of this form of treatment (66). Preoperative treatment with Lugol's solution decreased the rate of thyroid blood flow and vascularity, as assessed by Doppler evaluation. Lugol's solution also decreased intraoperative blood loss during thyroidectomy in another investigation (67). In contrast, US has also shown that preoperative iodide may increase the size of the thyroid gland, which could complicate surgery when a Graves' thyroid is very large before the Lugol's solution is administered (68).

Doppler examination has been used trans-vaginally in pregnant women with Graves' disease to depict and assess the size of the fetal thyroid gland. Clinical benefits might include facilitating adjustment of the mother's dose of antithyroid drug and anticipating or preventing fetal and neonatal hypothyroidism. The authors suggested that when reduction of the medication does not result in decrease in the size of the fetal goiter, trans-placental passage of thyroid stimulating immunoglobulin should be suspected (69).

SONOGRAPHY OF LYMPHOMA

In the author's experience, the value of US to predict lymphoma is very limited. However, the sonographic patterns of thyroid lymphoma have been classified into three types based on internal echoes within the suspected lesion, the border of the lesion, and the intensity of the echoes behind (deep to) the lesion. The echoes behind the lesion in each type of lymphoma are increased, presumably because of enhanced transmission of the ultrasound through the lesion. In the nodular type of lymphoma, the internal echoes within a nodule are uniform and hypoechoic (may be sufficiently hypoechoic to be pseudocystic). The border between lymphoma and non-lymphomatous tissue is well-defined and the borderline is described as "broccoli-like or coastline-like" irregularity. In the diffuse type of lymphoma internal echoes are also exceedingly hypoechoic but the border between lymphoma and non-lymphomatous tissues is not distinct. It is difficult to differentiate the diffuse type lymphoma from chronic thyroiditis. The mixed type lymphoma shows multiple, patchy hypoechoic lesions, each with enhanced posterior echoes (70).

SONOGRAPHY OF THE THYROID NODULE

The most frequent use of US is to refine the diagnosis of a thyroid nodule. US can identify thyroid nodules, even when they are too small to palpate. Sonography can demonstrate nodules that have an enhanced risk of malignancy with the best sensitivity of any non-invasive technique, but with only fair specificity. In addition, FNA of thyroid nodules should be performed under US guidance whenever possible.

Thyroid nodules can be identified by sonography because they distort the uniform shape or echo pattern of the thyroid gland. Thyroid nodules may be large or small. They may distort the surrounding thyroid architecture or may dwell within a lobe and be unobtrusive. They may be solid tissue or consist of solid areas interspersed with echo-free zones that represent fluid-filled hemorrhagic or straw-colored degenerative zones (Figure 3). A smooth, globular area without echoes generally represents an epithelial-lined cyst, which is a rare benign lesion (Figure 4) (71). Most thyroid nodules have a less dense ultrasound appearance than normal thyroid tissue and some are more echo-dense (6). A sonolucent rim, which is called a halo, may be present around a nodule. A halo represents a capsule or another interface, such as inflammation or edema, segregating the nodule and the rest of the gland. Doppler technique may demonstrate increased vascularity within a nodule or in a halo (Figure 5) (12). "Nodules" are not a single disease but are a manifestation of different diseases including adenomas, carcinomas, inflammations, cysts, fibrotic areas, vascular regions, and accumulations of colloid.

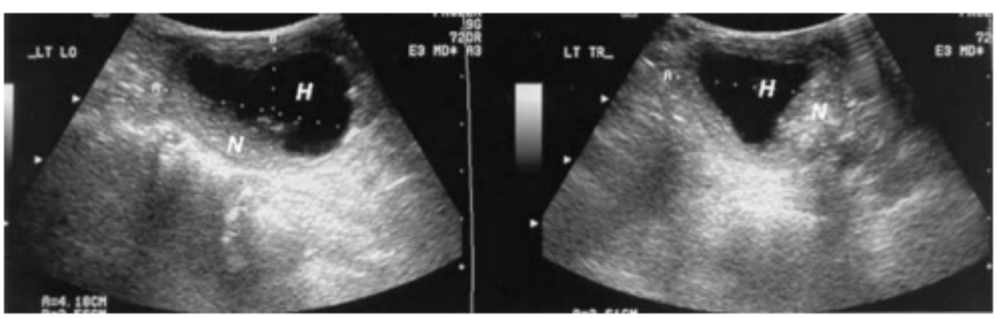

Figure 3. Sonograms showing longitudinal (left panel) and transverse (right panel) images of the left lobe containing a degenerated thyroid nodule. Note the thick wall and irregularity. N = nodule, H = hemorrhagic degenerated region.

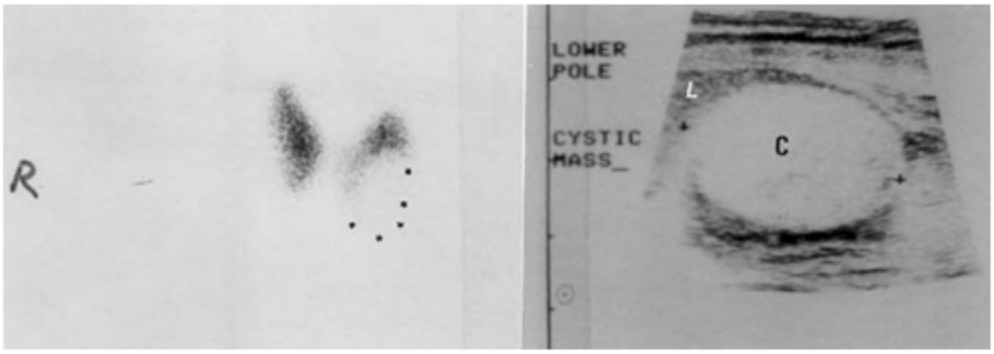

Figure 4. The left panel shows an anterior scintiscan of a euthyroid patient who had a firm nodule in the left thyroid lobe. The nodule is "cold". * * * = nodule. The right panel shows a sonogram of the neck in the longitudinal plane revealing that the nodule is a smooth-walled cystic structure without internal echoes. between the + + symbols. Note the dark dense echoes distal to the cyst. C = cyst, L = thyroid lobe.

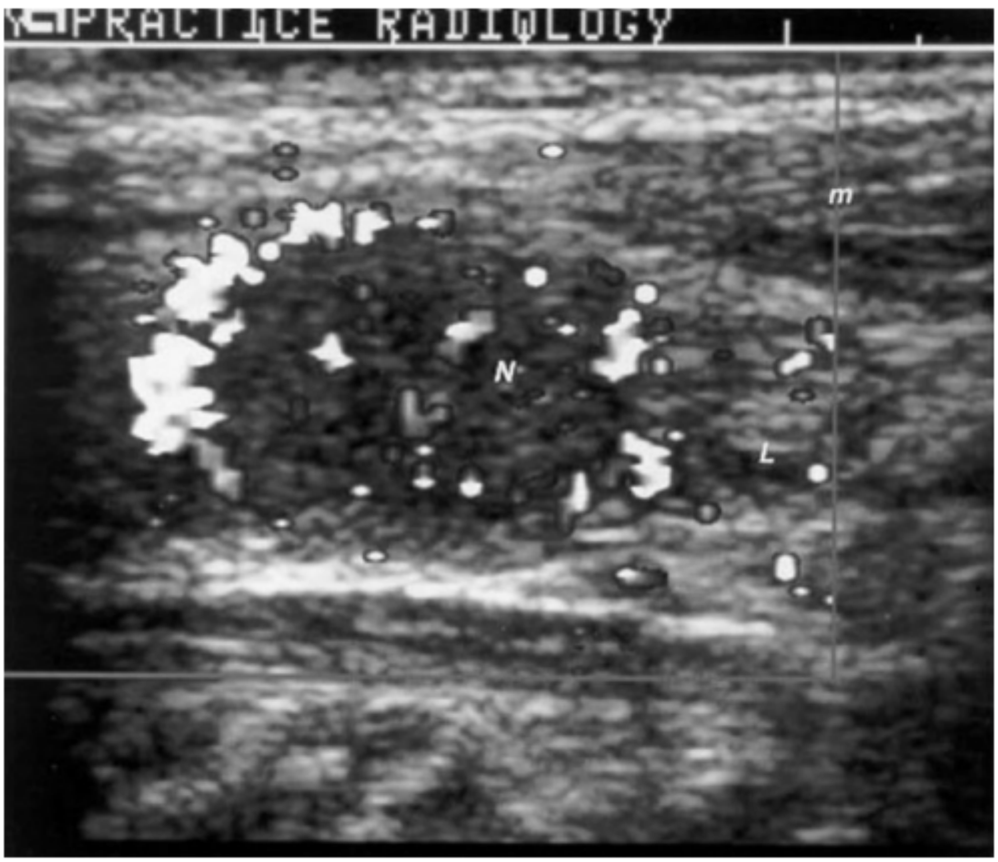

Figure 5. Sonogram of the neck in the longitudinal plane showing a hypoechogenic nodule that was surrounded by an echo free rim, called a halo. Doppler examination demonstrates great vascularity in the halo, identified as bright spots. Small blood vessels are also seen elsewhere. N = nodule, L = heterogeneous thyroid lobe, m = muscle.

The ultrasonic appearance of a thyroid nodule does not reliably differentiate a benign thyroid lesion and cancer (1,6) but it does offer strong clues that help the clinician in the process of triage. Nevertheless, sonography cannot identify a specific kind of tumor such as a Hürthle cell lesion (72). The most reliable sonographic indicator that a nodule is malignant is observing vascular invasion by tumor, which is rarely seen. However, there are distinctions in echo-density, calcifications, distortions of the rim, and vascularity that favor a benign or malignant diagnosis (73,74). These characteristics are summarized in Tables 1 & 2. But it is important to understand that the features described reflect statistical probabilities and not dependable criteria.

Table 1. Ultrasound Characteristics Associated with an Increased Thyroid Cancer Risk
1. Hypoechoic
2. Microcalcifications
3. Central vascularity
4. Irregular margins
5. Incomplete halo
6. Taller-than-wide
7. Significant enlargement of a nodule

Table 2. Ultrasound Characteristics Associated with a Low Thyroid Cancer Risk
1. Hyperechoic
2. Large, coarse calcifications (except medullary thyroid cancer)
3. Peripheral vascularity
4. No hyper-vascular center
5. Spongiform appearance (puff pastry appearance)
6. Comet-tail shadowing

An important aspect is that single or even a few US features may be inadequate to select some nodules for FNA or to reliably assess the risk of thyroid cancer. In contrast, selections based on multiple characteristics that are associated with elevated cancer risk are more dependable indicators of probable malignancy. Nevertheless, certain single features should prompt for FNA including microcalcifications, a taller-than-wide shape, or irregular margins. Absence of elasticity-will probably identify nodules with a clinically meaningful increased, perhaps even high risk for malignancy (75).

- **ECHOGENICITY:** Thyroid malignancies tend to be hypoechoic when compared with the rest of the thyroid (71,76-79). Since many benign thyroid nodules, which are far more common than malignancies, are also hypoechoic, this finding is not particularly useful except that it is reasonably safe to conclude that hyper-dense nodules are probably not cancerous. One group of investigators has concluded that hyperechogenic lesions occurring in thyroiditis-affected thyroid glands bear no-clinical relevance. Therefore, they advocate that aspiration biopsy of these nodules is not advisable (80) and many clinicians follow that practice.
- **CALCIFICATIONS:** The presence of calcification is also not a straightforward diagnostic aid. Microcalcifications are relatively more common in malignant than in benign lesions and may represent psammoma bodies. Microcalcifications have been reported as demonstrating a 95.2% specificity for thyroid cancer, but a low sensitivity of 59.3 % and a diagnostic accuracy of 83.8% (77). B-flow ultrasonic imaging may be particularly sensitive in detecting microcalcifications by demonstrating “twinkling” in some nodules (14). However, large coarse calcifications and calcifications along the rim of nodule are common in all types of nodules and reflect previous hemorrhage and degenerative changes. Thus, since some cancers may have been chronic and have undergone degenerative change, they may demonstrate peripheral or coarse internal calcification. Therefore, diagnostic FNA biopsy may be appropriate even when there are large, coarse, or eggshell calcifications to avoid missing a cancer (79). Indeed, in one investigation, among 64 thyroid nodules with peripheral calcifications 19 (30%) were benign, and 45

(70%) were malignant. Interruption and thickening of peripheral calcifications and decreased internal echogenicity of a thyroid nodule with peripheral calcifications were associated with malignancy in this study (81). In our estimation, considerably more than 30% of such nodules are benign; thyroid calcifications that are greater than pin-point size provides little practical help in identifying cancer in the individual patient. In one study, the highest incidence of calcification was found in thyroid cancer (54%), followed by multinodular goiter (40%), solitary nodular goiter (14%), and follicular adenomas (12%). The authors reported that calcifications in a "solitary" nodule in a person younger than 40 years should raise a strong suspicion of malignancy: relative cancer risk of 3.8 versus 2.5 in patients older than 40 years (82). In contrast to the prior statements, it is important to note that large calcifications are seen with increased frequency in medullary thyroid carcinoma (83).

- **HALO:** A halo around the nodule may be seen with benign or malignant conditions. It suggests that there is an acoustic interface around the nodule that does not reflect the ultrasound. It implies that there are two different types of histology in the region: the nodule and the surrounding thyroid (6,71,84). Some observers have suggested that cancer should be suspected when the periphery of a halo has a blurred appearance. We have not found that characteristic reliable. Since adenomas are more common than carcinomas, the finding of a halo is, in our opinion, more often seen with adenomas than carcinomas.
- **NODULE BORDER:** There have been investigations of a possible correlation between the degree of definition of the border of a nodule and the likelihood of malignancy and even of the predictability of aggressive characteristics of a papillary cancer. In one series of 155 cases, poor definition of a nodule's edge was observed in 21.5% of patients, all of whom showed worse disease-free survival ($p = 0.0477$) than those with a well-defined edge. Furthermore, this finding was directly linked to US-diagnosed lateral node metastasis ($p = 0.0001$) (85). Ultra-high frequency thyroid ultrasound (12–18 MHz) may reveal jagged edges and lobulated borders in 1 to 3 cm thyroid nodules. These findings have been reported to correlate with papillary thyroid cancer with a sensitivity of about 60 to 70% (86).
- **HEMODYNAMIC CHARACTERISTICS:** Increased blood flow in the central part of a nodule is more likely associated with cancer than when the vascularity is along the periphery. An analysis of the hemodynamic characteristics of a nodule by high resolution pulsed and power Doppler ultrasonography also may offer valuable preoperative diagnostic insights. For example, one study of 25 follicular adenomas and 10 follicular carcinomas compared the vascular pattern and the velocimetric parameters (such as peak systolic velocity), end-diastolic velocity, pulsatility index or resistance index. Eight of 10 patients with follicular carcinomas showed moderate increase of intra-nodular vascularity using "Power Doppler". In contrast, the 21 out of 25 follicular adenomas showed only a peripheral rim of color flow. Furthermore, the velocimetric analyses were significantly higher in the patients with cancer than those with adenomas (80).

  Bayes' mathematical theorem has been used to evaluate the cancer diagnostic value of enhanced intranodular blood flow by Doppler analysis in determining the probability of cancer in thyroid nodules that demonstrate follicular cytology. The sensitivity of enhanced intranodular flow by Doppler analysis for detection of thyroid carcinoma was 80%-86% and the specificity of indicating cancer ranged from 85% to 89%. In contrast, the probability that a nodule is thyroid cancer before a Doppler test was estimated at 12%-14%. After Doppler examination, the probability of thyroid cancer increased to nearly 50% in the presence of intranodular flow but declined to 3% when there was no central intranodular flow (87). In one investigation of 230 patients, 203 of whom were treated surgically, the addition of color flow Doppler imaging to conventional sonography increased the screening sensitivity and accuracy in identifying 36 malignant thyroid nodules from 71.9% to 83.3% (88). Thus, Doppler ultrasound may be a particularly useful predictor of the risk of malignancy in thyroid nodules (89).

  Doppler sonography employing ultrasound contrast medium may further enhance the diagnosis of thyroid cancer. In one investigation, carcinomas showed a significantly earlier arrival time of Levovist in the nodule than nodular hyperplastic benign nodules or adenomas (90).
- **SHAPE:** There have been observations that some cancers tend to have a non-globular, "tall" shape, as if

growing in one plane (i.e. the depth of the nodule is larger than the width in the horizontal plane). Nodules that are tall rather than wide should be viewed with considerable suspicion. This observation has recently been validated in 500 patients with thyroid microcarcinomas (91).

- **CYSTIC SPACES:** Especially large benign or malignant thyroid nodules tend to undergo hemorrhagic or cystic degenerative changes. It has been reported that features associated with cancer in a cystic thyroid nodule include more than 50% solid tissue, eccentricity of the cystic space, and micro-calcifications (92).
- **MISCELLANEOUS CHARACTERISTICS:** Ultrasonographers have observed that colloid nodules, which are benign with high probability, have a more or less characteristic appearance of a "stack of pancakes", "puff pastry like a Napoleon", or sponge. In one publication, among 201 nodules, no malignancies were found when the US appearance was greater than 75% "sponge-like" (spongiform) (93). There may be a small, echogenic, bright spot with "comet-tail shadowing" associated with colloid that must be differentiated from a pin-point bright spot. There seems to be triage-merit to these characteristics, which will require critical scrutiny. Furthermore, it is important to be aware that a cancer may co-occur in an otherwise nodular or colloid goiter. This issue will be further discussed below in the section on thyroid biopsy.

To summarize, the cancer-predictive value of ultrasonic characteristics varies considerably but is acceptable when multiple characteristics are considered together. The most supportive data we have found is that there was a 97.2% positive predictive value for cytologically diagnosed cancer and 96.1% predictive value for benign disease among 1,244 nodules in 900 patients who were stratified according to ultrasound characteristics on a scale of 1-5 assessing cancer-risk (85).

In contrast, the sensitivity for cancer, however, is lower as shown in the following studies. Retrospective examination of 849 nodules (360 malignant, 489 benign) revealed that statistically significant ($P < 0.05$) sonographic characteristics of malignancy included: a taller-than-wide shape (sensitivity 40.0%; specificity 91.4%), a spiculated margin (sensitivity 48.3%; specificity 91.8%), marked hypoechogenicity (sensitivity 41.4%; specificity 92.2%), microcalcification (sensitivity 44.2%; specificity 90.8%), and macrocalcification (sensitivity 9.7%; specificity 96.1%). The US findings for benign nodules were isoechogenicity (sensitivity 56.6%; specificity 88.1%; $P < 0.001$) and a spongiform appearance (sensitivity 10.4%; specificity 99.7%; $P < 0.001$). The presence of at least one malignant US finding had a sensitivity of 83.3%, a specificity of 74.0%, and a diagnostic accuracy of 78.0% (74). In an iodine-deficient geographic region where there is endemic goiter and thyroid nodules are frequent, among 2,642 consecutive patients (3,645 nodules) a numeric score was assigned to nodules based on ultrasonic high-risk of cancer. Nodules with a score of over 5.5 out of 10 had a 66% sensitivity and a 76% specificity for cancer, both of which were much higher values than when the scores were below 5 (94).

It is noteworthy that the results of sonography may influence a management decision even when the results of needle biopsy are only "suspicious". In one study, 303 patients who had thyroid nodules with an aspiration biopsy reading of merely suspicious for papillary thyroid cancer had surgery anyway. The pre-surgery ultrasound examination had a positive predictive value of 94.9%, and negative predictive value of 80.9% (95).

The use of a Bayesian classifier to differentiate benign and malignant thyroid nodules by using sonographic features is under investigation (96).

Preoperative US of a nodule that turns out to be thyroid carcinoma has a very limited ability to predict postoperative staging. In one study, the sensitivity of depicting metastases to lymph nodes was 36.7%, invasion of the muscles 77.8%, trachea involvement 42.9%, and esophagus 28.6% (97).

Postoperatively, sonographic features of nodules in a thyroid bed cannot reliably distinguish recurrent thyroid cancer and benign thyroid remnants (98). However, in remnants, increased vascularity, and microcalcifications of a lesion that is larger than 6 mm in size should be viewed with suspicion.

Perhaps more objective, computerized triage of ultrasound features of thyroid nodules will become possible. In one investigation an artificial neural network and binary logistic regression was significantly better than two experienced radiologists in distinguishing benign and malignant thyroid nodules based on 8 ultrasonographic parameters: size, shape, margin, echogenicity, cystic change, microcalcification, macrocalcification, and halo. The study included 109 pathologically proven thyroid lesions (49 malignant and 60 benign) in 96 patients (99).

It is important to note that there may be significant inter-observer variation in interpretation. The inter-observer variation in the interpretation of thyroid ultrasonograms among 4 experienced readers reviewing 144 patients, varied according to the characteristic examined. Echogenicity showed slight agreement (kappa = 0.34); composition, margin, calcification, and final assessment had fair agreement (kappa = 0.59, 0.42, 0.58, and 0.54, respectively); shape and vascularity showed substantial agreement (kappa = 0.61 and 0.64, respectively). Intra-observer variability showed better agreement (kappa > 0.61). For the four radiologists, the overall sensitivity was 88.2%, specificity 78.7%, positive predictive value 76.2%, negative predictive value 89.6%, and accuracy 82.8% (100).

There have been investigations into the differences in the biologic behavior of thyroid cancer based on preoperative US features. One study in patients with follicular variant of papillary thyroid cancer showed more aggressive cancer behavior when there were preoperative US characteristics that suggested malignancy when compared with those without such features (101).

In children, there is no consensus about the value of US characteristics as predictors of malignancy. One group is not enthusiastic (102). Another group of investigators who also did molecular genetics on aspirated thyroid nodules offered a more positive view (103).

SONOGRAPHY OF A PALPABLE DOMINANT NODULE IN AN ENLARGED OR NODULAR THYROID

We now know that a so-called “solitary nodule” in an otherwise normal thyroid gland often is a nodule in a gland that has sub-clinical nodules (see below). Even more frequently, clinicians encounter patients with a “dominant” nodule in an enlarged or nodular thyroid. It is generally agreed that for a dominant thyroid nodule FNA is the best test to assess malignancy. Furthermore, a diagnostic strategy using initial FNA was found to be more cost-effective than starting with ultrasonography or scintigraphy (104). Evidence is mounting in support of US for patients with palpable uninodular thyroid disease and goiter because non-palpable nodules are common and a few of these are cancerous. In many countries, US is being employed more often than previously especially when palpation is uncertain or skills are tentative. US has been reported to provide information to the clinician that importantly alters management in 63% (109/173) of patients who were referred to a tertiary endocrine group. Sonography showed an indication for needle aspiration or demonstrated that the procedure is not necessary. Among 114 patients who were referred because of a solitary thyroid nodule, US detected additional nonpalpable thyroid nodules that were at least 1 cm in diameter in 27 patients and no nodules in 23 subjects. Thus, among 50 patients US lead to an almost equal number of additional aspirations or no biopsy. Among 59 patients who were referred because of goiter, US showed no nodule in 20, thus avoiding biopsy, and revealed nodules at least 1 cm in diameter in 39 patients that required aspiration (27).

THE NON-PALPABLE THYROID NODULE OR INCIDENTALOMA

Sonography demonstrates micronodules (incidentalomas) of the thyroid that are less than 1 cm in diameter, non-palpable, common, and of questionable clinical significance (105) (Figure 6). Whereas palpable thyroid nodules occur in 1.5 - 6.4 % of the general population (106), the incidence of non-palpable nodules is at least ten fold greater when the population is screened by US (107). Non-palpable nodules increase with age to involve approximately 50% of older adults, especially women. The risk of malignancy among palpable nodules is approximately 10% and in micronodules had been thought to be considerably smaller (108). However, investigations reported a similar incidence of cancer in palpable and non-palpable thyroid nodules (109-111). One study actually reported a higher incidence of malignancy among incidentally discovered nodules than among clinically detected lesions (112). However, most microcarcinomas are clinically indolent. Yet, among 317 incidentalomas that were aspirated from 267 patients the rate of malignancy was 12% in a retrospective analysis. In addition, in this subgroup, 69% (25/36) of patients had either extra-thyroidal extension or regional node involvement and 39% had multifocal tumors at surgery, suggesting that the small size alone does not guarantee a low risk in incidentally found thyroid cancers (113).

Therefore, the clinical impact of incidentalomas is quite small but they cannot be ignored. Rather, they should be monitored at intervals with US for suspicious characteristics, size, adenopathy, other clinical features, and - perhaps – a thyroglobulin measurement.

How useful are the sonographic characteristics of non-palpable nodules as an index of malignancy? Some insight to this question has been gained from a study performed on 16,352 self-referred patients in a health care center. Among 1,325 non-palpable thyroid nodules in 1,009 patients, marked hypoechogenicity, an irregular shape, a taller-than-wide shape, a well-defined spiculated margin, microcalcification, and an entirely solid nature were significant predictors for malignancy (P < .05) (114).

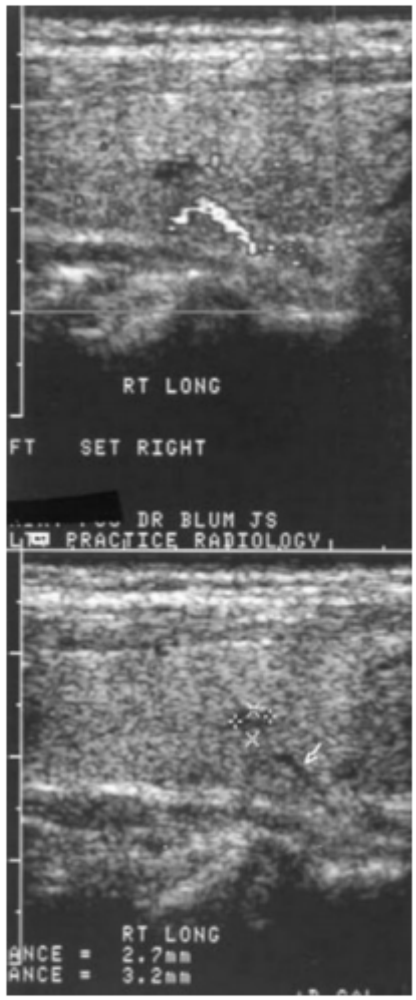

Figure 6. Sonograms of the right thyroid lobe in the longitudinal plane showing a 2.7 x 3.2 mm hypoechoic nodule that is delineated in the lower panel by the xx and ++ symbols. Note the linear hypoechoic structure below that (arrow). In the upper panel the bright structure is a Doppler signal and indicates a blood vessel below the nodule. The nodule is not vascular.

Non-palpable nodules or those that have escaped detection on examination are often discovered incidental to imaging of the neck for vascular or neurological reasons. They may be discovered during upper GI endoscopy (115). These thyroid lesions should be managed like other "Incidentalomas", with observation, dedicated thyroid US, aspiration biopsy, or even surgery, as indicated by the data and mature judgment. This opinion is supported by an investigation in which thyroid nodules were found in 9.4% (116) of 2,004 consecutive patients undergoing carotid duplex ultrasonography. There was high correlation of the nodules with standard thyroid ultrasonography (presence of nodules, 97% (64 of 66) and size, r = 0.95, P<.001). Twenty-one (32%) of the nodules were smaller than 1 cm. Only two patients with unilateral masses noted on carotid duplex had a normal thyroid sonogram. Twenty-nine of the 66 (44%) were selected for fine-needle aspiration biopsy due to cancer-risk criteria. These results lead to surgery in 13 of the 66 (19.7%); pathology included 5 patients with cancer (3 with papillary cancer, 2 with follicular cancer), 4 patients with a follicular adenoma, and 2 with lymphocytic thyroiditis (117).

How successful is ultrasound-guided cytological diagnosis of non-palpable nodules? Intuitively, it is generally believed that success varies inversely with nodule size but the data are not conclusive. The diagnostic yield with nodules as small as 10 mm has been reported as comparable to that of aspirating larger nodules (110). Adequate material for cytological analysis reportedly was obtained in 64% of 0.7-cm lesions and 86.7% of 1.1 cm nodules. For nodules ≥1 cm, the sensitivity was 35.8% and false-negative results were seen in 49.3% (118). In contrast, a study of aspirates from 317 nodules in 267 patients reported that the size of impalpable nodules (0.9 +/- 0.3 cm, a range of 0.2 cm to 1.5 cm) was not related to the probability of getting an adequate specimen for cytological diagnosis (105). Of 201 thyroid nodules that were 5 mm or smaller in size, in 180 patients, investigators reported that were 162 adequate specimens (81%) (115). Personally, we generally do not routinely aspirate nodules smaller than 8 mm but have had limited diagnostic success in sampling incidentalomas as small as 5 mm. Based on a review of the literature, Mazzaferri et al. have concluded that thyroid nodules 5 mm or smaller have a high rate of false positive ultrasound findings and often yield inadequate cytology on fine needle aspiration biopsy. Therefore, they advise that nodules of this size with no other suspicious clinical findings should not undergo routine needle biopsy, even if they appear ultrasonographically suspicious (119). In contrast, more optimistic results have been reported. When ultrasound-guided FNA was done on 5 mm or smaller nodules, surgical confirmation was obtained in 62 nodules and there were 34 (55%) true positives, 0 (0%) false positives, 23 (37%) true negatives, and five (8%) false negative results for malignancy (sensitivity 87%, specificity 100%, positive predictive value 100%, negative predictive value 82%, accuracy 92%, false positive rate 0%, and false negative rate 8%) (120). However, considering the minimal clinical impact of thyroid microcarcinomas, the clinical value of aspirating nodules this small is uncertain. Importantly, the American Thyroid Association guidelines recommend avoiding cytological evaluation of nodules less than 1 cm in size (1). A selected, population base study of 485 thyroid nodules suggested that this advice would not miss any thyroid cancers with high risk features (121).

US has changed our clinical perception of what is a normal thyroid gland and has advanced medical practice. Current high-resolution ultrasonography of the thyroid has permitted the clinical detection of nodules that are as small as 2 mm. It frequently demonstrates that what appears to be a normal gland, actually contains a non-palpable nodule or is a subclinical nodular goiter (78,108). It may show that a solitary nodule on palpation really is a clinically palpable nodule in a gland that is subclinically multinodular. Pathologists have long known about the ubiquitous nature of thyroid micronodules and the relative frequency of occult thyroid carcinomas, which are rarely of clinical consequence. Now the clinician is often confronted with the challenge that micronodules are discovered as a consequence of investigations for orthopedic, neurological, vascular pathology or other pathologies, or together with a palpable thyroid nodule. As a rule, their discovery often results in needless expense, concern, and therapy because it is not known which of the myriad nodules that have been revealed is, or will progress to become a cancer with clinical impact.

It remains for future investigation to determine the appropriate management for micronodules. Because it is rare for one of these lesions to represent an occult thyroid cancer and rarer still for one to become a clinically significant malignancy, non-selective surgery, which has an exceedingly small yield of cancer and is not risk-free, seems ill advised. Also inappropriate is dismissal of the problem as unimportant. Rather, to this author, periodic sonographic reassessment for possible growth of the nodule or change in characteristics appears preferable. The role of ultrasound guided needle biopsy in the management of these patients, especially when there is a history of exposure to therapeutic x-ray will be discussed below.

Not all "incidentalomas" in the neck are thyroid in origin. Parathyroid adenomas have been observed within the thyroid gland or in the usual parathyroid anatomic location when ultrasonography was performed to evaluate thyroid nodules (122,123). An example of a misidentified lesion that demonstrates the extent of the lack of specificity of a "sonographic nodule" is an esophageal tumor that was erroneously characterized as thyroid (124).

SONOGRAPHY OF LYMPHADENOPATHY

Even in a patient with thyroid cancer, enlarged benign thyroid lymph nodes are more common than malignant ones. Nevertheless, US may be useful to diagnose and if appropriate, periodically reassess lymphadenopathy in the patient with a history of thyroid cancer, or if there is a history of exposure to therapeutic radiation in childhood or adolescence. A high-resolution ultrasound system equipped with a high-energy linear probe, a 12 -15 MHz transducer, B-Mode and Doppler capability, experience, and diligence are required to detect lymphadenopathy.

NORMAL LYMPH NODES: Normal lymph nodes are depicted by sonography as approximately 1 X 3 mm, well-defined, elliptical, uniform structures that are slightly less echo-dense than normal thyroid tissue and that have an echo-dense central hilum. Lymphadenopathy that is reactive to infection may be larger but the lymph nodes tend to maintain an oval shape; in contrast, malignant nodes more often have a "plump" rounded shape (125) (Figures 7, 8).

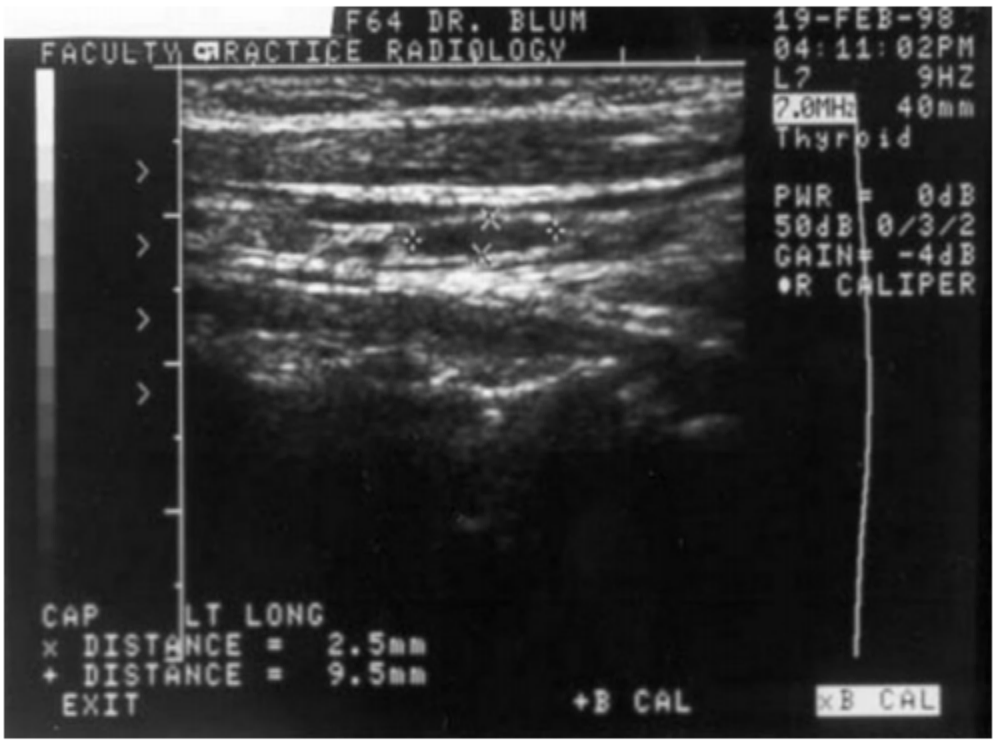

Figure 7. Sonogram in the longitudinal plane of the left side of the neck after thyroidectomy showing a small, elliptical benign appearing lymph node in the jugular region. It is delineated by the xx and ++ symbols.

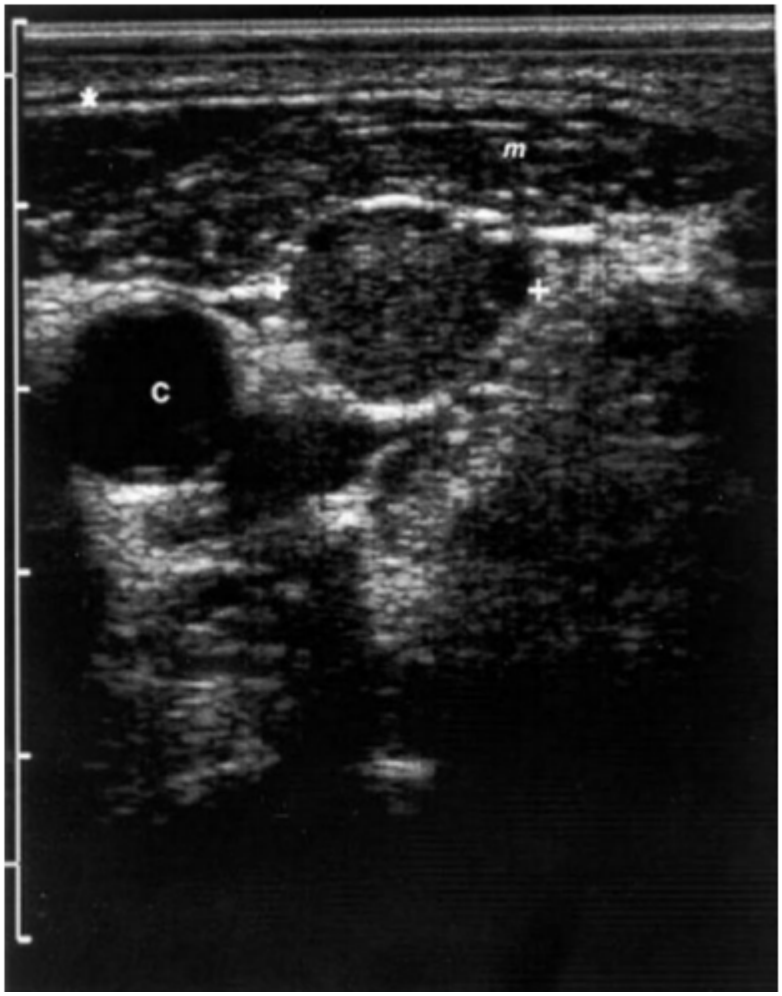

Figure 8. Sonogram in the transverse plane after thyroidectomy for cancer, from a muscular man. There was no palpable mass. The image shows a rounded lymph node that was cancer. C=carotid artery, m=muscle, ++ marks the node.

Especially in children, inflammatory lymphadenopathy is common, which may complicate a search for cancerous nodes. Tuberculous cervical lymphadenitis can mimic metastatic lymph nodes from papillary thyroid carcinoma (126). Indeed, especially in a region where tuberculosis is endemic, even when a patient is known to have papillary thyroid cancer, adenopathy reportedly is more commonly due to tuberculosis than to thyroid cancer (127).

A source of confusion in diagnosing lymphadenopathy especially in the elderly and obese subjects is fatty change in a node that may mimic a macro-metastasis at palpation. US can offer useful insight. In one study, of 110 selected patients with a total of 247 nodes, the central “fatty”, hyperechoic hilum was quite large, extending more than one third of the transverse diameter. The ratio of the long to short axes of the node and the parenchyma to fat (P:F) were obtained. Differences between mean P:F ratio in diabetic and nondiabetic patients were significant (p=0.045). The mean P:F ratio was negatively related to body mass index (BMI) (r=0.62, p=0.015) and age (r=0.54, p=0.024). All of the nodes examined with a mean P:F ratio ≤ 1.2 (58) were found in patients older than 72 years and with a BMI higher than 27.8 (30).

CHARACTERISTICS OF MALIGNANT LYMPHADENOPATHY: There are ultrasonic characteristics of lymphadenopathy that correlate in a clinically useful fashion with metastases from thyroid cancer. The features that correlate most highly include microcalcifications, a spherical shape, a large cystic space, loss of the hilum, and neo-vascularization that is characterized by blood vessels penetrating the node from its periphery rather than its hilum.

The results of investigations are reasonably confirmatory. In one study of 19 patients who were referred for lymph node dissection, 578 nodes were removed, 103 of which were ultrasonically detected. The authors analyzed only the 56 nodes (28 benign and 28 malignant) that were unequivocally matched for US and pathology. The authors reported that the major criteria of malignancy were: cystic appearance, hyperechoic punctations, loss of hilum, and peripheral vascularization. If there was only cystic appearance or hyperechoic punctations, the risk of malignancy was lower but still suspicious of malignancy. They were of the opinion that nodes with *"a hyperechoic hilum should be considered as benign, that peripheral vascularization has the best sensitivity-specificity compromise, and that round shape, hypoechogenicity, and the loss of hilum taken as single criterion are not specific enough to suspect malignancy"*. The reported sensitivity and specificity of these criteria were 46 and 64% for round shape (long to short axis ratio < 2), 100 and 29% for the loss of fatty hyperechoic hilum, 39 and 18% for hypoechogenicity, 11 and 100% for cystic appearance, 46 and 100% for hyperechoic punctations, and 86 and 82% for peripheral vascularization (128). In several other investigations, the two most useful diagnostic characteristics are the ratio of the longitudinal to the transverse diameter of a lymph node (L/T ratio) and the absence of a central echogenic hilum (125,129-131). In one study, the L/T ratio was less than 1.5 in 62% of metastatic nodes and greater than two 2 in 79% of reactive nodes (132). A wide cortex or narrow hilum was observed in 90% of malignant lesions, but only 45% of benign nodes. The absence of a hilum was observed in 44% of malignant lesions, but in only 8% of benign nodes. In this study the size and uniformity of a lymph node was not helpful in differentiating benign or malignant nodes.

The location of adenopathy in proximity to the thyroid in the central compartment of the neck may also be indicative of thyroid cancer. Multivariate analysis in an investigation addressing this question showed that only central location (odds ratio, 4.07; 95% confidence interval (CI), 1.64 to 10.10) and size (odds ratio, 5.14; 95% CI, 1.64 to 16.06) remained as significant corollaries of cancer (57).

It is not clear whether additional information about the nature of lymphadenopathy may be offered by color and spectral Doppler investigation. Although one group of investigators found that malignant nodes (29/32) more often than benign ones (6/16) demonstrate enhanced color flow signals (133), another group observed abundant color flow signals in all enlarged lymph nodes (134). There may be some diagnostic value to examining the ratio of systolic and a diastolic blood flow in a lymph node, which is called the resistive index. It has been reported that cancerous lymph nodes have a high resistive index (mean 0.92) while reactive nodes have a considerably lower value (<0.6) (134). Another investigator reported that metastatic nodes from papillary carcinoma frequently demonstrate prominent hilar vascularity similar to reactive nodes (135).

Among abnormal nodes that had cystic spaces, one study showed a high likelihood of papillary thyroid cancer as assessed by FNA. Cystic changes were not seen in 43 of 63 pathologic nodes that were either metastatic from other malignancies (22 patients) or benign reactive lymphadenopathy (21 patients) (136). Since cystic spaces due to necrotic material may be seen in tuberculous nodes, caution is warranted when one interprets the clinical meaning of this finding. An important diagnostic aspect of cystic masses that are lateral to the thyroid is demonstrated by one report that showed that among 37 adults (age 16-59 years), 10.8% of cervical cysts were lymphatic metastases from occult thyroid carcinoma (137). Others have reported similar observations and the point has been made that in younger patients, the lymph nodes might appear purely cystic, thereby mimicking branchial cysts (138).

In some studies, the addition of CT of the neck to US was found to be slightly superior to sonography alone for the detection of metastatic papillary thyroid cancer lymph nodes in the lateral compartment of the neck but not in the central compartment (139). Another investigation suggested that high-resolution ultrasound is accurate in preoperative evaluation for extra-thyroidal tumor extension and lateral lymph node metastasis. In contrast however, in this study, CT had greater sensitivity than ultrasound alone in the detection of central lymph node metastases (140).

In patients with suspected recurrent thyroid cancer, however, a combination of diagnostic techniques maybe necessary to differentiate a true recurrence and noncancerous images, called cryptic findings (141). Fused I-131 whole body scan SPECT when coupled with CT or PET can elucidate the nature of such images. Many of these findings prove to be inflammatory in nature, thereby avoiding unnecessary treatment with I-131 (142). Precisely directed US has been reported to enhance the specificity while maintaining sensitivity, especially in the neck and superior mediastinum (143).

Cytological, immunocytological, and biochemical (thyroglobulin) analysis of enlarged cervical lymph nodes, using the ultrasound-guided aspiration biopsy technique described below, can differentiate thyroid cancer metastases and inflammatory lymphadenopathy (144). It is important to add that is not necessary to require a classical cytological diagnosis of thyroid cancer in a lymph node aspirate. Any evidence of thyroid cells or the detection of thyroglobulin in the node is adequate proof of cancer; thyroid cells or thyroglobulin do not belong in non-cancerous nodes.

WHAT A THYROID ULTRASOUND REPORT SHOULD INCLUDE

The thyroid ultrasound report must answer the question that has been posed by the clinician and not be just a routine recitation. The ultrasonographer or the thyroidologist who interprets the images should note and record in the report the features listed in Table 3 and call specific attention to the features that reveal a higher than average risk of malignancy.

TABLE 3. ESSENTIAL ELEMENTS OF A THYROID ULTRASOUND REPORT
1. Each lobe and isthmus
A. Dimensions of Lobes (cm)
B. Shape of Lobes, (conventional shape or indentations and where they are)
C. Echogenicity of Lobes
Hyperechoic
Hypoechoic
Isoechoic
Heterogeneous
D. Vascularity of Lobes
Physiologic
Increased
Decreased
Avascular
E. Nodule(s) in Each Lobe or Isthmus
Location
Number of Nodules (1 or 2, a few, multinodular)
Do all nodules have uniform characteristics?
Does one nodule have noteworthy characteristics? *
Margins
Distinct
Ill-defined
Halo
Continuous
Discontinuous
Echogenicity of nodule
Hyperechoic
Hypoechoic *
Isoechoic *
Composition

Solid
Cystic
Complex (solid with cystic component)
Shape
Globular
Irregular
Taller-than-wide *
Vascularity
Physiologic
Decreased
Avascular
Increased
Peripheral
Central *
Calcifications
Punctate *
Coarse
Egg-shell
Other features
Puff-pastry “Napoleon-like” layers that are alternatingly echo-dense and echo-poor
Spongiform
Bright spot with “comet tail shadowing”
2. Lymph nodes *
Location
Ipsilateral to nodule
Contralateral to nodule
Standard levels or relation to another anatomic structure
Shape
Oval, elliptical
Globular *
Hilum
Fatty
Vascular
Absent *
Margin
Well-defined
Ill-defined *
Vascularity
Increased
Physiologic
Blood-flow from periphery rather than hilum *
Calcifications
Punctate *
Coarse
Egg-shell
Composition

Solid
Complex with cystic component *
Impact on surrounding structures
Deforming or infiltrating *
No impact
3. Extra-thyroid bed mass
Anatomic site (thyroglossal? sub-lingual?)
Ultrasonic characteristics
4. Comparison with prior examination, prior date, _____________
Comparison based on _____report or _____images?
Technically comparable? _____Yes _____ No
Compare characteristics of lobes
Compare characteristics of nodules
Compare characteristics of nodes

*Enhanced risk of thyroid cancer

It is both logical and useful to separate a report into: 1) a brief statement of the reason for the US in the context of the history including pathology if any, 2) an objective narration of the findings, which represents the anatomy as defined by ultrasound, and 3) a brief, subjective, summary and conclusion or opinion. Mixing concepts 2 and 3 can be confusing to the clinician by mistaking what the interpreter sees in distinction to what he/she thinks, which may lead to variance in management.

There have been several attempts to codify thyroid ultrasound reports and stratify cancer-risk. An example is the Thyroid Imaging Reporting and Data Systems (TIRADS). One of them has, for example, been correlated with needle-biopsy results in 1959 thyroid nodules. The classifications were expressed as 1-5 with the following percentages of malignancy: TIRADS 2 (0% malignancy), TIRADS 3 (<5% malignancy), TIRADS 4 (5-80% malignancy), and TIRADS 5 (>80% malignancy). In a sample of 1097 nodules (benign: 703; follicular lesions: 238; and carcinoma: 156), the sensitivity specificity positive predictive value, negative predictive value, and accuracy were 88, 49, 49, 88, and 94%, respectively. The major problems of this approach are that the classifications are subjective and, as we shall see below, environmental and other factors may influence ultrasound appearance of nodules. Nevertheless, uniform, reproducible, and relevant reporting should facilitate clinical management and help the clinician to select nodules for aspiration biopsy, surgery or observation (145).

In one investigation, the American College of Radiology TIRADS structured reporting improved the “quality” of thyroid ultrasound reports. The authors reported an improved description of features that were predictors of malignancy. In addition, there was an increased number of definitive management recommendations that resulted in reducing the number of biopsies. In this author’s opinion, the value of management advice and reduced biopsies based on image appearance alone needs to be established on more firm evidence than is currently available (146,147). Attempts are in progress to unify thyroid ultrasound reporting features and recommendations, as well as the various TIRADS systems, across the various medical specialty societies and also internationally (148).

Several novel computer-based approaches taking advantage of developments in artificial intelligence for malignancy risk assessment of thyroid nodules in ultrasound images have been suggested. Local echogenic variance and boundary features are utilized to incorporate information associated with local echo distribution. Analysis of variance is performed utilizing feature vectors derived from all combinations of the characteristics under study. The classification results are evaluated with the use of receiver operating characteristics that are capable of discriminating between medium-risk and high-risk nodules (149). This promising field Is it in its infancy.

SONOGRAPHY IN THE PATIENT WITH A HISTORY OF

HEAD AND NECK THERAPEUTIC IRRADIATION IN YOUTH

In the patient with a history of therapeutic irradiation to the head and neck in youth, the thyroid cancer risk may be as high as 30%. Since thyroid nodules may be detected with ultrasound before they become large enough to be palpable, sonography has been employed to screen irradiated people for tiny nodules. This selection process is quite inefficient because in the process, many more benign nodules are found than malignant ones. Furthermore, as has been observed after the nuclear event in Fukushima, Japan, the detected papillary microcarcinomas tend to be indolent (150). Consequently, some clinicians prefer not to detect micronodules contending that they are clinically irrelevant. In contrast, the author prefers to obtain a potentially useful baseline sonogram, but not to act on the presence of a micronodule unless a repeat sonogram after an interval of time demonstrates its growth or other circumstances that heighten the suspicion of malignancy. It is this author's practice to obtain a thyroglobulin level when a micronodule is detected and again a year later in order to assess whether it has risen significantly. However, this conjecture and its validity have not been studied rigorously.

SONOGRAPHY TO MONITOR CHANGES IN THYROID OR NODULE SIZE

Changes in the size of a nodule may be clinically important, but difficult to perceive clinically. However, sonography can accurately and objectively assess changes in the volume of thyroid nodule(s) and the thyroid gland over a period of time. This is especially important during the course of therapy with thyroid hormone, in patients with a history of exposure to therapeutic irradiation, and when there is a history of thyroid cancer. Interval studies on such patients may be performed without discontinuing thyroid suppressive therapy, administering recombinant human TSH, or any preparation of the patient. Consequently, it is a simple matter to compare serial records, which may lead to changes in thyroid management earlier than palpation alone would warrant. Furthermore, since most patients tend to change doctors and residence over a period of years, an objective assessment of the size and volume of the thyroid gland or nodules will greatly facilitate the continuity of care.

Caution is warranted in interpreting the meaning of changes in the volume of thyroid nodules shortly after fine-needle aspiration has been performed. Bi-directional volume changes after the biopsy have been reported (151). Therefore, it is appropriate to assess nodule size at least weeks after FNA. For the same reason, to assess nodule size after a period of observation or suppressive therapy, the US should be done before another FNA is performed.

A Downside to Serial Sonography to Monitor Changes in Thyroid or Nodule Size/Volume

Although it makes intuitive sense to repeat sonograms at some interval to detect early evidence of growth or malignant change, there is a downside to this practice too. There is indication that frequent screening with serial neck US is more likely to identify **false positive abnormalities** rather than significant disease. Therefore, coupling repeat US with clinically suspicious events or examination is warranted (152).

SONOGRAPHY IN THE PATIENT WHO HAD THYROID CANCER

Sonography has become a most useful imaging procedure in patients who have had either partial or complete thyroidectomy (Figure 8) (153). Sonography is done without interrupting the therapy with thyroid hormone, which is used universally in the thyroid cancer patient.

One study, in which 110 patients who had partial or total thyroidectomy for thyroid cancer were examined every 1-2 years, showed that ultrasonography is the most sensitive and important way to image postsurgical recurrences of thyroid carcinomas and lymphadenopathy in the neck (154). This observation is most important because recurrence in the neck is by far the most common location of reappearance of thyroid cancer. The authors suggest routine use of US in these patients.

Furthermore, a five-year observational study of 80 patients investigated the optimal initial follow-up strategy for patients who had near total thyroidectomy for papillary thyroid microcarcinomas (155). Sonography identified lymph node metastases not only in two thyroglobulin-positive patients but also in one thyroglobulin-negative patient. Importantly, after observation for 32 +/- 13 months after surgery, all US node-negative patients had undetectable thyroglobulin levels while on suppressive therapy and US remained negative. In contrast, whole body scanning showed no "pathological" uptake in any patient and was essentially useless, probably because differentiation of postoperative gland-remnants and tumor was not possible. Yet, radioiodine uptake in the region of the thyroid bed did correlate with recombinant human TSH (rhTSH)-stimulated thyroglobulin levels: 1 ng/ml or less in 45 patients without uptake and more than 1 ng/ml in 35 patients with uptake ($r = 0.40$, $P < 0.0001$). The authors concluded that in their population, the thyroglobulin probably derived mainly from small normal tissue remnants rather than cancer. Therefore, they contend that mild elevations of thyroglobulin are also of limited diagnostic value.

Sonography can detect post-operative thyroid remnants in the thyroid bed and thyroglossal region even when surgeons report a total thyroidectomy. One investigation found US remnants in 34 of 102 cases (156). This author believes that the frequency of remnants is highly experience- and surgeon-dependent.

It is important to appreciate that sonography may yield clinically erroneous or misleading results if it is performed during the initial several months following the surgery. During this time there may be abundant lymph nodes and heterogeneous, sono-dense regions that probably reflect postoperative changes such as edema and inflammation.

Sonography may serve to uncover unsuspected disease. After less than total thyroidectomy, sonography will detect nodules in the thyroid remnant, post-operative thyroid bed or in the contra-lateral thyroid lobe, which could be benign tissue or tumor. After total thyroidectomy but not following partial thyroidectomy, nodules and adenopathy are more likely to represent cancer when the concentration of thyroglobulin is elevated. Sonography may detect this disease even before it has grown sufficiently large to be palpable.

In patients in whom thyroid carcinoma has been diagnosed as the result of metastases to bone, lung or cervical nodes, sonography can detect an occult thyroid primary cancer even if the thyroid gland is normal to palpation.

One investigation has shown that rhTSH-stimulated serum thyroglobulin measurements combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma in children, and many investigators believe in adults also (157). One group of investigators has reported that even when thyroglobulin levels remain low or undetectable after stimulation with rhTSH, sonography may identify lymph node metastases from thyroid cancer (158).

It may be difficult to differentiate a suture granuloma from recurrent thyroid cancer. A case report demonstrated a nodule that mimicked recurrent thyroid cancer on sonography and 2-{fluorine-18}-fluoro-2-deoxy-D-glucose positron emission tomography, but the diagnosis of a suture granuloma was confirmed by a US-guided fine needle aspiration biopsy (159). The ultrasonic appearance of suture granulomas includes echogenic foci larger than 1 mm in diameter ($p<0.05$) that are paired ($p<0.05$), and usually are clustered centrally or on near the middle of the nodule, unlike those in recurrent carcinomas ($p<0.05$) (160).

US is useful in the operating room during surgery. Intra-operative ultrasonography may enhance the ability to locate and resect recurrent thyroid cancer that does not accumulate radioactive iodine. Experience in seven patients suggests that sonography was particularly helpful after external beam radiotherapy to identify tumor nodules of 20 mm or less that were invasive or adherent to the airway (161). One investigation reported that intra-operative ultrasound performed by the surgeon influenced the management in 57 percent (41/72) of patients by identifying non-palpable adenopathy (162). However, one wonders if resection of non-palpable or even larger deposits of differentiated thyroid cancer will affect outcomes since historically even bilateral radical neck dissection was not associated with enhanced results when compared with thyroidectomy alone. Nevertheless, excision of non-palpable nodules that are in proximity to a vital structure could be palliative if the cancer is removed before it invades. In this author's opinion intra-operative US could become standard to look for and remove undetected nodes after the surgeon has completed a thyroidectomy for cancer, even after a compartmental node dissection, before "closing".

Preoperative sonography in the cancer patient may be associated with decreased recurrences. One group of investigators studied 275 patients who underwent pre-operative US and had a median follow-up of 41 months.

They reported that patients who have had recurrence of papillary thyroid cancer were at an increased risk for subsequent recurrence of the tumor in the neck. US before the initial operation and followed by compartment-oriented surgery based on the US was related to decreased subsequent recurrence rates (162).

With respect to the lateral compartment of the neck, preoperative US is an excellent predictor of outcome for disease-free interval. Furthermore, a surgical approach based on preoperative US provides excellent long-term regional control (163).

SONOGRAPHY IN CONJUNCTION WITH NEEDLE BIOPSY

Fine needle aspiration biopsy of thyroid nodules and adenopathy in adults, children, and adolescents has become a major diagnostic tool that is safe and inexpensive (133,164-169). Major untoward effects are very uncommon and include bleeding (especially in patients who use anticoagulants or antiplatelet agents or those who have a bleeding diathesis), hoarseness, and infection. Many authorities, however, contend that it is reasonably safe to continue anticoagulants, including the newer novel agents, in patients who been taking these medications when performing an FNA (170). Having seen a few patients who have experienced excessive bleeding as a result of FNA while using aspirin or anticoagulants, it is this author's practice to discontinue any agent that interferes with coagulation of blood prior to performing and FNA. Actually, there have been very occasional reports of fatal cervical hemorrhage related to FNA (171). Furthermore, even if there is no increased risk of significant hemorrhage due to FNA, the specimen maybe diluted by unnecessarily abundant red blood cells, complicating cytological interpretation. Seeding the needle track with thyroid cancer is a remote consideration (172,173).

Indications

The major indications for ultrasound-guided FNA are summarized in Tables 4 and 5. Ultrasound has made placement of the needle more accurate especially for small or complex nodules or nodes. Cytopathological interpretation is usually clinically satisfactory and promises to improve with tissue marker analysis of specimens (174). However, the accuracy of the puncture varies considerably depending on factors that are related not only to the operator and the cytologist, but also to the patient. The latter conditions include the size, homogeneity and vascularity of the nodule or node, its location in the neck, sampling errors, and the habitus of the patient. These issues affect biopsy technique.

Table 4. Needle Biopsy with Ultrasound Guidance is Generally Reserved For:
1. A small nodule in an obese, muscular, or large framed patient.
2. Nodules that are barely palpable or non-palpable
3. Nodule size less than one centimeter.
4. A nodule that is located in the posterior portions of the thyroid gland.
5. A dominant or suspicious nodule within a goiter.
6. All nodules that yielded non-diagnostic results on a free-hand biopsy.
7. Complex degenerated nodules if a prior biopsy without ultrasound guidance has not been diagnostic.
8. Incidentalomas that have been detected ultrasonically in patients with high risk factors for thyroid cancer such as exposure to therapeutic x-ray.
9. Small lymphadenopathy.

Table 5. Features That Warrant Percutaneous Fine-Needle Aspiration Biopsy of a "Solitary" Nodule or a "Special" Nodule in A Goiter
1. Clinical Features
a. History of head and neck irradiation in youth

b. Family history of medullary (or signs & symptoms) or less so papillary thyroid cancer
c. Unusual firmness without calcification
d. Growth of nodule especially during suppressive therapy
e. Lymphadenopathy
2. Ultrasonic Features (at least two "suspicious" ultrasound features)
a. Hypoechoic nodules with one or more of the following
i. Irregular margins
ii. Enhanced intranodular vascular spots (central vascularity)
iii. Microcalcifications (punctate calcifications)
iv. Blurred margins
v. Taller-than-wide nodule shape
vi. Enlargement of a nodule when compared to prior examination
b. Lymphadenopathy (palpable or ultrasonographic)
3. In a goiter, biopsy the nodule that has "suspicious" ultrasonographic features rather than the largest nodule.
4. The size or number of nodules in a gland does not correlate with risk factors

Methods

Thyroid nodules or lymph nodes that are palpable are often biopsied directly. In some cases, correlation of the palpable anatomy with a sonographic film or screen image may be useful. In such cases, for small, complex, or deep nodules, or when a palpation-guided biopsy has resulted in an insufficient specimen, ultrasound-guided fine needle biopsy is employed (27,175), but with added cost ($289 by one estimate (176) and some inconvenience. Direct, real-time ultrasound guidance improves accuracy in puncturing the nodule. Ultrasound-guided biopsy is always required for impalpable incidentalomas and even then, it is difficult to reliably sample lesions smaller than 10 mm, as discussed previously.

Two methods for ultrasound-guided needle biopsy have been suggested: 1) A sonographer manipulates the transducer to locate the nodule and a second physician inserts the needle under direct vision. With practice, the assistance of a second operator is usually not required. 2) A special clamp is used to hold the transducer and fix the direction of insertion of the needle. Both require hand-eye coordination and experience is necessary to identify the spot on the skin over the target nodule to insert the needle. In our practice a dimple is produced on the skin with a blunt 1 mm wooden dowel directly over the nodule as the transducer identifies it. We have not found it appropriate to employ a "permanent marker" for this purpose, as has been suggested (177). Furthermore, this author finds the holder cumbersome and restrictive and prefers the free hand approach. With the free-hand method, the needle may be inserted parallel to, or at an angle to the ultrasound beam and at a short distance from the transducer, aiming at the nodule. The parallel approach may be technically challenging but is "comforting" to the operator because the image of the needle shaft may be viewed as it traverses the neck and into the nodule. Nevertheless, many experienced operators prefer an oblique to a perpendicular approach because of its simplicity and relatively fewer complications. The needle shaft is not imaged with this technique but its tip is seen as a very bright spot when it crosses the plane of the scan. The tip of the needle must be within the nodule during aspiration. However, even with ultrasound guidance, it is rather difficult to be certain that the tip of the needle is actually within a small nodule at the instant of aspiration, particularly if it is less than 7 or 8 mm in diameter (Figure 9).

Figure 9. Sonogram from an ultrasound guided fine needle aspiration biopsy showing a hypoechoic small nodule. The bright spot (above the arrows) is the tip of the needle within the nodule at the instant of aspiration. N=nodule.

Employing Doppler technique to identify and avoid puncturing blood vessels in the region of a nodule provides a distinct advantage of ultrasound-guided aspiration over palpation-guided biopsy. This precaution reduces the amount of blood in the aspirate and facilitates interpretation of the cytology (178). The same purpose is served by discontinuing antiplatelet and anticoagulant medication prior to a biopsy.

Samples of thyroid nodules and adenopathy may be obtained in either of two ways. One may aspirate the material with a syringe, employing a to and fro motion to produce a large quantity that frequently contains excessive blood, and complicates cytological examination. This author prefers the capillary technique that is done with a 25 or smaller gauge needle (without a syringe) using minimal trauma. The utility of a 27-gauge needle has been validated (179). Capillary action achieves a small, concentrated sample that remains in the needle shaft. The specimen is then expelled with an air-filled syringe quickly and gently on to a microscope slide (180). The diagnostic accuracy of the two methods is equivalent (181). One group has reported that the non-aspiration technique produces specimens of better quality and reduces inadequate results (182).

In this author's experience, the capillary action aspiration method results in a superior cytological yield and the syringe/larger needle aspiration should be reserved for low-yield or fibrotic lesions.

Microscopic assessment of aspirates onsite for adequate cells by a cytologist at the time of the biopsy significantly reduces the number of non-diagnostic reports especially when the operator is not optimally experienced (183). It is likely that on-site assessment of cytopathologic adequacy of aspirates would help reduce the costs of needle biopsy, reportedly, by as much as 35.5%, by reducing unsatisfactory specimens that are sent to off-site cytologists (184). Furthermore, in some centers cytologists actually do the aspirations (185).

Ultrasound-guided FNA is an accurate method for identifying suspected recurrence of thyroid cancer in enlarged lymph nodes or in the thyroid bed.

Specimens

Obtaining material that is sufficient for a reliable cytological diagnosis involves competing realities. It is often necessary to do multiple punctures of a thyroid nodule to obtain enough cells even when ultrasound guided aspiration is employed. Yet, the first puncture is likely to be associated with less blood than subsequent samplings and may therefore be the best one for the cytologist to interpret. Especially for small nodules and those that are very vascular, gentle technique and point of service examination of the aspirate with a microscope to assess adequacy are important factors. In some cases when a hematoma has been produced it may be prudent to delay completing the aspiration until another day when the blood has been resorbed. Furthermore, especially when there are only a few benign-looking cells, the clinician should not be convinced that a nodule has been sampled adequately. Rather, a repeat biopsy after an interval of time may be prudent. In contrast, high suspicion is warranted when there are even a few cells that have features that are associated with malignancy. Sometimes cytology cannot suitably assess the pathological potential of a nodule. Such nodules are referred to as Atypia of Unknown Significance (AUS) or Follicular Lesions of Unknown Significance (FLUS), which will be discussed elsewhere. Caution is appropriate in accepting a report of negative cytology when the aspiration was done because a nodule grew during the course of suppressive therapy. Occasionally, when the specimen is inadequate, a better specimen maybe obtained with a needle with a larger lumen (186).

Effectiveness

One investigation retrospectively evaluated the effectiveness of ultrasound-guided fine-needle aspiration, in 37 patients previously treated for thyroid cancer, in identifying as cancer those cervical nodules that were suspicious of recurrence. There were 29 true positives, 6 true negatives, 1 false negative, and 1 inadequate biopsy. Therefore, US-guided biopsy had a sensitivity of 96.7%, a specificity of 100%, and an overall accuracy of 97.2% in detecting recurrence (187).

Caution with Respect to Negative Cytology in Children and Adults When the US is Suspicious

In a retrospective investigation of 35 children and adolescents, the global accuracy of FNA was 83%, with a sensitivity of 75%, and a specificity of 94%. Fourteen FNAs suggested malignancy (40%), only 1 of which was a false positive (7%). In significant contrast, 5 of the 21 FNAs suggesting benign lesions were false negatives (24%). These 5 cases had US findings suggestive of malignancy (188). Thus, a cautious approach is warranted especially in children when US findings suggest malignancy even if the cytology is benign.

In the postoperative thyroid bed, ultrasound-guided FNA may be particularly useful. In one series, among 21 cases there were 15 recurrent cancers, 5 benign nodules such as a parathyroid gland or regenerated normal thyroid, and 1 false positive (189).

There is limited ability to reliably aspirate and accurately diagnose a non-palpable nodule or node even with ultrasound-guidance (190). Ultrasound-guided cytological diagnosis of non-palpable nodules depends on the size of the lesion. One study suggested that the diagnostic yield of aspirating incidentally discovered, non-palpable 10 mm or larger thyroid nodules was high (99). Another study found that sampling of material that is adequate for cytological analysis was 64% for a 0.7-cm lesion and it increased to 86.7% when a nodule was 1.1 cm. For nodules that are 1 cm or smaller, the sensitivity was 35.8% and false-negative results were seen in 49.3% (108). In contrast, similar success has been reported in aspirating nodules that were 4 to 10 mm in size when compared with larger ones (191).

We have had mixed diagnostic success in sampling nodules or nodes as small as 5 mm. A few micro-cancers have been discovered in this way. The cost-effectiveness of aspirating nodules this small is uncertain considering the small (if any) clinical significance of thyroid microcarcinomas. We biopsy small lymph nodes that are “plump”. Generally, the width/depth must be almost 1 cm to yield adequate cells.

The cancer-predictive value of measuring thyroglobulin in the wash-out obtained from a cell-poor aspirate of nodes has been mentioned. Assaying thyroglobulin in aspirates from a thyroid nodule is not useful as an index of malignancy.

Suspicious Nodules in Goiters

It has been reported from a goiter zone in Italy that as many as 52% of histological malignant nodules in goiters were found only with the aid of ultrasound-guided FNAB. Therefore, the authors concluded that ultrasound-guided aspiration should be used in areas where multinodular goiter is endemic to assess nodules that are deemed suspicious by virtue of a hypoechoic pattern, a "blurred halo", micro-calcifications, or an intranodular color Doppler signal (192). In another report of patients with endemic goiter, 44 were selected for surgery based on suspicious ultrasonography and among 24 of them who had a “cold” nodule, aspiration biopsy revealed 2 with papillary cancer and surgery disclosed 2 more cases of papillary cancer and one case of insular cancer (193).

Predictors

One group has investigated the predictors and optimal follow-up strategy for initial non-diagnostic ultrasound-guided FNAs of thyroid nodules. Among 1,128 patients with 1,458 nodules that were biopsied over a 6-yr period, 1,269 aspirations (950 patients) were diagnostic, and 189 (178 patients) were non-diagnostic. The authors reported that the only significant independent predictor of non-diagnostic cytology ($P < 0.001$) was a cystic content of each nodule and the fraction of specimens with initial non-diagnostic cytology increased with greater cystic space. As emphasized above, for pathologic lymph nodes, in distinction to thyroid nodules, cystic degeneration is typical of thyroid cancer metastases. For example, diagnostic ultrasound-guided FNA was obtained on the first repeat biopsy in 63% of nodules and was inversely related to increasing cystic content of each nodule ($P = 0.03$). One hundred and nineteen patients with 127 nodules returned for follow-up as advised, and malignancy was documented in 5% (194).

For non-palpable thyroid nodules, the relative importance of sonographic features as risk factors of malignancy and the use of ultrasound-guided aspiration cytology was studied in 494 consecutive patients with nodules between 8-15 mm. It is noteworthy that 92 patients (19%) had inadequate cytology and were excluded from the study. Cancers were observed in 18 of 195 (9.2%) solitary thyroid nodules and in 13 of 207 (6.3%) multinodular goiters. The prevalence of cancer was similar in nodules greater or smaller than 10 mm (9.1 vs. 7.0%). The authors recommended that ultrasound-guided FNA should be performed on all 8-15 mm hypoechoic nodules with irregular margins, intranodular vascular spots or microcalcifications (194). In another study, among 402 patients with 8 mm to 15 mm non-palpable nodules, the cancers were most likely to be hypoechoic and solid, and have microcalcifications, irregular borders, or central blood flow. Since 125 (31 %) of nodules met those criteria, biopsies could be avoided in 69 percent of nodules, incurring a risk of missing 13 percent of the cancers (111).

It would appear that that no single parameter satisfactorily identifies the subset of patients whose nodule should be subjected to biopsy. In one investigation of 6,136 nodules in 4,495 patients, the best compromise between missing cancers and cost-benefit was achieved with at least two “suspicious” ultrasound features. The most useful were nodule shape (taller-than-wide), microcalcifications, blurred margins, and a hypoechoic pattern (195). Enhanced intranodular blood flow on Doppler examination also was reported as a helpful criterion (81). Another investigation of 1,141 nodules reported that logistic regression analysis showed that the size of the nodule affected the utility of ultrasonic characteristics of nodules in assessing cancer risk and selection for needle biopsy. In nodules smaller than 15 mm in size, hypoechogenicity (odds ratios, OR: 3.18), microcalcifications (OR: 19.12), solitary occurrence (OR: 3.29) and height-to-width ratio ≥1 (OR: 8.57) were independent risk factors for malignancy. The authors concluded that all lesions presenting at least one of the above-mentioned features should be biopsied (sensitivity 98%, specificity 44%). With nodules larger than 1.5 cm, the mentioned selection criteria were less sensitive than for smaller nodules. Useful features included, hypoechogenicity, taller than wide or microcalcifications (sensitivity 84%, specificity 72%) (196).

It is difficult to decide which nodule in a multinodular goiter to biopsy. Guidelines include selection by size, the ultrasound characteristics mentioned above, and most importantly nodules that are clinically suspicious. Perhaps one may be reassured that the pathology is likely benign when there are very many nodules in a goiter rather than a few. In one investigation of thyroid nodules that underwent ultra-sound-guided FNA, the authors found that the cancer risk is similar for patients with one or two nodules (over 1 cm) and decreases with three or more thyroid nodules (197).

It is particularly difficult to effectively select nodules for biopsy in an endemic goiter zone where nodules are ubiquitous. In one investigation in an iodine deficient region, a numeric score was assigned to nodules based on ultrasonic high-risk of cancer. Among 2,642 consecutive patients (3,645 nodules), nodules with a score of over 5.5 out of 10 had a 66% sensitivity and a 76% specificity for cancer, which was much higher than for those with lower scores. The data strongly facilitated the decision of which nodules to biopsy (94).

Combining the results of cytology and the tumor marker thyroglobulin after a patient has had a total thyroidectomy may enhance the accuracy of either single predictor of residual/recurrent thyroid cancer. One investigation reported that among 340 consecutive patients with differentiated thyroid carcinoma, who had been treated with near-total thyroidectomy, 131-I thyroid ablation, and TSH suppressive doses of L-thyroxine, rhTSH-stimulated thyroglobulin alone had a diagnostic sensitivity of 85% for detecting active disease and a negative predictive value of 98.2%. After adding the results of neck ultrasound, the sensitivity increased to 96.3%, and the negative predictive value to 99.5% (198). However, in one study, US and FNA did not seem useful to detect recurrent papillary thyroid cancer when the serum thyroglobulin level was undetectable (199).

One should be somewhat more suspicious that an incidentaloma could be cancerous when the patient has another non-thyroid cancer. In one investigation of 41 patients who had another cancer and who had an incidentally discovered thyroid nodule, surgical pathology revealed 4 papillary thyroid cancers, 4 microscopic papillary thyroid cancers, 2 metastatic cancers, and 7 benign lesions (200).

Not Biopsying Nodules that are Not Likely Malignant by US Criteria

Several studies have recognized sonographic morphological patterns that correlate with benign thyroid disease. The authors advise not biopsying these nodules or goiters in the interest of cost-effectiveness (201-203). In one study, 650 patients were identified for whom both a pathology report and ultrasound images were available. From an alphabetized list, the first 500 nodules were reviewed retrospectively. Most of the diagnoses were based on cytological rather than histological findings. Four patterns associated with benign disease were identified and seemingly attributed to colloid: spongiform configuration, cyst (cystic), a “giraffe pattern” (light blocks separated by black bands), and diffuse hyperechogenicity (201). One characteristic has borne the test of time: thyroid cancer is rarely if ever hyperechogenic.

It is useful to know that one group has reported that not performing a biopsy on nodules less than 5 mm in size seemed safe because when they underwent later surgery because of a 2 or 3 mm enlargement, there was no evidence of distant metastases or fatalities (204).

The rationale supplied by the authors (201,204) for not biopsying these nodules is that fewer biopsies, will lead to less delay of “necessary” biopsies and less false-positives. This author completely agrees with not biopsying non-suspicious nodules unless there are other factors that indicate cancer-risk. Fortunately, small low risk nodules generally do not adversely affect quality of life or survival. However, the practical outcome of this “leave the nodule alone” philosophy may result in a mind-set that, in this author’s opinion, should be avoided. The difference between focusing clinical attention on biopsying suspicious nodules and confidently dismissing nodules that “can be left alone” may result in a difference in the risk of missing a cancer. The outcome of the difference is similar to misjudging that a dog *may bite*, and giving it wide berth to avoid getting bitten, and mistaking that a dog *does not bite* and getting mauled.

Thus, I feel that we should not use tentative data from limited investigation to make a pivotal decision not to biopsy certain thyroid nodules and selection against surgery. A simple, logical, safe, inexpensive, and more reliable clinical attitude is employing sonography to enhance the efficiency and accuracy of biopsying ultrasonically suspicious nodules and nodules that have clinical or historical features that are associated with higher than average cancer-risk, and paying reasonable but not invasive attention to the rest of the nodules and the gland as a whole.

If the pattern approach to selecting nodules not to biopsy is employed by ultrasonographers, they should be cognizant that cancerous thyroid nodules in a radiation-exposed population may often not exhibit the classic ultrasonic features of malignancy. Rather, benign characteristics are more often encountered. Therefore in this setting especially, benign-looking nodules should be biopsied and not “left alone” (205).

Repeat Aspiration Biopsy in Patients with a Previously Benign Result

There is no consensus about how often FNA should be repeated after previous aspirations have indicated benign disease. Considerations that enter the decision include periodic US, historical risk factors, changes in physical examination, and even the patient’s or the physician’s level of anxiety. It seems reasonable that growth of the volume of the nodule, the emergence of adenopathy, or symptoms that suggest pressure on cervical structures such as hoarseness or dysphasia should be viewed with suspicion. Sometimes the observations of an ENT consultant may influence management. In this author’s experience routine re-aspiration rarely results in a discovery of malignancy. In a retrospective review of records of patients seen at the Mayo Clinic between January 2003 and December 2013 of 334 nodules with benign FNA, 85.3% were benign, 7.2% suspicious, 5.7% non-diagnostic, and 1.8% malignant. Importantly, the repeat FNA altered clinical management in only 9.5% of cases (206).

Non-Cytologic Examination of Aspirates

Ultrasound-guided aspiration can facilitate biochemical analysis. Needle washings of adenopathy (not applicable to thyroid nodules) may contain Tg, revealing papillary thyroid cancer even when there are insufficient or inadequate cells. It is noteworthy that assay of Tg in tissue is reportedly not effected by serum anti-thyroglobulin antibodies (207). Furthermore, the aspirate of nodules or lymph nodes may contain calcitonin in medullary cancer, a tumor marker such as galectin-3 (208) in papillary thyroid cancer, or lead to a non-neoplastic diagnosis such as tuberculosis (209) or amyloidosis (210). One anticipates that one day aspirates may be studied routinely for biochemical products, sub-cellular components, and, bacteriologic, fungal, or viral material. Examination for molecular genetic tumor markers will be discussed elsewhere.

Core Biopsy

There is also interest in sonographically-guided core biopsy of thyroid nodules. One group has concluded that percutaneous acquisition of tissue for histological rather than cytological evaluation is an accurate and safe alternative to aspiration biopsy in the assessment of thyroid nodules (211). However, one needs to be aware that there may be greater risk from core biopsy, including an occasional fatal case, in contrast to fine needle aspiration biopsy (170). Other investigators have reported on the use of an ultrasound-guided special compound needle that can accomplish both aspiration and core biopsy and suggest its use when prior aspiration has been unsuccessful (212).

SONOGRAPHY BY THE THYROID SURGEON

Although preoperative thyroid ultrasonography is not essential for successful surgery, many surgeons have come to recognize that it may be useful to identify pre-operatively suspicious lymph nodes in patients with biopsy-proven papillary thyroid cancer. Indeed, respected surgical authorities assert that ultrasound is an essential modality in the evaluation of thyroid malignancy and that surgeon-performed ultrasound has proved invaluable in the preoperative, intraoperative and postoperative setting (213-215). It has become increasingly popular for surgeons personally to perform a pre-operative sonogram since metastatic disease may not be clinically apparent to them intra-operatively. Preoperative identification of metastatic disease by cervical ultrasound may result in altering the surgical approach in as many as 40 percent of patients (27,28,97,192,216,217). Furthermore, pre-operative thyroid ultrasonography followed by compartment-oriented surgery may decrease recurrence rates in patients if performed before their primary operation (162). It is noteworthy that ultrasound guided FNA for thyroid nodules has been incorporated into some general surgery residency programs. (218).

Preoperative Labeling Lymph Nodes or Intraoperative US may Facilitate Intraoperative Identification and Removal of Adenopathy

It may be difficult for a surgeon to identify at surgery a small node that was discovered by preoperative ultrasonography. Insertion of a hook 20-gauge needle into a US-suspicious lymph node pre-operatively facilitates identification and removal of the pathological lesion (219-221). Alternatively, pre-incision, ultrasound-guided injection of blue dye into abnormal lymph nodes was very useful in the re-operative neck to facilitate their safe and efficient removal in one study (222). Other investigations have employed ultrasound-guided, preoperative injection of charcoal suspensions to tattoo the lesion. The rate of success is reportedly as high as 84-96% in small studies. However, in 1 case the charcoal was found several centimeters away from the lesion, tattooing a lesion behind a large blood vessel has not been achieved, and in 2 of 55 patients a charcoal dot remained in the skin after the procedure. There were no reported serious adverse effects (223,224). In strong contrast to this approach, other surgeons eschew selective removal of nodes in favor of classical compartmental dissection.

Intraoperative sonography may be very useful (161,225,226). In 26 of 31 patients with papillary thyroid cancer who had preoperative sonographic identification of adenopathy, intraoperative palpation did not locate adenopathy but intraoperative ultrasonography located and facilitated removal of the lesions (smaller than 10 mm in diameter) in all patients (225).

A method that may help find a thyroid sentinel node preoperatively has been reported in a porcine experimental model. US contrast agent and methylene blue dye were injected trans-cutaneously into the thyroid glands of pigs and draining lymphatic channels and sentinel lymph nodes were identified ultrasonically. Subsequently, a sentinel node biopsy was conducted; bilateral neck and upper mediastinal dissection was performed. The lympho-sonography of the thyroid gland in this porcine model correlated well with blue dye-guided sentinel node surgical biopsy. If applied to humans, this technique might potentially enable a detailed analysis of thyroidal lymphatic drainage and enhance thyroid cancer surgery (227).

SONOGRAPHY IN CONJUNCTION WITH PERCUTANEOUS THERAPEUTIC INTERVENTION

After an aspiration and cytology have demonstrated that a nodule is benign, ultrasound-guided puncture of a nodule may have a role in therapy to deliver medication or other therapy precisely into the lesion and to spare the surrounding tissue.

Percutaneous injection of ethanol has been used to reduce the function of autonomous thyroid nodules (228). One investigation has observed 34 patients, for up to three years, who had percutaneous ethanol injection of autonomous thyroid nodules. The patients required 1-11 sessions of 3-14 ml of ethanol injection (total amount of ethanol per patient: 20-125 ml). The authors report recovery of extra-nodular uptake on isotope scan and normalization of TSH levels within 3 months from the end of the treatment in 30/34 patients and an average reduction in nodule volume of 62.9%. 4/34 patients were refractory to the treatment, 3 of whom had had nodule volumes > 60 ml. There were no recurrences during 6 to 36 months of observation (229). Another study examined 20 patients with autonomous thyroid nodules for 763 +/- 452 days after ethanol injection. A mean of 2.85 +/- 1.1 injections per patient, and a mean volume of 4.63 ml of ethanol were required (nodule volume-dependent). After a mean time of 50 +/- 23 days TSH normalized and was maintained in 16 patients (80%), whose nodular volume reduced 60.8%. Four patients (20%) did not completely respond to the treatment (230). Less impressive but “clinically acceptable” results have also been observed in a study that reported a "complete cure" in only 22 of 42 patients (52%), mainly in small nodules, and little or no hormonal response in 4 patients (9%). However, nodule volume decreased in all cases and there were no recurrences or serious adverse effects (231). In the reported series, "mild to moderate" local pain often occurred after the injections and lasted a day or two. Local hematomas were seen. Major complications like permanent dysphonia or vascular thrombosis seem to be very uncommon. However, transient paralysis of the recurrent laryngeal nerve may occur. Thus this technique may be an option for large, but not very large autonomous nodules that cannot or should not be treated surgically or with I-131 (232).

Percutaneous injection of ethanol has also been used to treat toxic nodular goiter (231,233) and thyroid masses that are recurrent after non-toxic nodular goiters have been treated surgically (233), with results that are similar to those described above.

Recurrent cysts, and cystic spaces in a degenerated solid lesion have been obliterated in this fashion (234,235). Perhaps the procedure will have use in cosmetically unacceptable or very large structures. Prospective studies will be required to ascertain if ultrasound-guided placement of medication will reduce the intensity or duration of pain after the injection and improve success over palpation-directed injection.

Sonographically guided percutaneous ethanol injection is a treatment option for patients with cervical nodal metastases from papillary thyroid cancer that are not amenable to further surgical or radioiodine therapy. In a study of 21 metastatic nodes in 14 patients, all treated lymph nodes decreased in volume, some impressively. No major complications occurred in this series (116). Yet, in other studies severe untoward effects have been reported including necrosis of the larynx and adjacent skin due to ethyl alcohol (236). It seems that this option may be palliative when there are large nodes that threaten to impact on surrounding structures. However, since ethanol-treated nodes may increase in size due to inflammation, caution is warranted especially when there are bulky nodes in the thoracic inlet or adjacent to vital structures.

Greater use of percutaneous administration of ethanol for a variety of benign and malignant conditions seems likely. However, prudence dictates that the injection should only be used when essential and not as an optional therapy to reduce the size of routine cysts, euthyroid nodules and goiters, or even non-threatening malignant nodules.

Thermal ablation techniques for benign thyroid nodules, toxic adenomas and even for papillary microcarcinomas are increasingly used, particularly in Korea and Europe (237). Both radiofrequency ablation (RFA) and laser ablation are used and have been shown to be efficient, cost-effective, and to have a low rate of complications (238,239). For example, one investigation evaluated the efficacy of ultrasound -guided laser thermal ablation in reducing the volume of hypofunctioning benign thyroid lesions that caused local compression symptoms or patient-concern in 20 patients, when the patients refused or were ineligible for surgical treatment. A 75-mm, 21-gauge spinal needle was inserted into the thyroid gland under ultrasound-guidance, and a flat-tipped 300-micron quartz fiberoptic guide was placed into the tissue that was to be destroyed with a 1.064-micron continuous-wave neodymium yttrium-aluminum-garnet laser for 10 minutes. Ultrasonograms were used to assess the decrease in nodule volume at 1 month and 6 months after therapy. The mean nodule volume decreased from a baseline value of 24.1 +/- 15.0 mL to 13.3 +/- 7.7 mL at 1 month (43.8 +/- 8.1%) and to 9.6 +/- 6.6 mL at 6 months (63.8 +/- 8.9%). Untoward effects included burning cervical pain, which rapidly decreased after the laser energy was turned off and treatment with betamethasone for 48 hours in 3 patients. No patient had local bruising, cutaneous burning, or dysphonia (240).

In a multicenter study on 44 patients with toxic adenomas or autonomous nodules and a follow-up of 19.9±12.6 months showed that the mean nodule volume decreased from an initial volume of 18.5±30.1 ml to 11.8±26.9 ml at 1 month and to 4.5±9.8 ml at the last month (241). The thyroid function tests improved significantly and 35 of the hot nodules became cold or normal when followed by scintigraphy, and 9 had a decreased uptake. There were no major complications.

Several studies have shown that radiofrequency ablation may be an alternative to active surveillance for papillary thyroid microcarcinomas (PTMC). For example, in a study involving 107 patients, the mean volume reduction ratio at 18 months was 0.999 ± 0.002 (range: 0.992-1) at 12 months (242). Thyroid function tests remained normal, and there was no tumor regrowth, local recurrence, or distant metastases during follow-up visits. In an Korean study with 152 biopsy-proven PTMCs from 133 patients complete disappearance was found in 91.4% (139/152) of ablated tumors (mean follow-up 39 months) (243). All patients were either of high surgical risk or refused to undergo surgery. In the 13 tumors that did not show complete disappearance, none of the PTMC showed regrowth of the residual ablated lesion during the follow-up period, and there were no local recurrences, lymph node or distant metastases in any of the patients. The complication rate was 3% (4/133), including one voice change.

SONOGRAPHY TO DISCOVER PELVIC THYROID TISSUE

Trans-vaginal and trans-abdominal pelvic sonography has been employed to identify a 16 cm mass in the right adnexa that was a cystic teratoma, a struma ovarii, containing a 5 mm focus of papillary cancer within the thyroid tissue (244).

SONOGRAPHY OF THE FETAL THYROID

Ultrasonography in pregnancy can be become a helpful tool to assess thyroid status *in utero*. Gestational age-dependent and age-independent nomograms for fetal thyroid size have been developed by performing ultrasonograms in 200 fetuses between 16 and 37 weeks of gestation (245). Fetal hyperthyroidism can be detected by the presence of increased blood flow within a goiter in contrast to peripheral vascularity when goiters are associated with hypothyroidism (246). Fetal goiters and hypothyroidism have been studied, and successful treatment has been reported (247). It is thought that intrauterine recognition and treatment of congenital goitrous hypothyroidism may reduce obstetric complications and improve the prognosis for normal growth and mental development of affected fetuses. One report cited a fetal goiter diagnosed at 29 weeks of gestation during routine ultrasound examination. Fetal blood sampling performed at this time documented fetal hypothyroidism and treatment was given using a series of intra-amniotic injections of tri-iodothyronine and subsequently, thyroxine. Following birth, neonatal serum TSH levels were within the reference range (248). A case of fetal goitrous hypothyroidism associated with high-output cardiac failure was diagnosed at 32 weeks of gestation based on ultrasound examination. The fetus' thyroid function was examined by amniocentesis and cordocentesis. The fetus was treated by injection of L-thyroxine into the amniotic fluid at 33 weeks of gestation. Thereafter, the goiter decreased in size, and the high-output cardiac failure improved (249). Similarly, fetal goiter and hypothyroidism that resulted from the treatment of maternal Graves' disease with propylthiouracil was diagnosed with trans-vaginal US and treated by levothyroxine injection into the amniotic fluid. Successful ultrasound-facilitated treatment of fetal goitrous hypothyroidism has been reported in 12 cases (250). Assessing the fetal thyroid size ultrasonically may also be beneficial in adjusting the dose of antithyroid drug in mothers with Graves' disease and in preventing fetal and neonatal goiter and hypothyroidism, as discussed before (67). In addition, determining fetal thyroid size with ultrasonography in mothers with a history of Graves' disease has been reported to facilitate achieving normal fetal thyroid function (251).

SONOGRAPHY OF THE THYROID IN THE NEWBORN

There are several uses of ultrasonography in newborn infants. Normative data in 100 (49 male) healthy term Scottish neonates showed a mean thyroid length of 1.94 cm (SD 0.24, range 0.9-2.5), width of 0.88 cm (SD 0.16, range 0.5-1.4), depth of 0.96 cm (SD 0.17, range 0.6-2.0), and volume of 0.81 ml (SD 0.24, range 0.3-1.7) (252). There was considerable variation (-0.8 to + 0.7 ml) between the two lobes in individual babies. Another investigation revealed that the ratio of thyroid width to tracheal width is a simple, practical parameter for estimating the size of the thyroid gland in neonates and small children (253).

In permanent primary congenital hypothyroidism, ultrasonography has been reported to identify 66 instances where the thyroid gland was not located in the usual anatomical position and hemiagenesis in one case. The diagnosis was confirmed by scintigraphy. The authors concluded that sonography might be used as the first imaging tool in patients with congenital hypothyroidism, but scintigraphy should be used to distinguish agenesis from ectopia (254).

EPIDEMIOLOGICAL USE OF ULTRASONOGRAPHY

Ultrasonography has been used effectively even in the field in undeveloped areas to evaluate thyroid anatomy and size in iodine-deficient regions or to search for cancer in radiation-exposed populations. Inter-observer agreement on estimates of thyroid volume has been good in epidemiologic studies but agreement on echogenicity has been poor (29). One study has revealed that in the Chernobyl population thyroid cancers often exhibit benign ultrasound characteristics, that malignant features are uncommonly encountered, and as many nodules as is feasible should be biopsied (205). Correlation of age, body size and thyroid volume in endemic goiter areas have been reported (255). Data for thyroid volumes that are specific to a geographic region, iodine status, sex, and pubertal stage may be more appropriate than a single age-specific international reference (256,257). Systematic ultrasound screening has been found useful in Belarus for the early detection of thyroid carcinoma in children 4-14 years of age who were exposed to radioactive fallout due to the Chernobyl accident (258).

After the nuclear accident in the Fukushima Daiichi Nuclear Power Plant, large-scale ultrasound screening has been implemented (for review see (259)). This led to a high rate of detection of thyroid cancer in younger individuals within the studied cohort of approximately 300,000 subjects in

Fukushima prefecture. This observation resulted in significant concerns in the population because it was felt that these cancers might have been caused by radiation. The current evidence indicates, however, that these findings are largely explained by the effect of screening.

Ultrasonography has also shown that the prevalence of thyroid cancer has not increased in a population exposed to the accidental release of I-131 in Hanford, Washington during 1944-1957 (260). Ultrasonography has also been used to monitor thyroid nodule development among workers in nuclear power plants (261).

The value of ultrasonographic mass screening to uncover thyroid carcinoma depends on the cancer-risk status of the population. In a population with average cancer risk the value of screening is controversial because of the presumed low benefit/cost of the screening as contrasted with subsequent discovery of the small number of tumors that will progress to palpable, clinical, but low-virulence tumor. One group studied 1401 women who were scheduled to undergo a breast examination. Thyroid nodules were detected in 25.2% and thyroid cancer in 2.6% of all subjects. The size of the tumors was significantly smaller in the ultrasound-studied group than that of a clinically detected cancer group ($P < 0.05$) (262). Another group studied thyroid sonography in 5549 patients who were undergoing breast sonography. Forty-two (0.76%) thyroid cancers were found; all were papillary carcinomas. The incidence of thyroid cancer was significantly higher in the group with breast cancer than in the group who did not have breast cancer (37). In contrast, epidemiologic investigation of the long-term risk of developing thyroid cancer has been useful in a population with a higher risk of cancer such as irradiated people. In a prospective ultrasound examination of 2637 atomic-bomb survivors the hazard ratio for cancer development was significantly high at 23.6 (95% confidence interval, 7.6-72.8) and even higher, 40.2 (95%, confidence interval, 9.4-173.0) in 31 people who initially had cytologically benign solid nodules. The hazard ratio was only 2.7 (95% confidence interval, 0.3-22.2) in 121 subjects who had thyroid “cysts”. Importantly, sex, age, TSH level, thyroglobulin level, radiation dose, nodule volume, and increase in nodule volume did not predict cancer development in the solid nodule group but sonography did reveal the risk of cancer (263).

ELASTOGRAPHY

Ultrasonography can estimate the rigidity or stiffness of tissue, which is called elastography. The deformability of a tissue may be assessed from a change in Doppler signal in response to externally applied pressure or vibrations, or by tracking shear wave propagation. This phenomenon may correlate with palpable consistency and cytology of a nodule or goiter. The technique may enhance the cancer-predictive value of sonography of non-cystic non-calcified thyroid nodules (75,264-267). However, it is premature to judge the clinical value of the test and the literature contains controversial data. One retrospective investigation revealed that among 16 malignant and 20 benign thyroid nodules elastography correlated with FNA in a sensitivity of 100% and specificity of 75.6% in detecting malignant thyroid nodules (267). Other investigators reported that elastography is not able to select cancers among follicular lesions of indeterminate significance (268). Elastography was not very useful in detecting thyroid cancer in patients affected by Hashimoto’s thyroiditis (269). Elastography may be useful in the diagnosis of inflammatory conditions of the thyroid like sub-acute thyroiditis (270).

OTHER USES OF ULTRASONOGRAPHY

There have been other novel and inventive applications of ultrasound to thyroidology and the list grows. Just as medical practices have evolved as a result of sonography, surgical techniques may change as well, as was discussed previously. Intra-operative diagnostic sonography is already used in the patient with thyroid cancer and one suspects that it will impact favorably on surgical methods, complications and outcome. Another example of the potential is a recent report that used ultrasonography to demonstrate that routine insertion of drains into the thyroid bed to prevent formation of hematoma or seroma following thyroid surgery may not be necessary. The authors contended that not draining the wound did not adversely influence the volume of the sequestered fluid ($p = 0.313$) and actually was beneficial by reducing morbidity and decreasing hospital stay ($p = 0.007$) (271).

Thyroid sonography may also be useful before neck surgery for non-thyroid disease. In a retrospective study of 1200 consecutive patients who were treated surgically for primary head and neck tumors and who had routine preoperative neck ultrasound by the surgeon, 47%, (477/1195) of the patients had coexisting thyroid disease. Preoperative fine-needle biopsy of sonographically detected thyroid nodules was performed in 20%, which was cost-effective in limiting concomitant thyroid surgery to fewer patients (6%; 21/350) (272).

Ultrasonic energy can be used therapeutically to destroy tissue, as discussed previously, and also to activate mechanical equipment. An example of the latter is ultrasonically activated shears for thyroidectomy that have been reported not to increase complications, shorten operative time, improve cosmetic results, and reduce the patient's pain, without greater expense than conventional methods (273). An ultrasonically activated scalpel significantly improved bleeding control during thyroid resections and may also be beneficial with respect to cost containment by reducing operative time (274). Ultrasound-guided percutaneous interventional procedures to deliver medications, enzymes, recombinant materials such as RNAS, monoclonal antibodies, or energetic forces to the thyroid gland, nodules, or nodes also challenge the imagination. US-guided high-intensity, focused ultrasound maybe use to ablate benign thyroid nodules (275).

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