The Role of Ultrasound in Thyroid Assessment

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Abstract

The recent prevalence of ultrasonography (US) has facilitated the early detection and qualitative evaluation of thyroid nodules. Furthermore, novel technical developments are extending the application range of US for other thyroid diseases.

The use of US to differentiate between thyroid carcinoma and benign nodule, between a metastatic lymph node and a reactive node, between thyroid lymphoma and chronic thyroiditis, and between destruction-induced thyrotoxicosis and Graves' disease is introduced.

Classification systems for thyroid nodule have shown high diagnostic accuracy for thyroid carcinomas except follicular carcinoma. US diagnosis of lymph node metastasis showed high specificity but low sensitivity. Patients who were suspected of thyroid lymphoma based on US findings should undergo incisional biopsy or thyroidectomy for diagnosis of the histologic type if fine needle aspiration biopsy findings suggest lymphoma. Patients should be carefully followed even if they were diagnosed as negative based on cytologic findings. Measurement of thyroid blood flow is helpful for diagnosing destruction-induced thyrotoxicosis, such as painless thyroiditis, by distinguishing the lesion from Graves' disease.

Ultrasonography is useful for diagnosing various thyroid diseases, including thyroid carcinoma. The remaining issue to be resolved is the diagnosis of follicular carcinoma. Trials using novel techniques to differentiate these lesions are expected.

Key words: ultrasound, thyroid assessment

Introduction

The thyroid gland can be evaluated using several imaging modalities such as radionuclide imaging, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Although each study has advantages and drawbacks, US is the most useful tool for detecting and diagnosing thyroid diseases, especially thyroid nodules. This is because US not only detects the nodules but also allows qualitative evaluation of these lesions. The recent prevalence and technical developments of US have resulted in its increased use for mass screening of the thyroid and carotid artery and have facilitated the incidental detection of nonpalpable thyroid nodules measuring > 3 mm. Using a combination of US and US-guided fine needle aspiration biopsy (FNAB), these nodules can be differentiated as benign or malignant [1].

Apart from the diagnosis of thyroid nodules, US is useful for the qualitative diagnosis of regional lymph nodes, which is important for determining the extension of lymph node dissection and evaluating the biologic behavior, including prognosis, of thyroid carcinoma patients. Furthermore, US can facilitate the differential diagnosis between thyroid lymphoma and chronic thyroiditis and between destruction-induced thyrotoxicosis, such as painless thyroiditis, and Graves' thyrotoxicosis. In this review, we introduce the utility of thyroid US based on data from our institution together with data from other institutions.

Since the late 1990s, several studies have been conducted to analyze the relation between specific sonographic features of thyroid nodules and malignancy [64, 65-66]. Although guidelines have been established, such as those of the Society of Radiologists in Ultrasound, the American Thyroid Association, and the European Thyroid Association [64, 67-68], they are commonly confusing and at times ignored in everyday practice, largely because of lack of familiarity with, and trust in, their validity. Common in the studies is a persistent limitation of specificity and sensitivity of specific ultrasound features in the prediction of malignancy. Some authors [69, 70] advocate a changed approach of recognition of specific patterns rather than individual ultrasound features in separation of nodules that require biopsy from those that do not. The purpose of our study was to evaluate the accuracy of such a morphologic feature-oriented approach to the identification of benign thyroid nodules.

Diagnosis of thyroid nodules

A thyroid nodule is a discrete lesion, sonographically distinct from the surrounding thyroid parenchyma [71]. Rather than a single disease, nodules are manifestations of a gamut of thyroid diseases [72]. Although some thyroid nodules may be discovered at physical examination, many are incidental findings of other imaging studies, such as CT and MRI of the neck or chest and carotid ultrasound imaging. FNA of thyroid nodules has replaced blind surgical excision as the procedure of choice in the diagnosis of thyroid nodules. Use of FNA has led to a considerable decrease in the number of surgical excisions and to a twofold increase in the diagnosis of carcinoma [73, 74, 75]. The relative ease of FNA compared with surgery and the increased frequency and refinement of imaging studies has resulted in what some authors have referred to as an epidemic of thyroid nodules [76, 77].

In view of their ubiquity, it is not feasible to biopsy every thyroid nodule discovered with ultrasound. Reasons for limiting thyroid biopsy, which is relatively painless and safe, include the small percentage of malignant lesions, the small number of cases of thyroid cancer in which early diagnosis may actually have an influence, the economic and societal costs, the strain on radiology resources, and the patient uncertainty and anxiety incumbent on a potentially malignant diagnosis. Hence, reliable guidelines for nodules that may not require biopsy have become essential.

Not surprisingly in view of the experience of other authors [78], we concluded that no individual sonographic feature had both high sensitivity and high specificity in the detection of malignancy. Nonetheless, many of these previously described high-risk features, such as calcification, hypoechogenicity, poor definition, and hypervascularity, were found to be absent over and over again in nodules that did not require biopsy.

The persistent combination of some of these common individual ultrasound characteristics, or, more properly, their absence, led us to consider a more pattern-oriented approach, such as that advocated by Reading et al. [69] as an alternative to the analysis of individual features. Those authors described eight typical appearances of commonly encountered benign and malignant nodules, allowing them to separate more than one half of thyroid nodules into those that could be observed versus those requiring biopsy. According to their results, the following four classic patterns necessitate biopsy: 1, a hypoechoic nodule with microcalcifications; 2, coarse calcifications in a hypoechoic nodule; 3, well-marginated, ovoid, solid nodules with a thin hypoechoic halo; and 4, a solid mass with refractive shadowing from the edges, which is believed to occur as a result of fibrosis. The four classic patterns of nodules that did not require biopsy in that series were the following: 1, small (< 1 cm) colloid-filled cystic nodules; 2, a nodule with a honeycomb appearance consisting of internal cystic spaces with thin echogenic walls; 3, a large predominantly cystic nodule; and 4, diffuse multiple small hypoechoic nodules with intervening echogenic bands, which are indicative of Hashimoto's thyroiditis.

Like Reading et al. [69], we found that use of a pattern approach to thyroid nodules is highly sensitive and specific for the presence of benignity. Our patterns differed somewhat from those proposed previously, yet there are definite similarities. Analysis of our data revealed four patterns that were invariably benign at FNA biopsy. The most common overall pattern is a nodule with diffuse internal linear cysts, described as spongiform or honeycomb, our type 1 pattern. In our cases, this finding was commonly described as a “puff pastry” pattern. This pattern was characteristic of colloid nodules or goiter. The only spongiform nodule not classically benign was a single nodule that also was intensely hypervascular. Our type 1 or spongiform nodule consequently is defined as avascular or, occasionally, isovascular in relation to the rest of the gland.

The second pattern (type 2) was a cystic nodule containing a central plug of avascular colloid, similar to the previously described small or large cyst patterns [69]. In our initial analysis of individual features, size of cyst was deemed insignificant. Important, however, was the characterization of the plug as avascular and puff pastry. All of these nodules were also colloid nodules. If the cystic portion of the lesion is subtracted visually, a type 1 spongiform nodule remains. The third pattern (type 3), or giraffe pattern, was characterized by globular areas of hyperechogenicity surrounded by linear thin areas of hypoechogenicity, similar to the two-tone blocklike coloring of a giraffe. This pattern was quite characteristic of Hashimoto’s thyroiditis. A variation of this pattern is our type 4 “white knight,” or hyperechoic, nodule, which was found commonly to be a regenerative nodule of Hashimoto’s thyroiditis.

Analysis of these patterns revealed more variability in final cytologic findings. Such nodules included both insignificant and significant lesions with such variability that prediction before biopsy was not reliable. These nodules had the four biopsy-recommendation patterns described earlier, such as isoechoic nodule with a surrounding halo or refractive edges, which came to be simplified as isoechoic nodules with or without a halo (types 7 and 8). A hypoechoic nodule with or without central microcalcification or with central macrocalcification in other series [79, 80, 81], for which biopsy was recommended, was the most worrisome pattern (type 6) in our study.

We identified other common patterns, including the type 5 “red light” pattern, or an intensely hypervascular lesion that on Doppler images glowed like a red stoplight. This pattern was commonly seen in lesions with abundant cellularity, including, commonly, follicular neoplasms and, less commonly, hyperplastic nodules and carcinoma. Other nodule types included type 9 ring-of-fire nodules with intense peripheral vascularity and nodules described as other (type 10), which did not fit any of the classic patterns. Calcification, although commonly seen in nodules requiring biopsy, was never seen as an isolated finding. The likelihood of benignity of these nodules (type 5-10) ranged from 60% (type 9, ring of fire) to 91% (type 10, other). Because of this lack of predictability, we believed that these nodules should be considered for FNA biopsy.
A prominent application of US is detection of thyroid nodules and the differential diagnosis between thyroid carcinoma, especially papillary carcinoma, and a benign nodule [2–6]. To date, several US features (e.g., microcalcifications, hypo echogenicity, irregular margins, halo signs) have been identified as indicating papillary carcinoma. In Japan, a multicenter study showed that a jagged border, irregular shape, and hypoechoic internal echo level are important characteristics for diagnosing papillary carcinoma [7].

To diagnose thyroid nodules accurately and immediately during mass US screening, a report along with scoring or categorization using a classification system is rational. Recently, classification systems for the diagnosis of thyroid nodules have been proposed.

Tae et al. [8] classified thyroid nodules into three categories based on their having one or more of four features: nodules with microcalcifications, an irregular or microlobulated margin, marked hypoechogenicity, and a shape that is taller than it is wide are classified as category 3 (malignant); nodules that show an absence of all of these features are classified as category 2 (benign); and anechogenic cystic nodules are classified as category 1 (benign). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 87%, 87%, 48%, and 98%, respectively, by comparing their findings with cytologic results.

In 2009, Horvath et al. [9] proposed the thyroid imaging reporting and data system (TIRADS). They established six categories (TIRADS 1 to TIRADS 6) based on US patterns and estimated the incidence of malignancy for each TIRADS class: 0% for TIRADS 1 and 2;\5% for TIRADS 3; 5–10% for TIRADS 4A; 10–80% for TIRADS 4B; [80% for TIRADS 5; and 100% for TIRADS 6. They diagnosed nodules with TIRADS 4 or greater as suspected of malignancy; they compared their classification results and FNAB findings and showed that the sensitivity, specificity, PPV, and NPV were 88, 49, 49, and 88%, respectively. In both studies, follicular lesions according to FNAB findings were classified as suspicious of malignancy.

We routinely evaluate nodules according to this system to diagnose the lesions as benign or malignant [10, 11]. The classification consists of five grades from US classes (USCs) 1 to 5 as summarized in Table 1.

Typical US profiles of each class are as follows: cyst for USC1; adenomatous nodule or, if multiple, multinodular goiter for USC2; follicular neoplasm (including minimally invasive follicular carcinoma) for USC3; thyroid carcinoma (papillary carcinoma, widely invasive follicular carcinoma, medullary carcinoma, and anaplastic carcinoma) for USCs 4 and 5. Furthermore, we set intermediate classes from USC 2 to USC 5—designated USCs 2.5, 3.5, and 4.5. Nodules showing cystic change but having a partially irregular shape and/or showing strong echoes and solid nodules with an irregular shape are classified as USC 2.5 and 3.5, respectively. A solid, irregularly shaped nodule showing minor extrathyroid extension is classified as USC 4.5. Nodules classified as USC 2.5 or lower are evaluated as benign nodules; those with USC 3 are evaluated as follicular neoplasms, including minimally invasive follicular carcinoma; and those considered USC 3.5 or greater are diagnosed as, or suspected of, thyroid carcinoma.

Table 1: US classification for thyroid nodules at Kuma Hospital

USC	Diagnosis
Round or oval anechoic lesion	Cyst
Regularly shaped nodule with cystic change (echo level of a solid lesion is similar to that of normal thyroid)	Adenomatous nodule Multinodular goiter
Solid, regularly shaped nodule (internal echo is homogeneous or may have strong echoes internally or at the capsule)	Follicular adenoma Minimally invasive follicular carcinoma
Solid, irregularly shaped nodule (internal echo is usually low and may have fine strong echoes internally)	Thyroid carcinoma
Solid, irregularly shaped nodule with extrathyroid extension	Thyroid carcinoma

When nodules are diagnosed as carcinoma on US and FNAB, the evaluation of their location is important. When carcinoma is located in the dorsal surface of the thyroid, it may extend to the adjacent organs—recurrent laryngeal nerve, trachea, esophagus—and require resection of these organs to achieve curative surgery. US can provide information to surgeons indicating whether a carcinoma carries a risk of extending to other organs. Tomoda et al. [12] investigated the diagnostic accuracy of US regarding tracheal invasion by papillary carcinoma and showed that the sensitivity, specificity, PPV, and NPV were 91, 93, 25, and 99%, respectively. However, such findings cannot be evaluated for tumors having severe calcifications, large size, or extension inferior to the clavicle. In their series, 32 of 509 patients (6%) could not be evaluated. Other imaging studies such as CT and MRI can be useful for evaluating such tumors.

One important issue that physicians must consider is the management of small carcinomas detectable on US, most of which are papillary carcinoma measuring < 1 cm (papillary microcarcinoma, or PMC). The incidence of PMC classified into USC 3.5 or greater does not differ from that of larger carcinomas [11], indicating that it is not difficult to detect and diagnose PMC on US and US-guided FNAB. However, we must note that there has been a high incidence of microcarcinomas detected in some autopsy studies [13–15], and thyroid carcinomas (mostly < 1.5 cm) have been found in as many as 3.5% of otherwise healthy women over 30 years of age during US mass screening and FNAB [16]. These findings definitely indicate that most low-risk PMCs lacking clinically apparent nodal and/or distant metastases and massive extension to adjacent organs are not harmful to patients throughout their lives.
Thus, we must carefully consider whether "early detection" of such small carcinomas and performing thyroidectomy routinely for them are truly beneficial for patients. In our institution since 1993, we have used observation alone for low-risk PMCs without immediate surgical treatment, with the result that only 6.7% of patients showed tumor enlargement after a 5-year follow up, and none of the patients showed distant metastasis or died of carcinoma during the observation [17–19]. It is suggested that routine surgical treatment for PMC forces unnecessary therapy on most PMC patients. Indeed, this is a pitfall of the technical development of imaging studies, and we propose observation without immediate surgical treatment for low-risk PMC as an alternative to initial treatment.

It is difficult to determine whether a nodule that has US features indicating a follicular tumor (USC 3 in our classification system) is follicular carcinoma or benign adenoma, which is a limitation of routine US [20, 21]. To date, several clinicopathologic features—tumor size, patient's sex, patient's age, indeterminate cytology, serum thyroglobulin level—have been reported as risk factors for follicular carcinoma [22, 23]. However, if more accurate evaluation on imaging studies becomes possible, the indications for surgery for such nodules could be narrowed.

Fukunari et al. [24] proposed a diagnostic grading system based on the findings of B-mode US and color Doppler findings, including tumor vascularity and blood flow analysis objectively indicated as the pulsatility index (PI). They reported favorable results of their examination, with the sensitivity 89% and the specificity 74%. Furthermore, real-time tissue elastography (RTE) may provide novel information for diagnosis of follicular carcinoma. Fukunari [25] reported that the sensitivity and specificity of RTE for follicular carcinoma were 83% and 98%, respectively. Also, Rogo et al. [26] demonstrated that RTE is a useful tool for diagnosing thyroid carcinoma, especially nodules with indeterminate cytology. Further studies for these new techniques by a number of institutions are desired to improve the diagnostic accuracy of follicular carcinoma on US.

Diagnosis of lymph node metastasis

Three prominent compartments of regional lymph nodes are affected by thyroid carcinoma: the central, lateral and mediastinal compartments. US is the most useful tool for evaluating lymph node metastasis except for that in the mediastinal compartment [27, 28]. Preoperative evaluation of lymph node metastasis of thyroid carcinoma is important because it determines the extent of lymph node dissection and predicts patient outcomes. We previously showed that metastasis in the lateral compartment detectable on US (N1b) is an independent prognostic factor for disease-free survival (DFS) and cancer-specific survival (CSS) on multivariate analysis [29, 30]. Furthermore, a study of a subset of N1b patients showed that those having five or more clinically apparent metastases, a metastasis> 3 cm, or extranodal tumor extension showed a more adverse prognosis than those having none of these features [31]. Of these three features, the former two can be preoperatively evaluated on US. Therefore, evaluation of metastasis, especially in the lateral compartment, on US is essential to determine if the surgeon should perform lateral compartment dissection (modified radical neck dissection, or MND) and to predict the clinical outcomes of patients.

To date, several US features—large size, round shape, hypoechoic structure, loss of hilar architecture, hyperechoic punctuations, microcalcifications, cystic appearance—have been proposed by various institutions [32–36]. In 1995, Antonelli et al. [37] proposed US criteria for lymph node metastasis: size larger than 1 cm; clear hypoechoic pattern or dyshomogeneous pattern, with alternating hypoechoic and hyperechoic areas; irregular cystic appearance; the presence of internal calcification; and rounded or bulging shape with an increased anteroposterior diameter. These criteria have been widely accepted, although our institution has not adopted lymph node size as a criterion.

The diagnostic accuracy of an US diagnosis of node metastasis is, however, not very high because the high specificity is offset by low sensitivity. Leboulleux et al. [38] compared various features of lymph nodes and pathologic diagnoses for 56 nodes in 19 patients and demonstrated that cystic appearance, hyperechogenic punctuations, and peripheral vascularization are useful criteria for node metastasis because their specificities are high, at 100, 100, and 82%, respectively. However, the sensitivities of the former two are low, at 11 and 46%, respectively. The sensitivity of peripheral vascularization was high at 86%, although the number of patients examined was small.

We also investigated the diagnostic accuracy of US for lateral node metastasis using a series of 3,974 patients who underwent therapeutic or prophylactic MND [31]. Although the specificity and PPV were high, at 97 and 95%, respectively, the sensitivity and NPV were low, at 30 and 43%, respectively. We have adopted FNAB for nodes suspected of metastasis along with the measurement of thyroglobulin levels in the washout of needles used for FNAB to confirm the diagnosis of metastasis [39]. It is useful to increase the specificity and PPV, but it does not improve sensitivity or NPV.

Kim et al. [40] showed that for preoperative detection of lateral node metastasis the combination of US and CT is more accurate than US alone, but the tendency toward high specificity and low sensitivity was not changed. As for metastasis to the central node, sensitivity and NPV were even worse, at only 12 and 37%, respectively [31]. This is probably because detection of lymph nodes is made difficult by the air-filled trachea and the thyroid itself.

The above findings indicate that US rather frequently overlooks lymph node metastasis in the central and lateral compartments and that there are many false-negative results in cases diagnosed as negative for node metastasis on US. These pitfalls distress surgeons trying to decide on the extent of lymph node dissection. Compartments showing clinically apparent metastasis definitely should be therapeutically dissected, but the indication for prophylactic dissection remains controversial. Dissection of the central compartment does not require wound extension and can be performed within the same surgical field as thyroidectomy. In addition, the diagnostic accuracy of central compartment metastasis on US is low and reoperation for recurrence to this compartment often causes recurrent laryngeal nerve injury and permanent hypoparathyroidism [41, 42].

In contrast, MND requires wound extension, is time-consuming and technically difficult, and increases patients' complaints, although some of these concerns can be compensated by the skill of the surgeon. Prophylactic MND is recommended for patients exhibiting a high incidence of recurrence to the nodes. The indication for prophylactic MND is affected by the incidence of nodal recurrence rates that patients and physicians can accept. Our department recommends prophylactic MND for patients having two or more of the following characteristics—male sex, > 55 years of age, tumor > 3 cm, and massive extra thyroid extension—because the 10-year lymph node DFS of those patients was < 90%; that is, lymph node recurrence rates were more than 10%, even though the patients underwent prophylactic MND [29]. Sugitani et al. [43] proposed that prophylactic MND is indicated for patients with a tumor >4 cm or metastasis to distant organs at surgery.

Diagnosis of malignant lymphoma of the thyroid

Malignant lymphoma of the thyroid accounts for 2–5% of all thyroid malignancies and usually arises from chronic thyroiditis [44–47]. This disease can usually be diagnosed on FNAB; to confirm the histologic type, surgical examination such as open biopsy or thyroidectomy is useful [48].

Furthermore, investigations for rearrangement of the IgH gene, CD45 gating, and chromosomal abnormality are helpful for diagnosis [49]. The prognosis of thyroid lymphoma is generally favorable if treated competently [50–53], but it can suddenly enlarge, causing life-threatening asphyxia. Therefore, early detection and diagnosis are mandatory to initiate appropriate therapy during an early phase of the disease.

For early detection of thyroid lymphoma, a differential diagnosis between thyroid lymphoma and severe chronic thyroiditis is essential; and US is an extremely useful tool for this purpose. There are three US-detected patterns of thyroid lymphoma: nodular, diffuse and mixed [54]. The nodular type displays hypoechoic, homogeneous internal echoes with a well-defined border showing a broccoli-like or coastline-like growth pattern. Posterior echoes are broadly

Table 2: Ultrasonographic classification of thyroid lymphoma

Ultrasonographic classification of thyroid lymphoma			
Type	**Internal echoes**	**Border**	**Posterior echoes**
Nodular	Hypoechoic and homogeneous nodular lesions	Broccoli-like Coastline-like	Enhanced
Diffuse	Internal echoes	-	Enhanced
Mixed	Internal echoes	-	Enhanced

enhanced. The diffuse type also displays hypoechoic internal echoes, but the border between the lymphoma and nonlymphomatous tissue is not clear. Therefore, it is difficult to differentiate diffuse-type lymphoma and severe chronic thyroiditis, although enhanced posterior echoes are useful for diagnosing lymphoma of this type. Patchy hypoechoic lesions can be observed in the thyroid in mixed-type lymphoma. The US profile of mixed-type lymphoma often resembles multinodular goiter, but each lymphoma lesion shows enhanced posterior echoes. The US classification of these three types is summarized in Table 2. Enhanced posterior echoes are typical findings of thyroid lymphoma regardless of type, and lesions having this feature should be suspected of being a thyroid lymphoma, in which case further analyses such as FNAB are recommended.

In Kuma hospital, among 170 patients suspected of having a thyroid lymphoma based on US findings between 2000 and 2004, a total of 74 (43.5%) were diagnosed as having or suspected of having lymphoma on FNAB [53]. In all, 69 of these patients underwent incisional biopsy or thyroidectomy, and 67 were diagnosed as having lymphoma on the pathology examination. Of 96 patients who were not cytologically diagnosed as having or suspected of having lymphoma, 20 underwent a surgical procedure because lymphoma was suspected by the attending physicians. Of these 20 patients, 12 were diagnosed pathologically as having lymphoma. In total, 79 of 170 patients (46.5%) were confirmed as having lymphoma on the pathology examination.

The number of patients diagnosed as having lymphoma is increasing because only 116 patients were treated with lymphoma between 1963 and 1990 in our institution [48]. This is definitely because the resolution power of US has enabled the detection of lymphoma in an early phase. In a series between 1963 and 1990, a total of 78% of patients complained of rapid enlargement of a goiter, but only 22% of patients in a series between 2000 and 2004 showed rapid goiter enlargement [54]. US-guided FNAB is the next step for diagnosing thyroid lymphoma. In our department, the PPV for FNAB is 97.1%, indicating that cytologic examination after candidates for FNAB are selected based on US findings contributed markedly to the diagnosis of lymphoma. However, at least 12.5% of patients (12/96 patients) were misdiagnosed on FNAB, indicating that all patients suspected of lymphoma on US should be followed carefully, even though the FNAB diagnosis is negative. We encountered a patient who exhibited a serial change from chronic thyroiditis to lymphoma over an interval of at least 7 years [55].

Surgical examination is also important for establishing the final diagnosis and confirming the histologic type to facilitate any decisions on therapy, such as irradiation only or irradiation with systemic chemotherapy. In the past, incisional or core needle biopsy was performed in most patients, but at present the incidence of thyroidectomy (e.g., lobectomy, total thyroidectomy) has increased significantly. Indeed, in our series between 2000 and 2004, a total of 65% of patients underwent thyroidectomy [54]. As indicated above, the incidence of early detection of lymphoma is increasing, and most patients show a low level of malignancy. For such cases, biopsy from the surface of the thyroid only causes misdiagnosis, and thyroidectomy should be actively performed to achieve an accurate diagnosis, which might also have therapeutic value.

Differential diagnosis between painless thyroiditis and Graves' disease

Thyrotoxicosis in patients without hyperfunctioning nodules is due to destruction-induced thyrotoxicosis and Graves' disease. Destruction-induced thyrotoxicosis may be observed in patients with painless thyroiditis, postpartum thyroiditis, and/or subacute thyroiditis [56]. It is often difficult to differentiate between painless thyroiditis and Graves' disease. There are several strategies to differentiate these diseases, among which are radioactive iodine uptake (RAIU) and the detection of anti-thyroid-stimulating hormone (TSH) receptor antibodies (TSH binding inhibitory immunoglobulin, or TBII). During the early postpartum period, destruction-induced thyrotoxicosis is more likely to occur than Graves' disease, although Amino et al. [57] showed that Graves' thyrotoxicosis may also occur 3–6 months postpartum. RAIU cannot be performed when patients are lactating; and not all clinics are equipped for this examination. TBII is, indeed, a useful marker of Graves' thyrotoxicosis because it is positive in 99–100% of patients [58, 59]. However, TBII was also positive in 6–15% of patients with painless thyroiditis, indicating that TBII is not always reliable for differentiating these two diseases [60–62].

Recently, measurement of thyroid blood flow (TBF) was reported to be another useful strategy for differentiating painless thyroiditis from Graves' disease [63]. The quantification of TBF can be expressed in a percentage as an advanced dynamic flow/region of interest (ADF/ROI) ratio by special software. ADF is a recently developed high-resolution power Doppler mode used as a quantitative method for calculating TBF; it can present clearer information of minute blood flow than traditional power Doppler mode. TBF was significantly higher ($p< 0.0001$) in Graves' disease than in painless thyroiditis, subacute thyroiditis, or normal controls. The TBF of patients with Graves' disease was always > 4%, and all other patients had TBF < 4%, indicating that 4% is the cutoff for distinguishing destruction-induced thyrotoxicosis and Graves' disease. The TBF of patients with painless thyroiditis and those with Graves' disease were significantly correlated with the RAIU [63]. This examination is a candidate for diagnosing thyrotoxicosis as an alternative to RAIU in the future.

Conclusions

Recent technical developments in US have facilitated the differentiation of malignant and benign nodules and metastatic and reactive lymph nodes; of whether a nodule is malignant or benign; whether lymph node is metastatic or reactive; whether a hypoechoic lesion is lymphoma or chronic thyroiditis; and whether thyrotoxicosis is due to painless thyroiditis or Graves' diseases. To establish an accurate and immediate diagnosis of thyroid nodules, the development of a classification system is rational. We established our own system in 1995 and showed favorable results. This system is simple and easy to use, indicating that it is appropriate for performing US in many patients over a short time in a screening process.

At present, thyroid nodules measuring 3 mm can be detected on US and diagnosed as malignant or benign on US-guided FNAB. However, due to the excessive resolving power of US, small and harmless thyroid carcinomas have frequently been found and a number of patients would undergo unnecessary surgical treatment if physicians recommended surgery for all such lesions. In our opinion, observation without immediate surgical treatment for low risk PMC can be a potent alternative initial treatment.

The diagnostic accuracy of US, especially the sensitivity, for lymph node metastasis is low, indicating that many metastatic nodes may remain undissected if the compartment is not dissected prophylactically. However, the incidence of such latent metastasis becoming clinically apparent is not high. In our opinion, prophylactic central node dissection should be performed to avoid severe complications at the time of possible reoperation in the future. Prophylactic MND is recommended for selected patients who have clinicopathologic features that predict a high incidence of lymph node recurrence. The indication for prophylactic MND is affected by the incidence of nodal recurrence rates that patients and physicians can accept.

Ultrasonography facilitates the selection of patients suspected of thyroid lymphoma. Early detection of thyroid lymphoma is now possible, which contributes to achieving a favorable prognosis for patients. Among patients who are suspected of having a lymphoma based on US findings, those diagnosed as having lymphoma on FNAB should immediately undergo surgical examination to confirm the histology. Thereafter, they should undergo appropriate therapy based on the pathologic findings. However, patients diagnosed as negative on FNAB should also be carefully followed because at least 13% of these patients were confirmed to have lymphoma in our series.

The biopsy of a large number of thyroid nodules can be avoided when a pattern approach to nodule characterization is used. Specific morphologic patterns are highly predictive of benignity. Specifically, a nodule that has a uniform nonhypervascular spongiform appearance, is a cystic lesion with a colloid clot, has a giraffelike pattern, or is diffusely hyperechoic can be observed rather than biopsied. If, conversely, a nodule does not correspond to one of these four patterns, according to our data biopsy should be performed regardless of the individual features or pattern of the nodule.

Routine analysis of TBF for patients with untreated thyrotoxicosis is helpful for differentially diagnosing patients with destruction-induced thyrotoxicosis from those with Graves' disease.

The remaining issue to be solved is the differential diagnosis between follicular carcinoma and benign adenoma. Trials using novel techniques are progressing at a number of institutions, and publication of their findings is expected.

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