Incidental Thyroid Nodules on Imaging
Relevance and Management

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KEYWORDS

• Incidental • Thyroid • Ultrasound • CT • Computed tomography • MR imaging • Diagnosis • Biopsy

KEY POINTS

- Incidental thyroid nodules are extremely common findings on extrathyroidal imaging examinations of the chest and neck.
- Most of the incidental thyroid nodules are benign and do not require further workup.
- Incidental nodules with increased metabolic activity on PET/computed tomography have a higher risk of malignancy and should be further evaluated by sonography and biopsy.
- Guidelines published by the American College of Radiology are helpful to guide management of incidental thyroid nodules.

INTRODUCTION

Thyroid nodules, defined by the American Thyroid Association (ATA) as discrete focal abnormalities within the thyroid, which are radiologically distinct from the surrounding thyroid parenchyma, are found in up to 68% of adults scanned with high-spatial resolution sonography.[1] Therefore, it is not surprising that they are frequently found on computed tomography (CT), MR imaging, PET, or ultrasound (US) (as well as PET-CT and PET-MR imaging) examinations performed for indications other than evaluation of a known or suspected thyroid nodule. Such findings are termed incidental thyroid nodules (ITNs) and are typically nonpalpable. Notably, some nodules demonstrated on a dedicated thyroid US may also be considered ITNs. For example, if a sonogram is performed to evaluate a palpable nodule in the right lobe, and a nodule is detected on the left side, the latter would be considered incidental. Similarly, thyroid nodules discovered on a carotid sonogram are ITNs.

The reported incidence of ITNs on imaging examinations varies considerably. Extrathyroidal US remains the most common modality that depicts ITNs, accounting for 20% to 67%, followed by CT and MR imaging (9%–25%) and PET/CT (1%–4.3%).[2–7] ITNs are more common in women, and their incidence increases with age.

IMAGING OF INCIDENTAL THYROID NODULES

Extrathyroidal Ultrasound

US examinations performed for indications other than thyroid nodule assessment account for most of the reported ITNs.[8] These include sonograms of the carotid arteries, parathyroids, cervical lymph nodes, internal jugular veins, and other structures in the neck. High-frequency transducers are used in all of these examinations. A dedicated thyroid US usually should be

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recommended for complete evaluation, except in situations where no further investigation is warranted because of the ITN's morphology and/or size based on a risk-stratification system or clinical circumstances.

Computed Tomography and MR Imaging

Any imaging examination that includes the lower neck may depict thyroid nodules. Most commonly, they are seen on CT of the chest, neck, or cervical spine; MR imaging of the neck soft tissues or cervical spine; or CT or MR angiography of the neck. The thyroid is also occasionally seen on the axial T2-weighted images of a breast MR imaging. Drake and colleagues[4] reported ITNs in 3.45% of MR imagings, 5.84% of chest CT scans performed with intravenous contrast, and 5.14% of noncontrast chest CT scans, in a population of 98,054 imaging examinations. The rate of malignancy in ITNs detected on CT and MR imaging scans varies from 0% to 11%.[9–11]

Normal thyroid tissue demonstrates intrinsic high attenuation on CT and enhances homogenously following intravenous iodinated contrast administration.[2] Typically, a solid or cystic nodule on CT will seem hypoattenuating compared with the adjacent thyroid tissue. However, neither CT nor MR imaging can be used to accurately characterize thyroid nodules, because they cannot depict the fine architectural features that enable identification of thyroid cancer. Both imaging modalities underestimate thyroid nodule size and number and are not as reliable as US for their characterization.[12]

On CT, an ITN may seem cystic or solid, with or without calcifications. Microcalcifications are strongly associated with papillary thyroid carcinomas (PTCs) but are usually not identified on CT (**Fig. 1**). Che-wei and colleagues found that multiple punctate calcifications were associated with a higher risk of malignancy compared with solitary small calcifications, whereas coarse and peripheral calcifications carried a lesser likelihood of cancer.[13] Another study found that 12% of ITNs were calcified on CT but were not correlated with malignancy.[12] As a result, some experts recommend that calcified nodules on CT should not be managed differently than noncalcified nodules.[14]

Thyroid cysts may be simple or complex, with septations and/or solid components. Simple cysts are less attenuating than cysts that contain hemorrhage or colloid and that may be isodense to muscle.[15] However, CT density measurements do not reliably distinguish cysts from solid nodules due to volume averaging and small size. Importantly, papillary carcinomas may seem cystic on CT. Assessment may also be hampered by beam hardening artifacts, particularly on chest CT, and nodules may not be well seen on nonenhanced CT. Larger thyroid malignancies that exhibit gross extrathyroidal extension or are accompanied by adenopathy should be readily visible, but these are often identified clinically before imaging. Abnormal lymph nodes with cystic components, calcifications, and/or increased enhancement are suspicious for malignancy.

On MR imaging, the normal thyroid is T1 hyperintense and T2 isointense to hypointense on

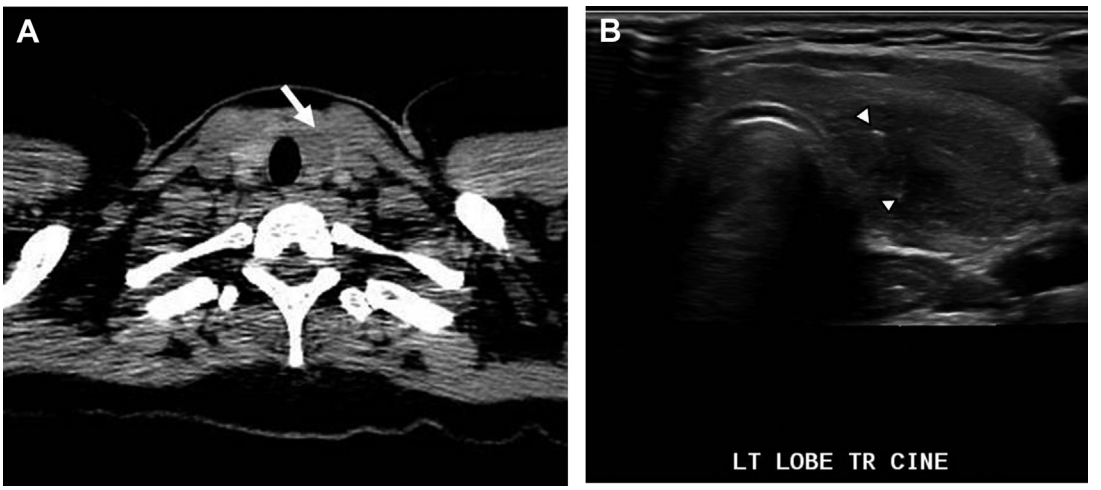

Fig. 1. A 28-year-old woman with an incidental nodule in left thyroid lobe on chest CT. (*A*) The CT shows a well-marginated hypodense nodule measuring 2.1 cm (*white arrow*). (*B*) Dedicated US was recommended, which showed a solid, hypoechoic 1.8 cm nodule with microcalcifications (*white arrowheads*), categorized as ACR TI-RADS-5. Fine-needle aspiration (FNA) biopsy of this nodule showed papillary thyroid cancer.

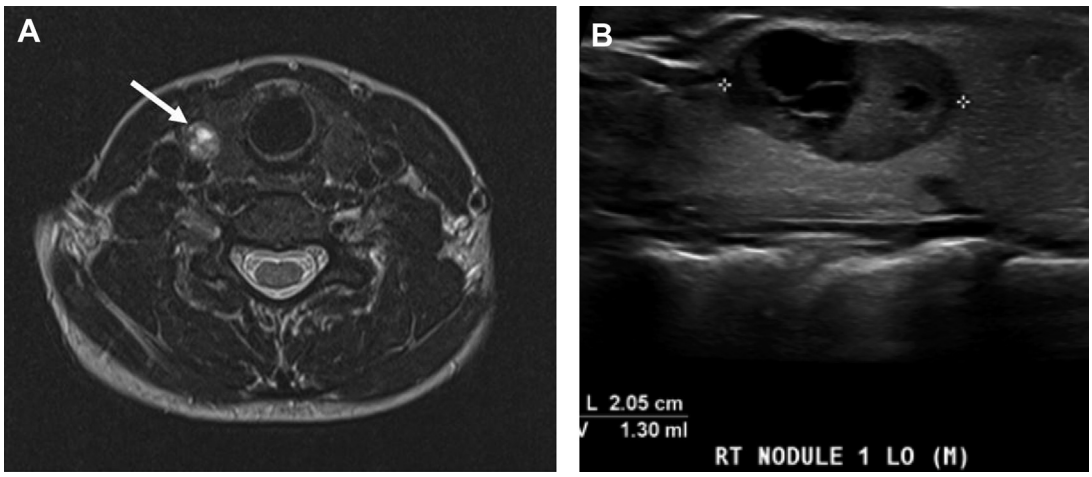

Fig. 2. A 37-year-old woman presented with neck pain and underwent MR imaging cervical spine. (*A*) On a T2-weighted axial MR image of the cervical spine, there is an incidental 1.8 cm hyperintense nodule (*arrow*) in the right thyroid lobe. (*B*) Dedicated ultrasound was recommended, which showed a solid-cystic right thyroid nodule (calipers), which was classified as ACR TI-RADS 3, which is considered as intermediate risk, and follow-up was recommended.

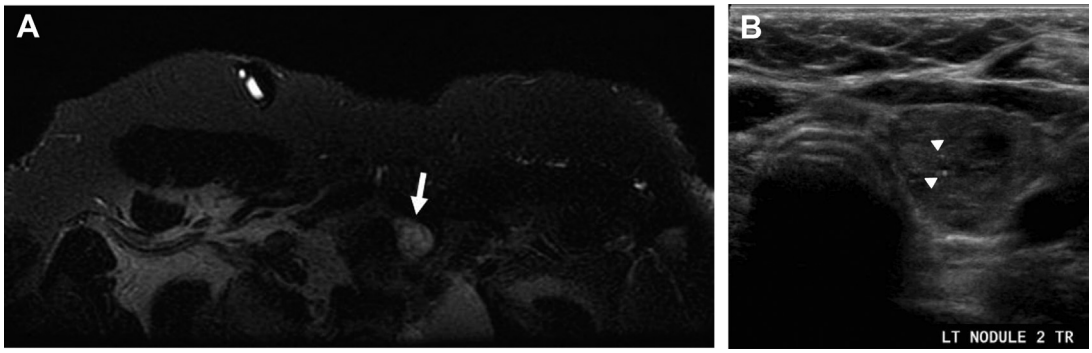

Fig. 3. A 65-year-old woman presented with an incidental thyroid nodule in the left lobe on MR imaging of the breasts. (*A*) T2-weighted axial images of the breasts that included lower neck show a focal hyperintense nodule (*arrow*). (*B*) Ultrasound demonstrated a hypoechoic solid nodule with punctate echogenic foci (*white arrowheads*) and was classified as ACR TI-RADS 5. FNA biopsy was recommended, which showed follicular neoplasm. Left hemithyroidectomy was subsequently performed, which showed nodular thyroid hyperplasia.

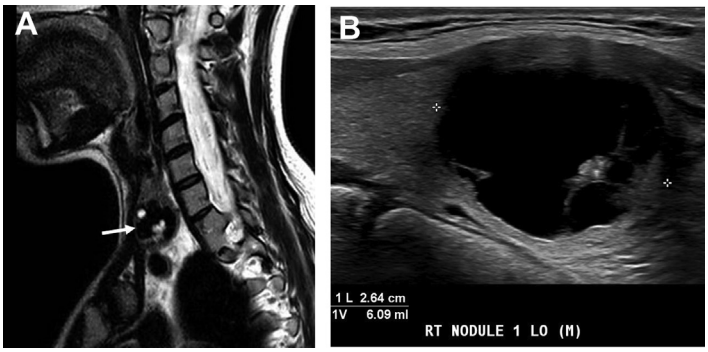

Fig. 4. A 36-year-old woman with an incidental solid-cystic right thyroid nodule on the cervical spine MR imaging performed for neck pain. (*A*) Sagittal T2-weighted MR image shows a 2.4 cm mixed high and low signal intensity right thyroid nodule (*arrow*). (*B*) Dedicated ultrasound was recommended, which showed a predominantly cystic nodule (calipers), classified as ACR TI-RADS 2 (considered benign), without any follow-up or biopsy recommended.

noncontrast images and enhances homogeneously after gadolinium administration. Both malignant and benign thyroid nodules may be isointense on T1-weighted sequences and hyperintense on T2-weighted sequences[16] (**Figs. 2–4**). Some studies have demonstrated that papillary carcinomas may have significantly lower T2 signal intensity than benign thyroid nodules.[17] Diffusion-weighted images, which are often obtained on MR imaging examinations performed for evaluation of the neck soft tissues or cervical spine, may help characterize some ITNs. A significant difference in the apparent diffusion coefficient (ADC) value was found between benign and malignant thyroid nodules, with ADC values in malignant nodules being lower than in benign nodules. Thus, T2 hypointensity and reduced ADC signal in an ITN may indicate malignancy. However, the ADC value in a benign thyroid nodule may be reduced by its contents, including colloid, necrosis and cystic change, hemorrhage, fibrosis, and calcium.[18]

Molecular Imaging Techniques

ITNs may be seen on some molecular imaging examinations, most commonly PET with fluorodeoxyglucose F 18 (^{18}F-FDG PET)/CT. The thyroid usually demonstrates mild homogeneous ^{18}F-FDG avidity. Diffusely increased uptake on ^{18}F-FDG PET-CT may be seen with inflammatory processes, that is, thyroiditis. However, focal increased uptake is a cause for concern (**Fig. 5**). Although the incidence of PET-detected ITNs is low, ranging from 1.2% to 4.3%,[2,5,6] the risk of malignancy can be as high as 30%.[5–7] In a recent study, Guevara and colleagues evaluated 5100 whole-body ^{18}F-FDG-PET/CT examinations and found nodular thyroid uptake in 2.3%, approximately 48% of them were biopsied, of which 50% were malignant on fine-needle aspiration (FNA) or surgery. This study showed that benign nodules showed significantly lower ^{18}F-FDG uptake, with a maximum standardized uptake value of 5.0 as the best threshold value to distinguish between benign and malignant nodules.[19]

Mallick and colleagues reviewed 2413 SPECT-CT examinations and evaluated them for incidental nonparathyroid abnormalities. They found that 27% patients had nonparathyroid findings; the most common were thyroid nodules (49%). Of these nodules, 6.9% were found to be malignant, and papillary microcarcinomas were the most common diagnosis.[20] Papillary thyroid microcarcinoma (PTMC) is a papillary cancer that is 1.0 cm or less in diameter.

ITNs are uncommonly seen on nuclear medicine examinations such as technetium-99m methoxyisobutylisonitrile (MIBI) and indium-111 octreotide scans. Both adenomas and thyroid cancers can show uptake on MIBI and octreotide scans. Two small series of selected patients with incidental MIBI-avid thyroid nodules showed that the rate of malignancy varied from 22% to 66%.[21,22] More recently, whole-body gallium-68 prostate-specific membrane antigen (PSMA)-based PET/CT or MR imaging has been used for whole-body primary staging of

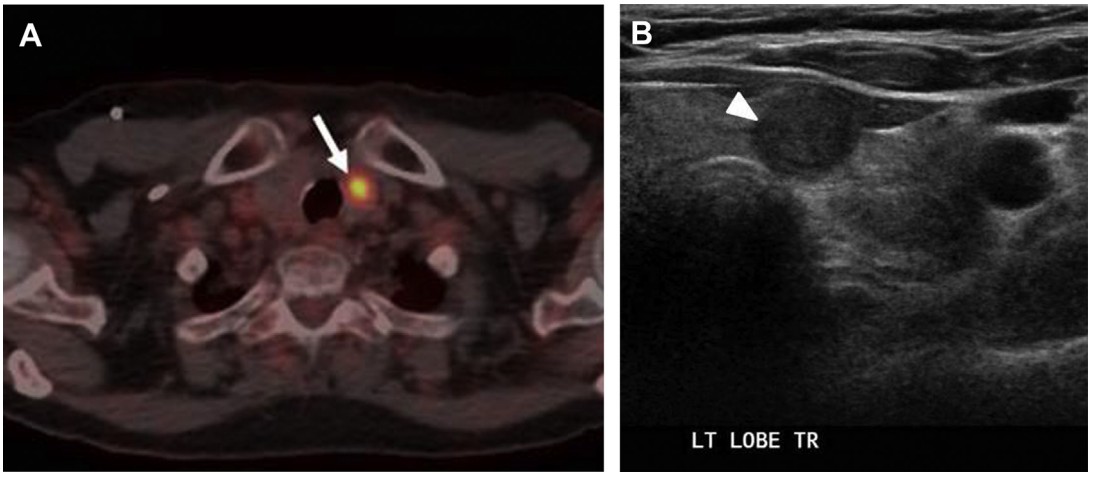

Fig. 5. A 68-year-old woman with an incidental left thyroid nodule on staging PET-CT for lung cancer. (*A*) The fused PET image shows hypermetabolic activity of the left thyroid nodule (*arrow*) in the axial plane. (*B*) The nodule was evaluated with dedicated ultrasound, which showed 1.0 cm round hypoechoic solid nodule (*arrowhead*) in the left thyroid lobe, categorized as ACR TI-RADS 4. Biopsy and thyroidectomy performed subsequently revealed papillary thyroid cancer.

intermediate- or high-risk prostate cancer, and some of these examinations can show thyroid uptake. In a systematic review, Bertagna and colleagues[23] found that 26% of PSMA-detected ITNs were malignant, and these were mostly PTCs.

CLINICAL EVALUATION AND PROBLEMS WITH WORKUP OF INCIDENTAL THYROID NODULES

Before proceeding to further investigations, the referring clinicians should ask the patient about any relevant historical factors associated with thyroid malignancy. These include a prior history of radiation, a personal history of breast cancer, a family history of thyroid cancer, or inherited syndromes associated with thyroid cancer, such as multiple endocrine neoplasia (MEN) type 2, familial non–MEN-associated medullary carcinoma, familial papillary carcinoma, familial polyposis coli, Cowden disease, or Gardner syndrome.

The prevalence of thyroid malignancy increases with age and peaks at a slightly earlier age in women than men. Only a small proportion of ITNs are found in young patients, in part because they undergo fewer imaging examinations than older individuals. However, the ratio of malignant to benign ITNs is likely to be higher in young patients, particularly those younger than 35 years.[2,12] A screening thyroid stimulating hormone (TSH) level should be measured in all patients with ITNs, and a serum calcitonin level should be obtained if there is family history of medullary thyroid cancer or multiple endocrine neoplasia type II. Routine measurement of serum thyroglobulin and serum calcitonin is recommended in patients with ITNs.

Once an ITN is detected, the most important question for the clinician is to whether to do further workup or follow-up. The actual risk of malignancy in ITNs varies from 1.6% to 12%. The highest rate was seen in a study of patients undergoing biopsy.[24,25] This rate of malignancy also depends on the clinical characteristics of the population studied and the percentage of detected ITNs that undergo further workup. Based on available evidence, most small thyroid cancers will have an indolent course without any treatment, and these patients will typically die from causes other than thyroid cancer.[26] The 5-year survival for individuals with most common type, papillary thyroid cancer, was approximately 98.3% (2010–2016).[27]

The last few decades have seen a significant increase in the incidence of thyroid cancer, and this has been attributed to various factors, most important of which is increasing use of highly sensitive imaging modalities along with increasing rates of FNA and thyroid surgery. However, multiple studies have demonstrated that the increased incidence of TC detection has not been associated with a commensurate risk in mortality. This may be due to increasing detection of slow-growing small thyroid cancers and the low potential for recurrence or mortality associated with PTC and PTMC.[28] About 50% to 60% of adults are found to have incidental nodules on autopsy, indicating the benign nature of most such tumors.[29] A 5-year study reported by Ito and colleagues[30] indicated that 70% of nonoperated PTMCs remained stable and/or decreased in size. Thus, overdiagnosis and overtreatment (ie, detection and treatment of disease that would never become clinically relevant or associated with significant mortality or morbidity) is a substantial problem.

Thyroid nodules characterized as suspicious by US are ultimately referred for FNA to obtain tissue for cytologic analysis. Nodules are usually classified by the Bethesda System for Reporting Thyroid Cytopathology, which includes 6 categories: (I) nondiagnostic, (II) benign, (III) atypia of undetermined significance/follicular lesion of undetermined significance, (IV) follicular neoplasm/suspicious for follicular neoplasm, (V) suspicious for malignancy, and (VI) malignant.[31] In the past, Bethesda III and IV nodules, collectively termed indeterminate, were often subjected to a second biopsy. If the repeat biopsy results were still indeterminate, many surgeons preferred resection (diagnostic thyroid lobectomy). However, the introduction of molecular (genomic) testing has offered an additional management option for indeterminate nodules. For example, the 2015 ATA guidelines recommend consideration of molecular testing in lieu of surgery for Bethesda IV nodules after taking into account sonographic and clinical features (see **Fig. 3**). The number of thyroid FNAs performed in the United States doubled between 2006 and 2011, accompanied by a significant increase in thyroidectomy rates.[32] A recent study found high sensitivity (94%) but low specificity rate (54%) for FNA, indicating that some of the patients who undergo surgery will not have cancer on final pathology.[33] However, no studies have evaluated the adverse effects related to treatment of incidental nodules compared with symptomatic nodules, to the authors' knowledge. Although thyroidectomy is generally considered safe, complications such as permanent hypoparathyroidism, hypocalcemia, and recurrent laryngeal nerve palsy are relatively common.[28]

Considering the increasing costs of imaging services and surgery, it is prudent to limit interventions to instances that are likely to meaningfully improve survival and/or quality of life. The annual

cost of care for thyroid cancer in the United States is estimated to reach $3.5 billion in 2030, with expenses for imaging, surgery, and adjuvant therapy for newly diagnosed patients constituting the major expenditures.[34] In the United States, the overall costs associated with unnecessary medical care are estimated at around $210 billion annually.[35] Most such treatment is done because of practitioners' fear of being sued for malpractice, a concept that also applies to the thyroid nodule management based on recent surveys.[36,37] These costs will continue to increase due to an enlarging population and increasing thyroid cancer detection. Reducing the rate of overdiagnosis and overtreatment will be critical to limit costs and reduce physical and psychosocial harm to patients. Similar considerations apply in other countries.

GUIDELINES FOR INCIDENTAL THYROID NODULE MANAGEMENT

The first step in ITN management is to decide if a nodule needs further workup, which typically begins with a dedicated thyroid sonogram, followed by application of a sonographic risk stratification system to guide further management. Multiple guidelines published under the auspices of professional societies worldwide are available. They include the American College of Radiology Thyroid Imaging Reporting and Data System (ACRTI-RADS), the ATA guidelines, the European Union EU-TIRADS, and the Korean K-TIRADS. Only a few guidelines provide recommendations on management of ITNs, as summarized here:

A. American College of Radiology white paper[2] (**Table 1**) by Hoang and colleagues is largely based on the Duke 3-tiered system and provides specific recommendations for evaluation of ITNs on various modalities. Size is the most important imaging feature used for assessment of nodule risk. Thyroid nodule size, although not strongly correlated with risk of malignancy, is associated with prognosis.[38,39]

The ACR ITN white paper recommends no further evaluation be performed in patients for whom the clinician and patient feel that the associated comorbidities or limited life expectancy may increase the risk of morbidity and mortality more than the thyroid cancer treatment itself. At the authors' institution, they follow the ACR ITN recommendations for nodules detected on US, CT, or MR imaging. Occasionally, nonrecommended dedicated thyroid sonograms are still performed at the referring clinician's or patient's request, however.

The thyroid nodule risk stratification system by the ACR TI-RADS committee published in 2017[40]

Table 1
Imaging recommendations for incidental thyroid nodules based on American College of Radiology white paper (2015)[2]

Imaging Modality	Age (y)	Size	Recommendation
CT or MR Imaging	Any	Any	Dedicated US thyroid
• Extrathyroidal invasion, atypical enlarged neck lymph nodes with associated cystic change, calcification, or increased enhancement	<35	≥1 cm	Dedicated US thyroid
	≥35	≥1.5 cm	Dedicated US thyroid
	Any	Any	Dedicated US thyroid
• No above suspicious features: if multiple nodules, recommendation is based on the largest nodule			
• Enlarged heterogenous thyroid without any discrete nodule			
^{18}F-FDG PET avid ITNs:	Any	Any	Dedicated US thyroid and guided FNA
ITNs on MIBI and octreotide scans	Any	Any	Dedicated US thyroid
Extrathyroidal US:	Any	Any	Dedicated US thyroid
• Microcalcifications, marked hypoechogenicity, lobulated or irregular margins, or taller-than-wide shape on transverse view (if any present)	<35	≥1 cm	Dedicated US thyroid
	≥35	>1.5 cm	Dedicated US thyroid
• Without abovementioned features, such nodules should be managed similar to CT/MR detected nodules using size and age criteria			

is now widely used for characterization of ITNs on US. It classifies thyroid nodules into 5 risk levels according to their sonographic features. Management recommendations include no follow-up, US surveillance, and biopsy. This system has been evaluated in multiple comparative studies, which have demonstrated that ACR TI-RADS leads to a significant reduction in biopsy of benign nodules. Although ACR TI-RADS does not recommend sampling of subcentimeter nodules, these may be followed sonographically, lessening the likelihood of missing cancers. In one study, there were fewer recommendations for sonographic workup of findings considered to be insignificant (from 35% to 7%), with estimated cost savings of more than $300,000 for the hospital system.[41]

B. 2015 American Thyroid Association Management guidelines[42]: the ATA guidelines recommend that all ITNs larger than 1 cm in adults be evaluated with a dedicated thyroid sonogram.

Solid hypoechoic nodules 1 cm with or without one or more: irregular margins, microcalcifications, taller than wide shape, rim calcifications with soft tissue extrusion, or extrathyroidal extension.

Solid hypoechoic nodules greater than or equal to 1 cm in greatest dimension with intermediate to high suspicion sonographic pattern (irregular margins, microcalcifications, taller than wide shape, rim calcifications with soft tissue extrusion, or extrathyroidal extension).

C. The British Thyroid Association (BTA) guidelines[43] recommend initial clinical assessment of all ITNs. If no abnormalities are found on clinical evaluation, there is no need for any further assessment. However, suspicious nodules that demonstrate tracheal invasion, extracapsular invasion, or associated abnormal lymph nodes on imaging should undergo further investigation. An important limitation of these guidelines is that the recommended clinical examination is not sensitive for detection of smaller nodules and is subject to interobserver variability. The committee recommends nodules detected by PET-CT with focal FDG activity should be investigated with US and FNA, unless disseminated disease is identified, and the prognosis from an alternative malignancy would preclude further investigation.[43]

D. American Association of Clinical Endocrinologists[44] recommends US evaluation of all ITNs detected by CT or MR imaging before consideration of FNA biopsy, whereas those detected by PET-CT should undergo US evaluation and FNA because of the high risk of malignancy.

E. NCCN (National Comprehensive Cancer Network)[45] recommends all incidental thyroid nodules be evaluated by US thyroid and TSH

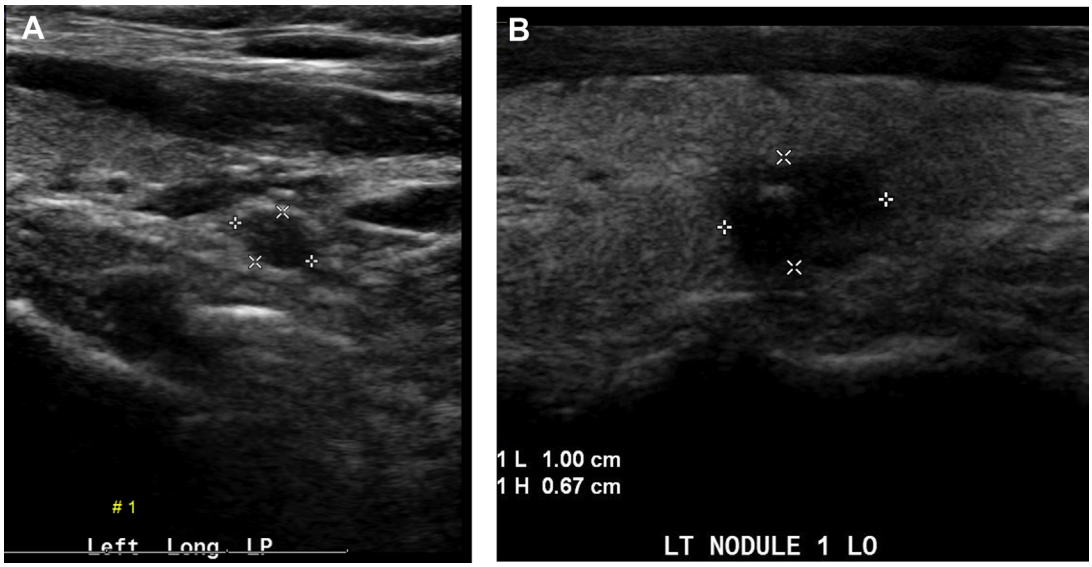

Fig. 6. A 45-year-old man with hyperparathyroidism. (*A*) Ultrasound of the left lower neck in longitudinal axis shows a hypoechoic nodule caudal to the lower pole of left thyroid lobe (calipers). (*B*) An incidental 1.0 cm solid markedly hypoechoic nodule (calipers) with macrocalcification was identified in the left thyroid lobe. This nodule was categorized as TIRADS-5, which was biopsied and subsequently resected in the same setting of parathyroidectomy, which revealed papillary thyroid microcarcinoma, follicular variant. The nodule caudal to the lower pole of left thyroid nodule was a parathyroid adenoma on pathology.

measurement. If TSH levels are normal or elevated, they recommend further assessment based on US characteristics.

F. ITNs on parathyroid US: another scenario involves management of ITNs found during parathyroid US in patients with hyperparathyroidism (**Fig. 6**). A recent study suggested that intermediate- to high-suspicion nodules greater than 1.5 cm may be resected at the same time as parathyroidectomy, potentially eliminating the risk of future reoperation with reduction in surgical complications, operating time and hospital stay, and cost of continued surveillance of such nodules.[46]

It is worth noting that patients are now frequently able to review their radiology reports, facilitating their participation in decision-making. Therefore, radiology reports should be standardized and ITNs should be appropriately addressed in the body and conclusion sections of the report, which should provide specific recommendations.

SUMMARY

The increasing prevalence of thyroid cancer imposes significant clinical and economic burdens on the health care system. Advanced imaging technology has led to an "epidemic" of ITNs, of which fewer than 10% are cancer. Many of these nodules are subjected to further investigations, invasive tests, and sometimes resection, all of which are associated with risks and economic implications. Radiologists should be cautious when recommending further investigations on ITNs. Recommendations should be based on guidelines such as those from the ACR and should be clearly stated. Further workup usually begins with sonography, with subsequent management based on a published risk stratification system in shared decision-making with the referring physician and the patient.

DISCLOSURE

Dr M.E. Lockhart: Deputy Editor, Journal of Ultrasound in Medicine; Chair, ACR Appropriateness Criteria Committee; Book Royalties, Elsevier.

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