Recommendation and Guideline | Thyroid

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2021 Korean Thyroid Imaging Reporting and Data System and Imaging-Based Management of Thyroid Nodules: Korean Society of Thyroid Radiology Consensus Statement and Recommendations

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Incidental thyroid nodules are commonly detected on ultrasonography (US). This has contributed to the rapidly rising incidence of low-risk papillary thyroid carcinoma over the last 20 years. The appropriate diagnosis and management of these patients is based on the risk factors related to the patients as well as the thyroid nodules. The Korean Society of Thyroid Radiology (KSThR) published consensus recommendations for US-based management of thyroid nodules in 2011 and revised them in 2016. These guidelines have been used as the standard guidelines in Korea. However, recent advances in the diagnosis and management of thyroid nodules have necessitated the revision of the original recommendations. The task force of the KSThR has revised the Korean Thyroid Imaging Reporting and Data System and recommendations for US lexicon, biopsy criteria, US criteria of extrathyroidal extension, optimal thyroid computed tomography protocol, and US follow-up of thyroid nodules before and after biopsy. The biopsy criteria were revised to reduce unnecessary biopsies for benign nodules while maintaining an appropriate sensitivity for the detection of malignant tumors in small (1–2 cm) thyroid nodules. The goal of these recommendations is to provide the optimal scientific evidence and expert opinion consensus regarding US-based diagnosis and management of thyroid nodules.

Keywords: *Thyroid nodule; Thyroid neoplasm; Lymph nodes; Ultrasonography; Computed tomography; Fine needle aspiration*

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INTRODUCTION

The management of thyroid nodules is controversial because of the high detection rate of thyroid nodules and the increasing incidence of thyroid cancer. Although the prevalence of palpable thyroid nodules is low (3%–4%) [1,2], incidental thyroid nodules are detected at a rate of 17%–67% with ultrasonography (US) [3-6], 16%–17% with neck computed tomography (CT) or magnetic resonance imaging (MRI) scans [7,8], 1%–2% with 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT scans [9,10], and 60% in autopsy specimens [11]. Thyroid malignancy was detected in 5% of patients with palpable thyroid nodules [12], in 8%–12% of non-palpable nodules evaluated using fine-needle aspiration (FNA) [13,14], and in 36% of the evaluated autopsy specimens [15]. Although the incidence of all sizes and stages of thyroid cancer, as well as thyroid cancer-related mortality, has increased [16,17], early detection of low-risk small papillary thyroid carcinomas (PTCs) by US has contributed to the increased incidence of thyroid cancer over the last 20 years. Increased detection of low-risk small PTC is associated with overdiagnosis and overtreatment [18-20]. Therefore, the risk profiles of patients and thyroid nodules should be taken into consideration in the diagnosis and management of thyroid cancer.

US is the primary imaging modality for the evaluation of thyroid nodules [21]. US-based risk stratification systems (RSSs) or Thyroid Imaging Reporting and Data System (TIRADS) can be used to assess the malignancy risk in nodules, identify poor prognostic factors in cancer, select patients for biopsy, and determine the optimal management plan for patients with thyroid nodules. In 2011, the Korean Society of Thyroid Radiology (KSThR) published consensus recommendations and an RSS for the US-based management of thyroid nodules [22]. The Korean-TIRADS (K-TIRADS), a US-based RSS for thyroid nodules, was endorsed by the KSThR and Korean Thyroid Association in 2016 [23]. However, recent advances in the diagnosis and management of thyroid nodules have necessitated a revision of the K-TIRADS, as well as the previous recommendations [24-28]. For this purpose, the KSThR organized a taskforce in January 2021. This taskforce recommended major revisions to the US lexicon, biopsy criteria used for the K-TIRADS, US criteria for extrathyroidal extension (ETE), thyroid CT protocol, and recommendations for US follow-up before and after biopsy of thyroid nodules. The aim of these recommendations is to present the best scientific evidence and expert opinion consensus regarding US-based diagnosis and management of thyroid nodules.

Methodology

Two authors searched MEDLINE via PubMed for articles published between January 2015 and December 2020, using keywords provided by the taskforce members. The members reviewed the retrieved articles and suggested modifications to previous recommendations based on these articles. The updated relevant articles continued to be searched and reviewed through July 2021. Frequent online communications and a few in-person meetings were conducted during the revision process due to the pandemic. The modified Delphi method was used to reach consensus, especially regarding the benefits (median value ≥ 7: significant net benefits) and harm (median value ≤ 3: harms outweigh benefits). Fifteen panels comprising an expert committee in thyroid radiology discussed the recommendations. A coefficient of variation of less than 0.5 indicated a reasonable internal agreement. The revision process was discussed and validated by a methodology specialist.

US Lexicon for Thyroid Nodules

The US lexicon should be simple, easy to use in clinical practice, objective with high interobserver agreement, and useful for the risk stratification and determination of the optimal management thyroid of nodules. Despite differences in US lexicons between various guidelines by professional societies, interobserver agreement is fair to moderate for most US features used for risk stratification of thyroid nodules [29-32]. The US features highly predictive of malignant nodules (punctate echogenic foci [microcalcifications], nonparallel orientation [taller-than-wide], irregular margin) or benign nodules (isoechoic or hyperechoic spongiform, intracystic echogenic foci with comet-tail artifact, pure cyst) should be strictly determined only when these features are clearly found in nodules. This will increase the specificity and interobserver agreement of these US features. Table 1 summarizes the major US lexicons, descriptors, and definitions.

Composition

Nodules are categorized based on the ratio of cystic to solid portion into solid (no obvious cystic content),

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Table 1. Recommended Terminology and Definitions of the Major US Lexicon for Thyroid Nodules

US Lexicon	Descriptor	Definition	Synonym
Composition			
	Solid	No obvious cystic component	
	Predominantly solid	Cystic portion ≤ 50%	
	Predominantly cystic	Cystic portion > 50%	
	Cystic	No obvious solid component	Pure cyst
	Spongiform	Microcystic changes > 50% of solid component	Honeycomb
Echogenicity			
	Marked hypoechogenicity	hypoechoic or similar echogenicity relative to the anterior neck muscles	
	Mild hypoechogenicity	hypoechoic relative to the normal thyroid parenchyma and hyperechoic relative to the anterior neck muscles	
	Isoechogenicity	Same echogenicity as that of the normal thyroid parenchyma	
	Hyperechogenicity	Hyperechoic relative to the normal thyroid parenchyma	
Orientation (shape)			
	Parallel	Anteroposterior diameter ≤ transverse diameter in the transverse plane	
	Nonparallel	Anteroposterior diameter > transverse diameter in the transverse plane	Taller-than-wide shape
Margin			
	Smooth	Obviously discernible smooth edges	Regular, circumscribed
	Irregular	Obviously discernible, but non-smooth edges with spiculations or microlobulations	Infiltrative, non-smooth, jagged edges, lobulated
	Ill-defined	Poorly demarcated margins, which cannot be obviously differentiated from the adjacent thyroid tissue	Indistinct
Echogenic foci (calcifications)			
	Punctate echogenic foci (microcalcifications)	Punctate (≤ 1 mm) hyperechoic foci within the solid component of a nodule	
	Macrocalcifications	Large (> 1 mm) hyperechoic foci with posterior acoustic shadowing	Coarse calcifications
	Rim calcification	Peripheral curvilinear hyperechoic line surrounding the nodule margin with or without posterior shadowing (complete or incomplete)	Peripheral, egg shell calcification
	Intracystic echogenic foci with comet-tail artifact	Intracystic echogenic foci showing comet-like echogenic tail	

US = ultrasonography

predominantly solid (cystic portion ≤ 50% of nodule), predominantly cystic (cystic portion > 50% of nodule), and cystic (no obvious solid content). Nodules without obvious anechoic cystic portions were categorized as solid. Nodules with minimal cystic changes (< 10%) are categorized as predominantly solid because their malignancy risk is similar to that of nodules with cystic changes (≥ 10%) (Fig. 1) [33]. The solid composition of a nodule is an independent predictor for malignancy (sensitivity: 78.7%–95.1%; specificity: 27.0%–53.8%; positive predictive value [PPV]: 12.9%–35.4%) [34-39].

The spongiform appearance of a nodule is defined as the aggregation of multiple nodular or linear microcystic components greater than 50% of the solid component in the partially cystic nodule (Supplementary Fig. 1). In the K-TIRADS, a spongiform nodule defined as an isoechoic or hyperechoic partially cystic nodule with a spongiform appearance is classified as benign, with a malignancy risk of < 1% [40-42]. Spongiform appearance is found exclusively in benign nodules [43,44]. This appearance may rarely be found in cystic papillary carcinomas [45]. Additionally, the malignancy risk may be increased in a hypoechoic nodule with a spongiform appearance [40,42].

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Echogenicity

The echogenicity of the nodules is determined as compared to that of reference structures (normal thyroid parenchyma and anterior neck muscles, including the strap and sternocleidomastoid muscles). The strap muscle is relatively thin and frequently has an increased echogenicity due to reverberation artifacts. Conversely, the sternocleidomastoid muscle is relatively thick and less affected by artifacts. Thyroid nodules are categorized based on the echogenicity of their non-calcified solid components into markedly hypoechoic (hypoechoic or similar echogenicity relative to the anterior neck muscles), mildly hypoechoic (hypoechoic relative to the normal thyroid parenchyma and hyperechoic relative to the anterior neck muscles), isoechoic (same echogenicity as that of the normal thyroid parenchyma), or hyperechoic (hyperechoic relative to the normal thyroid parenchyma) (Fig. 2). For nodules with heterogeneous or mixed echogenicity of the solid component, the predominant echogenicity is used to categorize the nodules and stratify the risk of malignancy [46]. In cases of abnormal thyroid parenchyma hypoechogenicity due to diffuse thyroid diseases, nodule echogenicity should be determined relative to the anterior neck muscle and presumed normal thyroid echogenicity (instead of the surrounding parenchymal echogenicity) to avoid misclassification.

The malignancy risk is similar between nodules with decreased echogenicity and nodules with similar echogenicity relative to the anterior neck muscles, and nodules with marked hypoechogenicity have a greater malignancy risk than nodules with mild hypoechogenicity [46]. Hypoechogenicity of nodules is an independent predictor of malignancy (sensitivity: 74.7%–94.0%; specificity: 56.7%–74.2%; PPV: 16.7%–52.7%) [35-39].

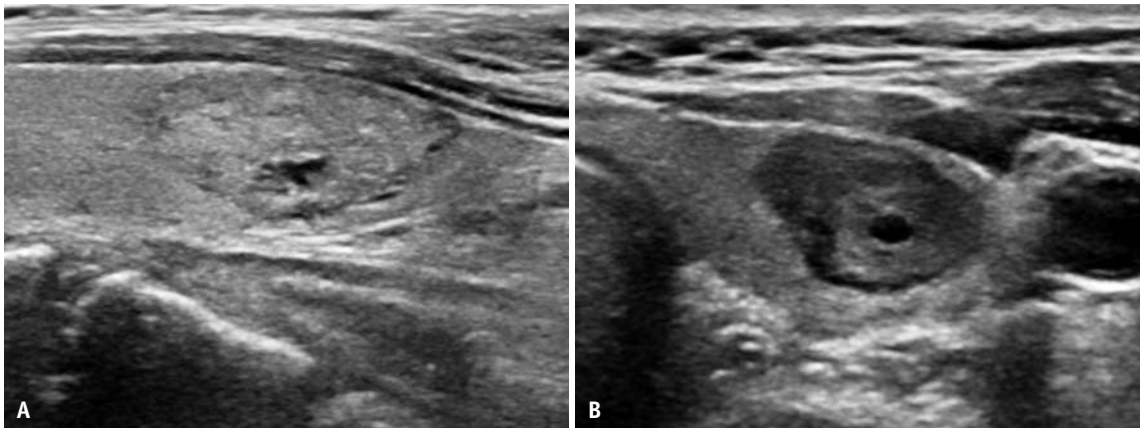

Fig. 1. Nodules with minimal cystic changes.
A. Predominantly solid and isoechoic nodule with focal minimal cystic changes (K-TIRADS 3, low suspicion). Diagnosis: benign follicular nodule. **B.** Predominantly solid and mildly hypoechoic nodule with focal minimal cystic change (K-TIRADS 3, low suspicion). Diagnosis: benign follicular nodule. K-TIRADS = Korean Thyroid Imaging Reporting and Data System

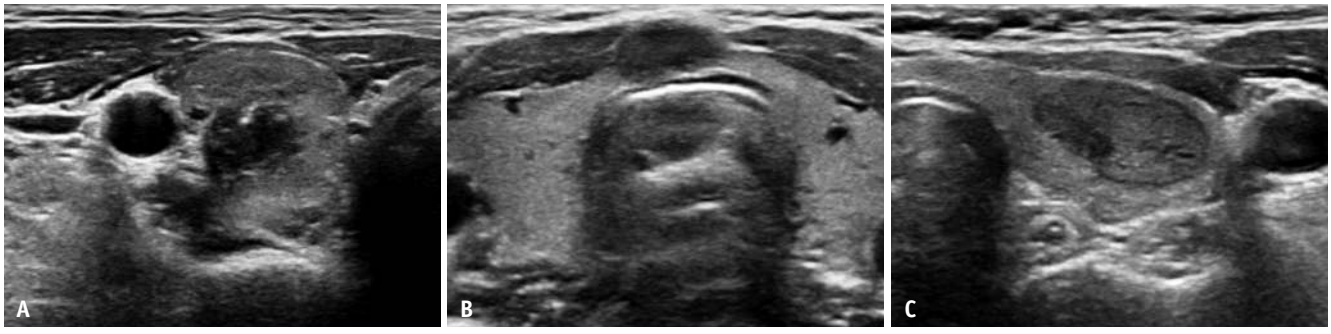

Fig. 2. Nodules with marked and mild hypoechogenicity.
A. Solid nodule with marked hypoechogenicity, which is hypoechoic relative to the anterior neck muscles, and punctate echogenic foci (K-TIRADS 5, high suspicion). Diagnosis: papillary carcinoma. **B.** Solid nodule with marked hypoechogenicity, similar to the anterior neck muscles (K-TIRADS 4, intermediate suspicion). Diagnosis: papillary carcinoma. **C.** Solid nodule with mild hypoechogenicity (K-TIRADS 4, intermediate suspicion). Diagnosis: benign follicular nodule. K-TIRADS = Korean Thyroid Imaging Reporting and Data System

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Orientation (Shape)

The orientation of the thyroid nodules is determined by their direction of growth. The nonparallel orientation is the same US feature as the "taller-than-wide shape" [47,48]. The orientation of nodules in the transverse plane is categorized as parallel (anteroposterior diameter ≤ transverse diameter) or nonparallel (anteroposterior diameter > transverse diameter). The committee selected the transverse plane as a reference for the nodule orientation because there was no difference in the diagnostic performance of RSSs between US image planes (transverse plane vs. either transverse or longitudinal plane) [49]. However, the use of the transverse plane is simpler and may be associated with less interobserver variability.

The nonparallel orientation (taller-than-wide shape) of nodules is an independent predictor of malignancy (sensitivity: 15.2%–53.0%; specificity: 88.2%–98.7%; PPV: 47.3%–77.5%) [34-38,40]. The malignancy risk of nodules with a nonparallel orientation depends on their composition and echogenicity [35,36]. The malignancy risk of nonparallel orientation is higher in solid hypoechoic nodules (77.0%–87.7%) than in partially cystic or iso-/hyperechoic nodules (10.5%–31.3%) [35,36,49].

Nodules may be round to ovoid or irregular, irrespective of their orientation. However, these US features were not included in the lexicon used for risk stratification of the nodules. Although nodules with round to ovoid shapes are frequently benign, these features are not specific for benign nodules and may be found in follicular carcinomas or the follicular variants of PTCs [50-52]. Irregular shapes are not specific for benign or malignant nodules [40,53,54].

Margin

Although the definition of a nodule margin is controversial, current guidelines for the US lexicon have used similar categories and definitions of margins [23,47,48,55]. Nodule margins can be categorized as smooth, irregular, or ill-defined. Obviously discernible margins are categorized as either smooth (obviously discernible smooth edges) or irregular (obviously discernible, but non-smooth edges with spiculations or microlobulations). Poorly demarcated margins that cannot be clearly differentiated from adjacent thyroid tissue are categorized as ill-defined.

Spiculated or microlobulated margins were categorized as irregular. Nodules without irregular margins, but with mixed smooth and ill-defined margins, were categorized based on the dominant feature. A smooth margin is commonly found in hypoechoic or hyperechoic nodules, isoechoic nodules with hypoechoic halos, and cystic or partially cystic nodules. An irregular margin is commonly found in infiltrating malignant tumors, mostly in hypoechoic nodules or rarely in isoechoic nodules with a partly hypoechoic portion or irregular hypoechoic rim. Additionally, ill-defined margins are commonly found in isoechoic hyperplastic nodules without encapsulation [54] and in some hypoechoic nodules including focal thyroiditis [56,57] and infiltrative malignant tumors.

Smooth or ill-defined margins do not increase the risk of malignancy [40,54]. However, irregular margins are an independent predictor for malignancy (sensitivity: 29.0%–71.4%; specificity: 87.1%–98.6%; PPV: 32.1%–86.7%) [35-39]. The malignancy risk of nodules with irregular margins is less dependent on the US pattern of composition or echogenicity [35,36]. The malignancy risk for irregular margins in solid hypoechoic nodules (80.0%–86.6%) is similar to or higher than that for partially cystic nodules that are isoechoic or hyperechoic (47.8%–88.9%) [35-37].

The hypoechoic halo around a thyroid nodule is composed of the capsule or pseudocapsule of the surrounding capsular vessels, fibrous connective tissue, compressed thyroid parenchyma, and chronic inflammatory infiltrates [58,59]. A hypoechoic halo is more commonly found around benign nodules. The absence of a halo is associated with an increased risk of malignancy [60,61]. However, the presence or absence of a hypoechoic halo is not specific for benign [54,62-64] or malignant [61,65] nodules, respectively. The hypoechoic halo is also frequently found in follicular neoplasms (FNs) [50,66,67]. A thick halo may be associated with an increased risk of follicular carcinoma [67].

Echogenic Foci (Calcifications)

Echogenic foci (calcifications) are defined as focal regions that are hyperechoic to the rest of the nodule and the surrounding normal thyroid parenchyma. They are categorized as punctuate echogenic foci (PEF, microcalcifications; echogenic foci ≤ 1 mm within the solid component), macrocalcifications (echogenic foci > 1 mm with posterior shadowing), or as complete or incomplete rim calcification (peripheral curvilinear hyperechoic line surrounding the nodule margin with or without posterior shadowing).

PEF have the same US features as those described for microcalcifications. The committee recommends using

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the descriptor 'PEF' because it may also correspond to other pathologic entities, such as inspissated colloid, as well as psammomatous or coarse microcalcifications [68]. PEF usually indicate psammomatous calcifications in PTC. However, PEF are also common in benign nodules, which rarely contain psammomatous calcifications (Supplementary Fig. 2). The majority of PEF do not show posterior acoustic artifacts, however PEF rarely show posterior acoustic shadowing or comet-tail artifacts in PTC (Fig. 3). PEF are an independent predictor for malignancy (sensitivity: 36.9%–59.6%; specificity: 78.6%–94.6%; PPV: 25.8%–68.3%) [35-40]. The malignancy risk of PEF depends on their composition and echogenicity [35,36]. The malignancy risk of PEF is substantially higher for solid hypoechoic nodules (60.7%–81.3%) compared to partially cystic or iso-/hyperechoic nodules (11.6%–25.9%) [35-37].

Intracystic echogenic foci with comet-tail artifacts

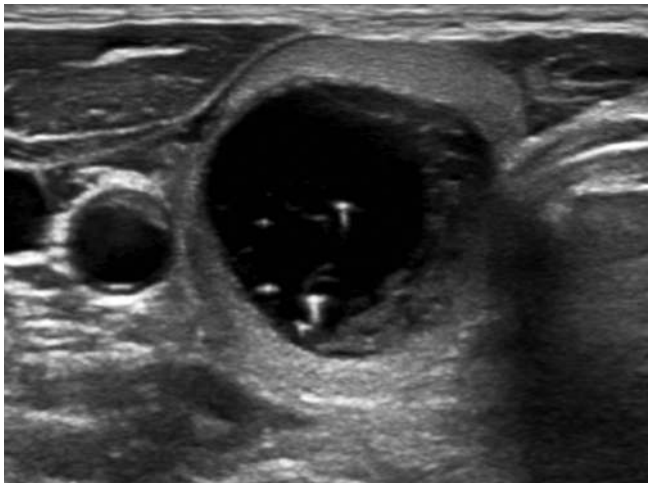

Fig. 4. Nodule with intracystic echogenic foci and comet-tail artifact. Predominantly cystic and mildly hypoechoic nodule with intracystic echogenic foci showing comet-tail artifacts (Korean Thyroid Imaging Reporting and Data System 2, benign). Diagnosis: benign follicular nodule.

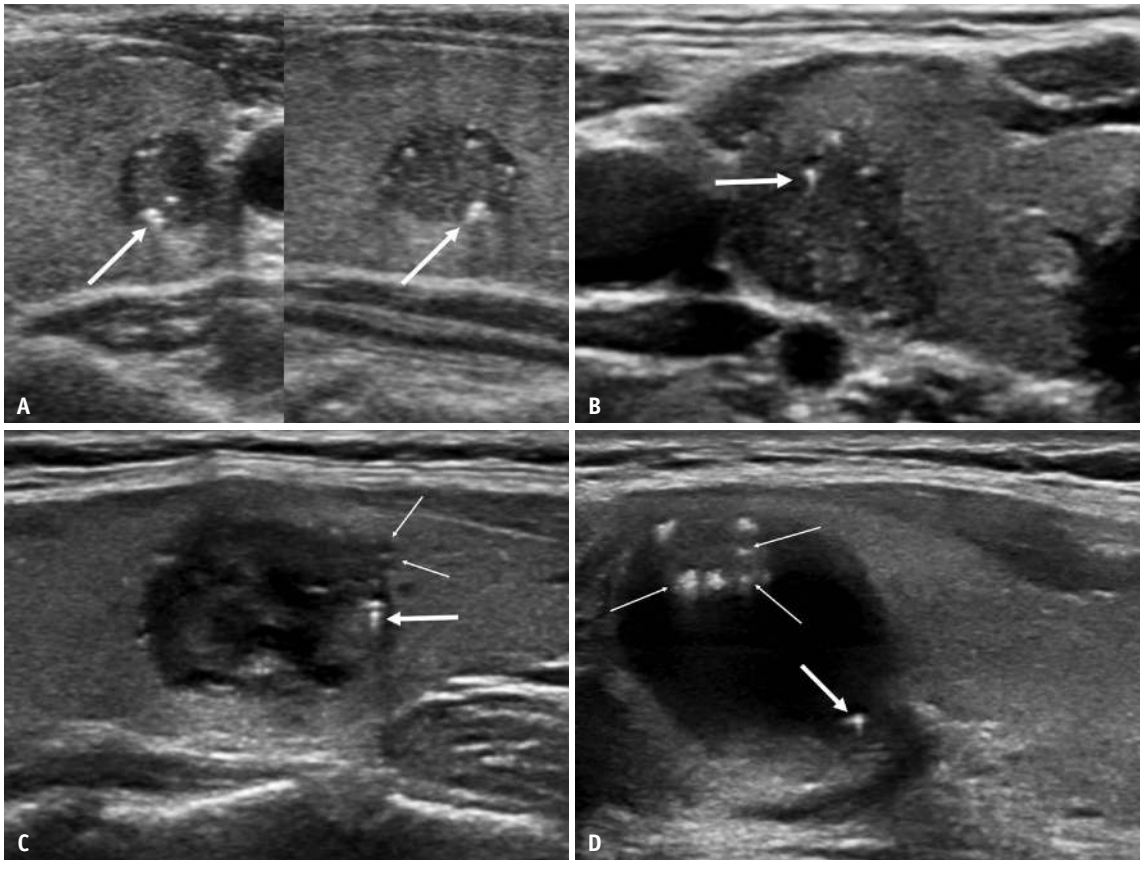

Fig. 3. Papillary carcinomas with echogenic foci and posterior acoustic artifacts.
A. Solid and mildly hypoechoic nodule with punctate echogenic foci (K-TIRADS 5, high suspicion). Punctate echogenic foci with posterior acoustic shadowing are observed in the lower part of the nodule (arrows). **B.** Solid and markedly hypoechoic nodule with punctate echogenic foci accompanying the comet-tail artifact (arrow) (K-TIRADS 5, high suspicion). **C.** Predominantly solid and markedly hypoechoic nodule with punctate echogenic foci accompanying the comet-tail artifact (thick arrow) (K-TIRADS 4, intermediate suspicion). US image shows irregular nodule margins (thin arrows). **D.** Predominantly cystic and mildly hypoechoic nodule with echogenic foci accompanying the comet-tail artifact at the margin of the cystic component (thick arrow) (K-TIRADS 4, intermediate suspicion). US image shows punctate and large echogenic foci within the solid component of the nodule (thin arrows). K-TIRADS = Korean Thyroid Imaging Reporting and Data System, US = ultrasonography

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are most commonly found in benign cystic nodules and reliably predict the benign nature of nodules (malignancy risk < 1%–2%) (Fig. 4) [35,69-72]. Although echogenic foci with comet-tail artifacts at the margin of the cystic component are commonly found in benign nodules [69,73], they are not specific for benign nodules (Fig. 3) [73]. Notably, echogenic foci with comet-tail artifacts within the solid component or at the margin of the cystic component should not be considered as US features of benign nodules [72-75]. Intracystic echogenic foci with comet-tail artifacts are strongly correlated with the colloid content of benign nodules [70]. However, it is unclear whether intrasolid echogenic foci with comet-tail artifacts are a result of inspissated colloid or psammomatous calcifications in PTC [74,76,77].

Macrocalcifications were defined as large (> 1 mm) echogenic foci with posterior acoustic shadowing in a nodule. They include centrally located curvilinear calcifications or non-curvilinear macrocalcifications at the nodule margin. Entirely calcified nodules (isolated macrocalcifications) are rare (1.2%) and are defined as calcified nodules with posterior acoustic shadowing in which any soft tissue component is not identified due to the dense posterior acoustic shadowing on US [78]. The majority of entirely calcified nodules found on US were complete or partial coarse macrocalcifications and some were dense rim calcifications on CT scans [79]. The malignancy risk of entirely calcified nodules (≥ 1 cm) is 18.4%–23.3%. All malignant tumors reported with entirely calcified nodules were PTCs and the majority exhibited aggressive behavior [78]. Many previous studies have reported an increased risk of malignancy with macrocalcifications [35,37,40,80]. However, it is uncertain whether this association represents an independent risk of malignancy [35,37,40]. Rim calcifications are peripheral curvilinear hyperechoic lines that surround the nodule margin with or without posterior shadowing. Several studies [39,80-82] have reported that rim calcification increases the risk of malignancy in thyroid nodules. However, other studies reported conflicting results [37,40,54,83]. Therefore, it is uncertain whether rim calcification is a reliable predictor of malignancy.

Nodule Size and Growth

The size of clinically significant nodules should be measured in three dimensions. Nodule growth should be estimated using the maximal nodule size or volume. The committee adopted the American Thyroid Association (ATA) criteria for nodule growth to define significant nodule growth, which requires an increase in size > 20% in at least two dimensions and an increase > 2 mm, or a change in volume > 50% [84]. Accurate estimation of nodule growth is essential for active surveillance and management of suspected or proven papillary thyroid microcarcinoma (PTMC), especially during follow-up.

It is uncertain whether nodule size predicts malignancy risk [85-91]. A recent study [92] reported that significant nodule growth, based on the ATA criteria, occurred in 14% of benign nodules and 25% of malignant nodules. Although some studies have suggested that the rate of nodule growth may predict the malignancy risk [92,93], it remains controversial. This is because many malignant nodules may not significantly grow [92] and some benign nodules grow slowly or rapidly [94-96]. However, rapid growth of a solid nodule may be a clinical manifestation of a high-grade malignancy, such as anaplastic thyroid carcinoma or lymphoma.

Vascularity

Color or power Doppler US can be used to evaluate nodule vascularity, which is categorized into pattern types 1–4 (type 1: no vascularity; type 2: perinodular vascularity only [circumferential vascularity at the nodule margin]; type 3: mild intranodular vascularity with or without perinodular vascularity (vascularity < 50%); type 4, marked intranodular vascularity with or without perinodular vascularity [vascularity ≥ 50%]) [23]. Intranodular vascularity was observed in 16.7%–91.7% of malignant nodules and 30.7%–65.3% of benign nodules [13,64,97-101]. Although intranodular vascularity may predict malignancy risk, no consistent associations have been reported for vascularity patterns with malignancy risk [101-103]. Several studies have reported that intranodular vascularity did not predict malignancy risk and was not superior to gray-scale US alone for the prediction of malignancy risk in all thyroid nodules [35,101]. A meta-analysis reported that the use of color Doppler US may not predict the malignancy risk of thyroid nodules [104]. Various US techniques for detecting vascular flow have been developed for use in clinical practice. However, their use as complementary imaging modalities for the diagnosis of thyroid malignancies has not yet been established. Higher resistive or pulsatile index values of spectral Doppler US may predict malignancy risk [102,105]. Contrast-enhanced US or superb microvascular imaging is an emerging technique. Hypoenhancement and heterogeneous

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enhancement of thyroid nodules on contrast-enhanced US may predict an increased malignancy risk [106]. Superb microvascular imaging may be more accurate than color or power Doppler US for the assessment of malignant thyroid nodules [107].

Elastography

US elastography is a technique that measures tissue elasticity. Cancer tissue is usually harder and firmer than normal thyroid parenchyma or benign nodules. Two representative elastography techniques are used to quantify tissue strain. "Strain elastography" evaluates the degree of tissue deformation induced by compression or acoustic forces. "Shear wave" speed measurement, measures the speed of shear waves that propagate orthogonally to the direction of tissue displacement. The propagation speed is generally higher in malignant thyroid nodules than in benign nodules [108,109]. Early clinical studies [110,111] reported that US elastography had a similar or better performance than gray-scale US. However, recent studies have reported that elastography is not superior to gray-scale US for use alone or as a complementary imaging modality for the diagnosis of thyroid malignancy [112,113]. Several studies have reported a potential diagnostic role for US elastography in the diagnosis of thyroid nodules with indeterminate or non-diagnostic cytology [114-116] or indeterminate US features [117]. Further studies are required to establish the complementary role of US elastography in the risk stratification of thyroid nodules.

US Assessment of Extrathyroidal Tumor Extension

ETE, defined as the direct extension of primary thyroid cancer into the perithyroidal structures [118], occurs in 11.5%–30% of differentiated thyroid carcinomas. It increases the risk of locoregional recurrence and disease-specific mortality [119,120]. The eighth edition of the American Joint Committee on Cancer staging system categorizes ETE as minor (identified by histological examination) and gross (identified preoperatively or intraoperatively) [118]. Minor ETE to perithyroidal soft tissue no longer constitutes a T category, and gross ETE to strap muscles constitutes category T3b, while ETE to major neck structures constitutes category T4. Therefore, the identification of minor and gross ETE on US is important for accurate preoperative staging of thyroid cancer. The recommended US criteria for minor and gross ETEs are summarized in Table 2.

For thyroid cancer that is in contact with the anterolateral thyroid capsule, US features that predict ETE include capsular abutment, disruption, protrusion, and replacement of strap muscles [121-130]. Capsular abutment is defined as a lack of intervening tissue between the cancer and capsule [125]. This is graded by the perimeter ratio (abutment perimeter/nodule perimeter x 100%) [123,126] or diameter ratio (abutting diameter/whole tumor diameter x 100%) [127]. Capsular disruption is defined as a loss of the anterolateral perithyroidal echogenic line at the site of contact with the cancer [123,125]. Capsular protrusion is defined as a bulge in adjacent structures with or without capsular disruption [128-130]. Replacement of the strap muscle by thyroid cancer is identified as protrusion of cancer into the strap muscle, with indistinct strap muscle margins [129]. Because US can overestimate the extent of ETE, US features with the highest PPV for ETE to the anterolateral thyroid capsule may be suitable for clinical application. The most predictive US feature for

Table 2. Recommended US Criteria for the Diagnosis of ETE of Thyroid Cancer

Category	US Feature	Description
Minor ETE		
Anterolateral	Capsular disruption	Loss of the perithyroidal echogenic line at the site of contact with the thyroid cancer
Posterior	Protrusion	Bulging across the expected margin of thyroid gland, and bulging into the perithyroidal soft tissue
Gross ETE to strap muscle	Replacement of strap muscle	Thyroid cancer protruding into the strap muscle, with indistinct strap muscle margins
Gross ETE to RLN	Protrusion into TEG	Protrusion of thyroid cancer into the TEG, beyond the expected margin of normal thyroid gland
Gross ETE to trachea	Obtuse angle	Obtuse angle formed by the surfaces of thyroid cancer and tracheal cartilage

ETE = extrathyroidal extension, RLN = recurrent laryngeal nerve, TEG = tracheoesophageal groove, US = ultrasonography

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minor ETE to the anterolateral thyroid capsule was capsular disruption (sensitivity: 61.6%; specificity: 87.1%; PPV: 58.5%; negative predictive value [NPV]: 88.5%; accuracy: 81.3%) and that for gross ETE to the strap muscle is replacement of strap muscles by thyroid cancer (sensitivity: 45.4%; specificity: 99.1%; PPV: 75.9%; NPV: 96.7%; accuracy: 96.0%), respectively (Fig. 5) [129]. US features that suggest minor ETE to posterior perithyroidal soft tissues have not been determined. However, the possibility of minor ETE to posterior perithyroidal soft tissue should be considered if the cancer abuts and protrudes beyond the expected posterior margin of the thyroid gland.

If thyroid cancer extends into the lumen of the trachea, tracheal invasion can be definitively diagnosed. However, tracheal invasion is difficult to diagnose if the cancer only abuts the tracheal wall. For thyroid cancers that abut the tracheal wall, tracheal invasion by thyroid cancer can be assessed based on the angle formed by the surfaces of the cancer and trachea. An obtuse angle between the cancer and trachea showed the highest sensitivity, NPV, and accuracy for the prediction of tracheal invasion (sensitivity: 85.7%; specificity: 98.9%; PPV: 40.0%; NPV: 99.9%; accuracy: 98.8%) (Fig. 6) [129]. Similar findings have been reported for PTMC [129,131]. The risk of recurrent laryngeal nerve (RLN) invasion can be assessed based on the presence or absence of a normal rim of the thyroid between the tracheoesophageal groove (TEG) and cancer and protrusion of the cancer into the TEG. Protrusion of cancer into the TEG showed the highest accuracy for the prediction of RLN invasion compared to other US features (sensitivity: 83.3%; specificity: 96.5%; PPV: 25.6%; NPV: 99.8%; accuracy: 96.3%) (Fig. 7) [129]. The US-based diagnostic criteria for ETE remain controversial. Well-organized prospective studies are required to validate the diagnostic performance of the US criteria for ETE.

Diagnosis of Cervical Metastatic Lymph Nodes on US

Classification of the Cervical Lymph Nodes on US According to the Risk of Nodal Metastasis

The frequency of metastasis to the cervical lymph nodes (LNs) in PTC is as high as 60%–70% [132,133]. LN metastases are associated with greater locoregional recurrence, rather than disease-specific mortality [134,135].

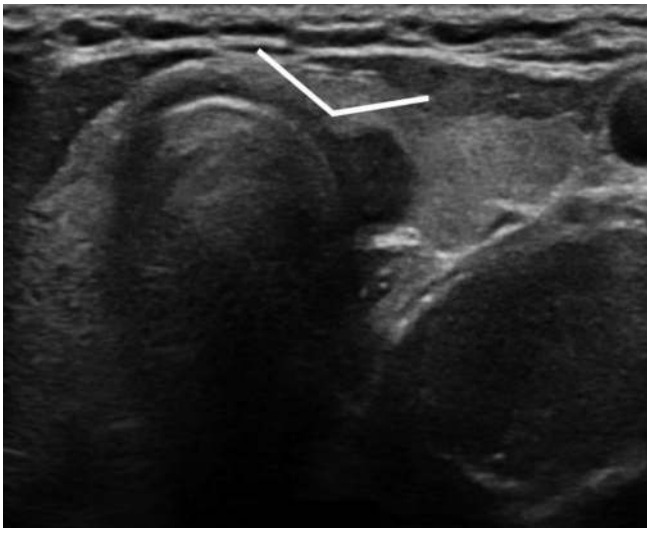

Fig. 6. Ultrasonography feature of extrathyroidal extension of thyroid cancer to the trachea. An obtuse angle (white line) was formed between the surfaces of the trachea and thyroid cancer. Diagnosis: gross extrathyroidal extension to the tracheal wall. Adapted from Chung et al. Korean J Radiol 2020;21:1187-1195 [129].

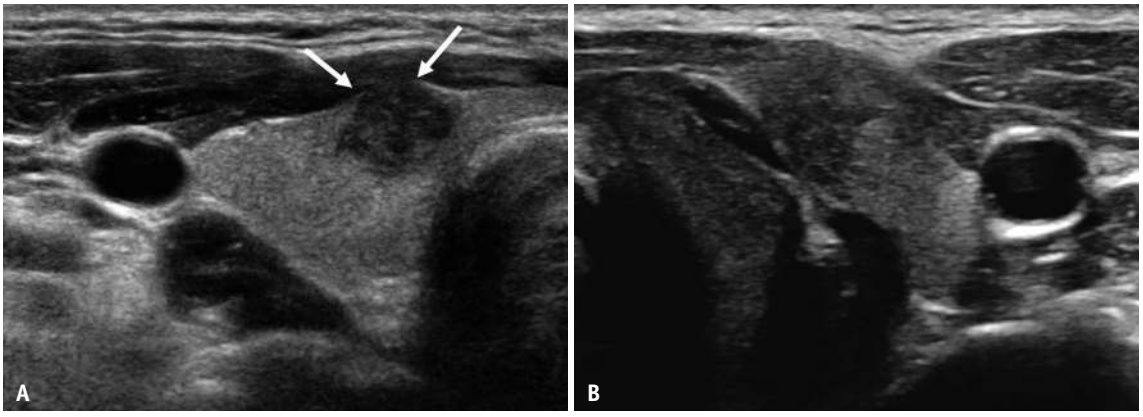

Fig. 5. Ultrasonography features of extrathyroidal extension of thyroid cancer beyond the anterolateral thyroid capsule.
A. Loss of the perithyroidal echogenic line (arrows) at the site of contact with the thyroid cancer. Diagnosis: minor extrathyroidal extension.
B. Thyroid cancer protruding into the strap muscle, with indistinct strap muscle margins. Diagnosis: gross extrathyroidal extension to the strap muscle. Adapted from Chung et al. Korean J Radiol 2020;21:1187-1195 [129].

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US is the established primary imaging modality for the assessment of LNs in patients with thyroid nodules or cancer.

With regard to the risk of LN metastasis, cervical

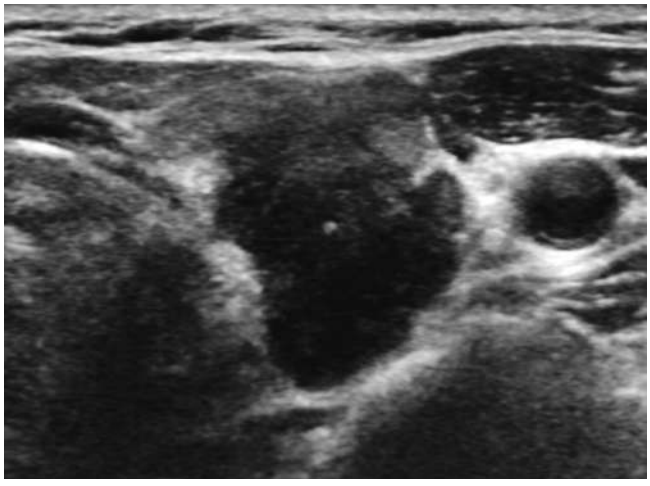

Fig. 7. Ultrasonography feature of extrathyroidal extension of the thyroid cancer to the recurrent laryngeal nerve. Protrusion of thyroid cancer into the tracheoesophageal groove. Diagnosis: gross extrathyroidal extension to the recurrent laryngeal nerve. Adapted from Chung et al. Korean J Radiol 2020;21:1187-1195 [129].

Table 3. US-Based Risk Stratification for Cervical Lymph Node Metastasis in Patients with Possible or Proven Thyroid Carcinomas

Category	US	Malignancy Risk (%)[§]
Suspicious*	Any of four suspicious features	73–88
	Cystic change	97–100
	Echogenic foci (calcifications)	86–100
	Cortical hyperechogenicity (focal/diffuse)	79–96
	Abnormal vascularity (peripheral/diffuse)	77–84
Indeterminate[†]	Loss of echogenic hilum and hilar vascularity	20
Probably benign[‡]	Echogenic hilum	< 3
	Hilar vascularity	

*Lymph nodes with suspicious imaging features are included in this category, regardless of the presence of imaging features of probably benign or indeterminate lymph nodes, [†]Lymph nodes not included in suspicious or probably benign categories, [‡]Lymph nodes with any imaging feature of echogenic hilum or hilar vascularity are considered probably benign, if there are no suspicious imaging features, [§]Estimates based on previous studies [127,137-140]. US = ultrasonography

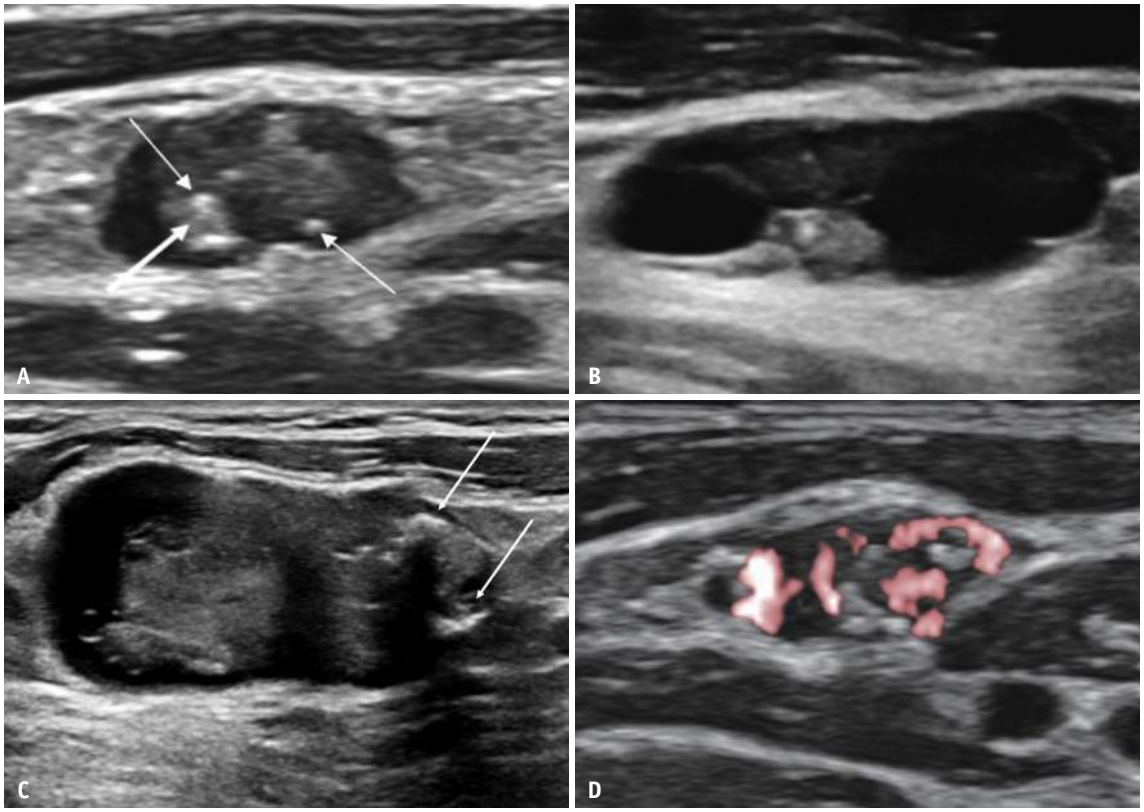

Fig. 8. Ultrasonography features of suspicious lymph nodes.
A. Focal cortical hyperechogenicity (thick arrow) and punctate echogenic foci (microcalcifications) (thin arrows) in a metastatic lymph node. **B.** Multifocal cystic changes in a metastatic lymph node. **C.** Large echogenic foci with posterior shadowing (macrocalcifications) (arrows) in a metastatic lymph node. **D.** Abnormal vascularity in a metastatic lymph node. Diagnosis: metastatic papillary carcinoma **(A-D)**.

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LNs can be classified as suspicious, indeterminate, and probably benign based on their US features (Table 3, Fig. 8, Supplementary Figs. 3, 4) [23,136]. LNs with any of the following features are regarded as suspicious: cystic changes, echogenic foci (calcifications), cortical hyperechogenicity (focal/diffuse), or abnormal vascularity (peripheral/diffuse). These features were reported to be highly specific and predictive of LN metastases (approximately 73%–88%) in node-by-node correlation studies (Table 3) [127,137-140]. Probably benign LNs are defined as those that do not have any imaging features of suspicious LNs and display typical imaging features of either an echogenic hilum or radiating hilar vascularity. Indeterminate LNs are those that have no imaging features of suspicious or probably benign LNs. They include LNs of any shape (ovoid or round) that have a loss of echogenic hilum and hilar vascularity on US. However, these imaging features for indeterminate LNs are not specific to metastatic nodes [136,140]. In a recent node-by-node correlation study of preoperative thyroid cancer patients, the malignancy risk of indeterminate LNs (19.5%) was significantly higher than that of probably benign LNs (2.8%); however, it was lower than that of suspicious LNs (78.4%) (Table 3) [137]. There were no significant differences in the short and long diameters and in the size ratios between benign and metastatic among the indeterminate LNs classified by US [137].

Although US is useful for the evaluation of cervical LN metastasis in patients with thyroid cancer, it has a relatively low sensitivity for the detection of metastatic LNs in the central compartment [132,141-143]. The sensitivity may be low because of the overlying thyroid gland in the central neck and poor visualization of nodal micrometastases (diameter ≤ 2 mm). Nodes with macroscopic metastases have a high risk of postoperative recurrence. Conversely, micrometastatic nodes are not associated with an increased risk of disease recurrence and have a recurrence rate like that of pathologically negative nodes [134,144-148]. Therefore, preoperatively identified macroscopic metastatic LNs have prognostic significance and are regarded as clinically apparent metastatic LNs, whereas most micrometastatic nodes that are undetected by imaging have little clinical significance [134]. Recent studies have investigated the roles of advanced US imaging modalities, such as US elastography [149-153], contrast-enhanced US [154-157], and US microvascular imaging [158]. However, there are insufficient data on their clinical utility.

Indications for FNA of the Cervical Lymph Nodes

The role of US in the preoperative evaluation of cervical LNs is to detect clinically apparent and macroscopic metastatic LNs, which are the targets of surgery. Therefore, accurate preoperative imaging is crucial for the complete surgical removal of macroscopic metastatic LNs in patients with thyroid cancer. Inadequate preoperative assessment of cervical LNs can lead to persistent or recurrent disease in the neck. Therefore, we recommend FNA of suspicious LNs with a short diameter > 3–5 mm, and indeterminate LNs with a short diameter > 5 mm in preoperative patients with possible or proven thyroid cancer (Table 4). When FNA is performed for LNs, measurement of tissue-washout thyroglobulin is recommended for LNs in the lateral neck and selectively in the central neck.

Recent studies have reported that postoperative suspicious metastatic lesions in the thyroid bed or lateral neck usually remain stable and have a low potential for structural disease progression [159,160]. Surgical resection was successful at the time of structural disease progression. There was no evidence of local invasion or distant metastases. These data suggest that appropriately selected patients can be closely monitored with serial serum thyroglobulin measurements and neck US. The decision regarding whether and when to perform US-guided FNA for suspicious recurrent lesions in postoperative patients with thyroid cancer should be based on the location of the LN or suspicious lesion and the management plan (re-operation, non-surgical ablation therapy, or active surveillance). Considering the high risk of postoperative complications following repeat surgery, FNA may be deferred for small indeterminate or suspicious LNs < 8–10 mm (short diameter on US and CT images) at the operative bed in postoperative patients if US surveillance is considered instead of re-

Table 4. Recommended FNA Indications for Cervical Lymph Nodes in Patients with Possible or Proven Thyroid Carcinomas

1) Suspicious lymph node: size > 3–5 mm (short diameter on US or CT images)*†
2) Indeterminate lymph node: size > 5 mm (short diameter on US or CT images)*†

*Measurement of tissue-washout thyroglobulin is recommended for lymph nodes in lateral neck and selectively in central neck, †If US surveillance is considered instead of re-operation or ablation therapy for suspicious recurrent lesion at operative bed in postoperative patients, FNA may be deferred for small indeterminate or suspicious lymph nodes < 8–10 mm (short diameter on US and CT images). FNA = fine-needle aspiration, US = ultrasonography

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operation or ablation therapy for suspicious recurrent lesions (Table 4).

US-Based Risk Stratification and the Revised 2021 Korean Thyroid Imaging Reporting and Data System

Structure of the 2021 K-TIRADS

The 2021 K-TIRADS uses a pattern-based system that stratifies the malignancy risk of a nodule using a combination of composition, echogenicity, and suspicious US features [23]. The malignancy risk of a nodule cannot be accurately estimated using a single US predictor. Therefore, a combination of several US features should be used [161]. The predictability of suspicious US features (PEF, irregular margins, and nonparallel orientation) for malignancy heterogeneously depends on nodule composition and echogenicity [35,161]. The aforementioned data form the basis of the K-TIRADS structure. Compared to the 2016 K-TIRADS, the 2021 K-TIRADS has minimal differences in structure and suggested malignancy risk (Table 5, Fig. 9). Thyroid nodules are classified on the basis of their malignancy risk, based on US patterns, into those with high suspicion (K-TIRADS 5), intermediate suspicion (K-TIRADS 4), low suspicion (K-TIRADS 3), and benign categories (K-TIRADS 2). K-TIRADS 1 indicates no nodules in the thyroid gland. The 2021 K-TIRADS categorizes entirely calcified nodules as K-TIRADS 4 [78,162]. Extensive parenchymal PEF (microcalcifications) without discrete nodules (suspicious for diffuse sclerosing variant of PTC), and diffusely infiltrative lesions (suspicious for infiltrative malignancy, such as metastasis or lymphoma) are categorized as K-TIRASDS 4. Nodules with US patterns of K-TIRADS

Table 5. US Pattern and Malignancy Risk of Thyroid Nodules and Biopsy Size Thresholds in the 2021 K-TIRADS

Category	US Patterns	Suggested Malignancy Risk (%)	Nodule Size Threshold for Biopsy[§]
High suspicion (K-TIRADS 5)	Solid hypoechoic nodule with any of the three suspicious US features (punctate echogenic foci, nonparallel orientation, and irregular margins)	> 60	> 1.0 cm[‖]
Intermediate suspicion (K-TIRADS 4)*	1) Solid hypoechoic nodules without any of the three suspicious US features or 2) Partially cystic or iso-/hyperechoic nodule with any of the three suspicious US features 3) Entirely calcified nodules[†]	10–40	> 1.0–1.5 cm[¶]
Low suspicion (K-TIRADS 3)	Partially cystic or iso-/hyperechoic nodule without any of the three suspicious US features	3–10	> 2.0 cm
Benign (K-TIRADS 2)[‡]	1) Iso-/hyperechoic spongiform 2) Partially cystic nodule with intracystic echogenic foci and comet-tail artifact 3) Pure cyst	< 3	Not indicated**
No nodule (K-TIRADS 1)	-	-	-

*Extensive parenchymal punctate echogenic foci (microcalcifications) without discrete nodules (suspicious for diffuse sclerosing variant of PTC) and diffusely infiltrative lesions (suspicious for infiltrative malignancy, such as metastasis or lymphoma) are considered to be intermediate suspicion (K-TIRASDS 4) nodules, [†]Entirely calcified nodules with complete posterior acoustic shadowing, with no soft tissue component identified due to dense shadowing on US (isolated macrocalcification), [‡]Regardless of coexisting suspicious US features (punctate echogenic foci, nonparallel orientation, or irregular margin), [§]In cases with poor prognostic risk factors, including suspected cervical lymph node metastases, obvious extrathyroidal extension to adjacent structures (trachea, larynx, pharynx, recurrent laryngeal nerve, or perithyroidal vessels), confirmed distant metastases, or suspected medullary thyroid cancer, biopsy of the most suspicious nodule should be performed, regardless of the nodule size, [‖]Biopsy is recommended for small (> 0.5 cm and ≤ 1 cm) high suspicion (K-TIRASDS 5) nodules with high-risk features, including attachment of nodules to the trachea or posteromedial capsule along the course of the recurrent laryngeal nerve considering the potentials of high-risk microcarcinomas requiring immediate surgery. Biopsy may be considered for small (> 0.5 cm and ≤ 1 cm) K-TIRASDS 5 nodules without high-risk features to decide the management plan in adults. In children, biopsy should be considered for small K-TIRASDS 5 nodules (> 0.5 cm and ≤ 1 cm) to decide the management plan considering the clinical context, [¶]Cutoff size for biopsy should be determined within the range of 1 and 1.5 cm, based on the ultrasound features, nodule location, clinical risk factors, and patient factors (age, co-morbidities, and preferences), **Although biopsy is not routinely indicated, it may be performed for nodules that demonstrate continuous and significant growth or for nodules prior to ablation therapy or surgery. K-TIRADS = Korean Thyroid Imaging Reporting and Data System, PTC = papillary thyroid carcinoma, US = ultrasonography

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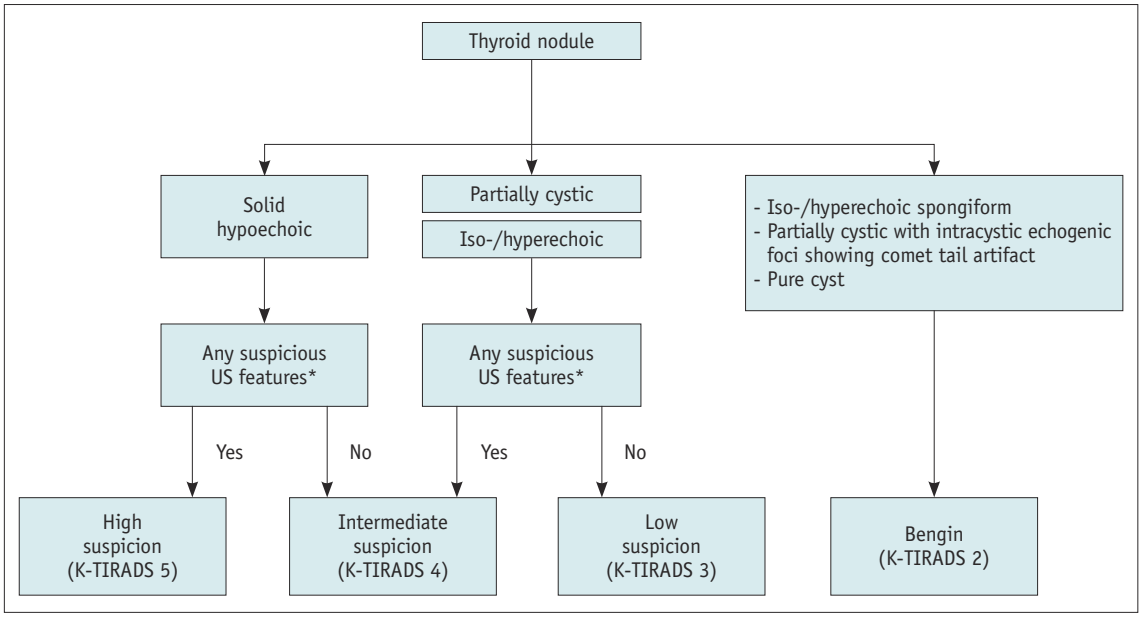

Fig. 9. Algorithm of the 2021 K-TIRADS for malignancy risk stratification based on the nodule composition and echogenicity, and suspicious US features. *Punctate echogenic foci (microcalcifications), nonparallel orientation (taller than wide shape), and irregular margins. K-TIRADS = Korean Thyroid Imaging Reporting and Data System, US = ultrasonography

2 were classified as K-TIRADS 2 regardless of coexisting suspicious US features (these nodules were classified as K-TRADS 4 in the 2016 K-TIRADS). The modifications made to the malignancy risks of K-TIRADS 3 and 4 were based on two recent large cohort studies [163,164].

Selection of Patients for US-Guided Biopsy

Table 5 summarizes the biopsy size cutoff values and malignancy risks corresponding to the nodule categories in the 2021 K-TIRADS. Recent comparative studies reported that US-based FNA criteria of the 2016 K-TIRADS had the highest sensitivity for thyroid cancers and the highest rate of unnecessary FNA for benign nodules among the RSSs in thyroid nodules ≥ 1 cm [25-27,165,166]. The differences in diagnostic performance are attributed mainly to differences in the size threshold for biopsy rather than differences in the structure (pattern-based or point-based system) or US criteria for nodule classification [28]. The diagnostic performance of various RSSs was similar for the same size cutoff value for biopsy in simulation studies [27,28]. The diagnostic performance estimated by each classification category was comparable among the RSSs [167].

US-based RSSs require an appropriate sensitivity for the detection of malignant tumors in nodules > 1.0 cm, while reducing unnecessary biopsies for benign nodules. However, determining the diagnostic performance of US-based RSSs for thyroid malignancy remains controversial. Because tumor size is closely related to prognosis [168-171], the diagnostic performance of RSSs should be stratified according to nodule size. The risk of distant metastasis increases for tumors > 2 cm, and the risks of local tumor invasion, nodal metastasis, and distant metastasis increase with tumor size [170,171]. Therefore, a strategy to increase the sensitivity at the expense of a higher rate of unnecessary biopsies may be appropriate for large nodules (> 2 cm). This is considering the higher risk of aggressive behavior and low predictability of the current RSS for non-PTC malignant tumors, such as encapsulated follicular variant PTC or follicular thyroid cancer [172-174]. The strategy to reduce unnecessary biopsies at the expense of decreased sensitivity may be appropriate for small nodules (1–2 cm) without aggressive sonographic features, considering the slow growth rate of most low-risk thyroid cancers. Unnecessary biopsies of small nodules (1–2 cm) place a significant burden on the healthcare system, leading to considerable anxiety in patients and unnecessary diagnostic surgical procedures due to indeterminate FNA results.

Based on the aforementioned evidence, the 2021 K-TIRADS recommends biopsy for nodules > 1 cm in size for K-TIRADS 5, > 1–1.5 cm for K-TIRADS 4, and > 2 cm for K-TIRADS 3. The 2021 K-TIRADS recommends a cutoff size range (1–1.5 cm) for biopsy of K-TIRADS 4 nodules to allow feasible clinical application. If there are no particular risk factors, the 2021 K-TIRADS recommends biopsy for

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nodules > 1.5 cm for K-TIRADS 4. However, within this range (1–1.5 cm), the decision for biopsy should be determined based on the ultrasound features, nodule location, clinical risk factors (FDG avid on PET scan, familial cancers, worrisome symptoms, such as dysphonia, etc.), and patient characteristics (age, comorbidities, and preference). Biopsy is not routinely indicated for K-TIRADS 2 nodules. However, it may be performed for nodules that demonstrate continuous and significant growth or for nodules prior to ablation therapy or surgery.

Biopsy should be performed regardless of the size of the most suspicious nodule in cases with poor prognostic factors, including suspected cervical LN metastases, obvious ETE to adjacent structures (trachea, larynx, pharynx, RLN, or perithyroidal vessels), confirmed distant metastases, or suspected medullary thyroid cancer. Biopsy is recommended for small (> 5 mm and ≤ 1 cm) K-TIRASDS 5 nodules with high-risk features, including adherence of nodules to the trachea or posteromedial capsule along the course of RLN. This is considering the possibility of high-risk microcarcinomas that require immediate surgery [175]. In adults, biopsy can be considered for small (> 5 mm and ≤ 1 cm) K-TIRASDS 5 nodules without high-risk features to determine the management plan. In children, biopsy should be considered for small K-TIRASDS 5 nodules (> 5 mm and ≤ 1 cm) to determine the management plan considering the clinical context [176].

Diagnostic Performance of the 2021 K-TIRADS Biopsy Criteria

A recent multicenter retrospective study of 5708 thyroid nodules (malignancy rate, 19.5%) reported that the 2021 K-TIRADS 4 biopsy cutoff size of 1.5 cm had a sensitivity of 76.1%, specificity of 50.2%, and unnecessary biopsy rate for benign nodules of 40.1% [163]. A K-TIRADS 4 biopsy cutoff size of 1.0 cm had a sensitivity of 91.0%, specificity of 39.7%, and unnecessary biopsy rate for benign nodules of 48.6%. Using the biopsy cutoff size of the 2016 K-TIRADS, the sensitivity was 94.9%, specificity was 24.4%, and unnecessary biopsy rate for benign nodules was 60.9%. Compared to the 2016 K-TIRADS, the 2021 K-TIRADS significantly reduced the rate of unnecessary biopsies by 19.2%–32.8% in small nodules (≤ 2 cm) while maintaining a very high sensitivity (98.0%) for detecting large malignant tumors (> 2 cm) [163].

The unnecessary biopsy rate of small nodules (≤ 2.0 cm) with the use of the 2021 K-TIRADS 4 biopsy cutoff size (1.5 cm) was significantly lower (17.6%) than those of the American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi medical guidelines, the European-TIRADS, and the American College of Radiology (ACR) TIRADS (18.6%–28.1%). Additionally, the 2021 K-TIRADS afforded a significantly higher sensitivity for the detection of large malignant tumors (> 2 cm) compared to the ACR TIRADS (98.0% and 89.7%, respectively) [177].

Follow-Up for Nodules that Do not Meet the Biopsy Criteria

The optimal strategy for US follow-up of nodules that do not meet the biopsy criteria has not yet been established. The committee recommends that US follow-up of these nodules should be based on the K-TIRADS category, with frequent follow-ups for nodules with a higher K-TIRADS category. In accordance with the active surveillance strategy for PTMC, we recommend US scans every 6 months for 1–2 years for K-TIRADS 5 nodules, followed by once every year, if there is no growth on US [175,178]. For K-TIRADS 3 or 4 nodules, US follow-up should be performed at 1, 3, and 5 years. If there is no change in nodule size at 5 years, US may be performed every 3–5 years for K-TIRADS 4 nodules and in 5 years for K-TIRADS 3 nodules. For K-TIRADS 2 nodules, the first US follow-up may be performed at 2–5 years depending on the nodule size, considering their very low malignancy risk (< 3%), which is similar to the malignancy risk of biopsy-proven benign nodules. For biopsy-proven benign nodules, the interval of US follow-up can be extended to more than 2 years [94,179,180]. No studies have evaluated the criteria for discontinuation of US follow-up for thyroid nodules. However, the growth rate does not reliably distinguish between benign and malignant nodules [92,93,181]. If there is no growth in nodule size in 5 years, US follow-up may be deferred and clinical follow-up may be performed for K-TIRAD 2 or 3 nodules. Frequent US or clinical follow-up may be performed for large K-TIRAD 2 or 3 nodules that demonstrate symptomatic growth. Follow-up may be delayed or discontinued for these nodules < 1 cm.

Regardless of the K-TIRADS category, there are common considerations during follow-up. For nodules that enlarged significantly during follow-up but remained below the biopsy size threshold for their K-TRIADS category, continued US follow-up is warranted. If the K-TIRADS category changes during follow-up, follow-up or biopsy should be

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performed according to the new K-TIRADS category, except for nodules with a significantly decreased size. If the nodule size significantly decreases during follow-up, US follow-up can be delayed or discontinued. For patients with compressive symptoms or neck bulge due to an increase in nodule size, US should be performed and biopsy can be considered regardless of the initial K-TIRADS category. The US follow-up strategy can be modified based on clinical judgment after considering the clinical risk factors and patient preferences.

US-Based Management of Thyroid Nodules after FNA

Management of nodules after FNA should be based on US and clinical features, as well as the FNA results. The combined use of US-based risk stratification and the Bethesda system may allow early detection of thyroid cancer and assist in making optimal management decisions after FNA (Table 6) [84,182-184].

Non-Diagnostic or Unsatisfactory Cytology

The estimated malignancy rate for nodules with non-diagnostic FNA is 5%–10% [182]. A meta-analysis reported a malignancy rate of 2.7% for all nodules with non-diagnostic FNA and 16.8% for surgically resected nodules [185]. The malignancy risk of nodules with non-diagnostic FNA increases with an increase in the K-TIRADS score [184]. Although the malignancy rate of nodules with non-diagnostic FNA is low (but not negligible), FNA should be repeated with US guidance for nodules in this category if there is no decrease in nodule size after FNA [84,182,183]. Core needle biopsy (CNB) can be performed by an experienced operator to achieve higher diagnostic adequacy for nodules with initial or repeated non-diagnostic cytological results [186-189]. Thyroid nodules with high suspicion US patterns should be followed with a repeat biopsy within 6 months of the initial FNA. Intermediate or low suspicion US patterns may be followed with a repeat biopsy within 12 months. The timing of repeat FNA should be decided based on nodule size, clinical features, patient preferences, and US features. It is not necessary to delay a repeat biopsy for 3 months [190-192].

Benign Cytology

Although the estimated malignancy rate for FNA-proven benign nodules is low (0%–3%) [182], the follow-up strategy for these nodules should be determined by US-

Table 6. Management of Thyroid Nodules Based on FNA Results and US Patterns

FNA Diagnosis	US Pattern (K-TIRADS)	Management
Nondiagnostic	High suspicion	Repeat FNA or CNB* within 6 months†
	Intermediate or low suspicion	Repeat FNA or CNB* within 12 months†
Benign	High suspicion	Repeat FNA within 12 months
	Intermediate or low suspicion	US follow-up at 24 months
AUS/FLUS	High suspicion	Repeat FNA or CNB* within 6 months†
	Intermediate or low suspicion	Repeat FNA or CNB* within 12 months†
		US surveillance‡ or molecular test
FN/SFN	All nodules	Diagnostic surgery (lobectomy)§
		US surveillance§ or molecular test
Suspicious for malignancy	High or intermediate suspicion	Surgery
	Low suspicion	Repeat FNA or surgery
		Active surveillance‖
Malignant	All nodules	Surgery
		Active surveillance‖

*CNB may be considered instead of a repeat FNA if an experienced operator is available, †The optimal timing of repeat FNA or CNB should be determined based on nodule size, presence of poor prognostic factors (such as suspected nodal metastasis or gross extrathyroidal extension), clinical factors, and US features, ‡US follow-up may be considered, depending on the nodule size, US features, cytological features, clinical features, patient preferences, and, if possible, molecular test results. If the repeat FNA cytology findings are inconclusive, frequent US follow-up or diagnostic surgery may be considered, §US follow-up, instead of immediate surgery, may be considered in selected patients, depending on the nodule size, US features, clinical features, patient preferences, and, if possible, molecular test results, ‖Active surveillance instead of immediate surgery can be considered for adults with probable or proven low-risk papillary microcarcinoma. AUS/FLUS = atypia/follicular lesions of undetermined significance, CNB = core needle biopsy, FN/SFN = follicular neoplasm/suspicious for follicular neoplasm, FNA = fine-needle aspiration, K-TIRADS = Korean Thyroid Imaging Reporting and Data System, US = ultrasonography

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based risk stratification [184,193-196]. A meta-analysis reported that the estimated malignancy rate of nodules with benign cytological results was 3.7% in surgical specimens [185], and 1%–3.2% determined by repeat FNA or long-term follow-up [184,194,196,197]. Whether false-negative FNA rates are higher [86,198-200] or similar [85,201-203] for large nodules compared to small nodules is controversial. However, the false negative rates of FNA are relatively high (3.1%–18.2%) for high suspicion thyroid nodules [184,194-196]. Therefore, we recommend that thyroid nodules with high suspicion US patterns should undergo repeat FNA within 12 months of the initial FNA, unless there is a decrease in nodule size. Thyroid nodules with intermediate or low suspicion US patterns should undergo the initial follow-up US evaluation 24 months after FNA, repeated every 2–4 years [179,204]. Repeat FNA is not routinely recommended for nodules with benign FNA results that increase in size because of the low malignancy risk of these nodules. However, it can be selectively performed based on US features, nodule size, and clinical features [181,197].

Atypia/Follicular Lesions of Undetermined Significance Cytology

The malignancy risk for thyroid nodules with atypia/follicular lesions of undetermined significance (AUS/FLUS) on cytology is estimated to be 6%–30% [182]. The reported malignancy rates for AUS/FLUS nodules are variable. A meta-analysis estimated the malignancy rate to be 15.9% [185], whereas other studies have reported a range of 26.6%–37.8% [205]. Although limited use is recommended for this diagnostic category (< 10%) [182], AUS/FLUS are diagnosed in 0.8%–27.2% of all thyroid FNA samples [185].

For the AUS/FLUS nodules, current guidelines [84,182,183] recommend a repeat FNA, which leads to a definitive diagnosis and avoids the need for diagnostic surgery [185,206]. However, a repeat FNA may be controversial because of the high rates (up to 65.4%) of repeatedly inconclusive results [207-209]. The CNB method may lead to more conclusive results for AUS/FLUS nodules compared to a repeat FNA [189]. Previous studies [187,210-212] have consistently reported lower rates of inconclusive results (categories I and III) with CNB compared to FNA for nodules initially diagnosed as AUS/FLUS (repeat FNA: 34.9%–63%; CNB: 1.0%–40.9%).

In accordance with the RSSs and TIRADS, the malignancy risk of AUS/FLUS nodules with high suspicion US features is much higher (25%–70.7%) than in those without high suspicion US features [184,213,214]. The malignancy risk of the AUS/FLUS nodules may vary according to their subcategory. Nodules with nuclear atypia have a higher malignancy risk than those with architectural or other atypia [205,213,215,216]. Management decisions should be based on the cytological subcategory and US features of the nodules [213,217-220]. We recommend that FNA or CNB should be repeated within 6 months for thyroid nodules with high suspicion US patterns. FNA or CNB should be repeated within 12 months for those with intermediate-or low-suspicion US patterns, instead of immediate surgery. If the repeat biopsy results are inconclusive, US surveillance or diagnostic surgery can be performed after considering the estimated malignancy risk based on the US pattern and cytopathologic features, nodule size, clinical features, and patient preferences. US surveillance, instead of diagnostic surgery, may be considered for small nodules with low suspicion US patterns and cytologic features of architectural atypia, if there are no clinical risk factors. Molecular testing is not routinely recommended. It can be considered in select cases to stratify the malignancy risk [221-223].

Follicular Neoplasm or Suspicious for Follicular Neoplasm Cytology

The US features of follicular adenomas and carcinomas overlap substantially. The RSSs are not accurate and have limited ability to stratify the malignancy risk of nodules diagnosed as FN or suspicious for FN (FN/SFN) [172,184,214,224]. Although large thyroid nodules may have a higher risk of follicular thyroid cancer [85,91,225], it is uncertain whether nodule size predicts malignancy risk in FN/SFN nodules [224,226,227]. FN/SFN nodules that exhibit growth may have a higher risk of malignancy [181]. However, the growth rates were similar for benign and malignant FN/SFN nodules [224].

Diagnostic surgery is generally recommended for FN/SFN nodules [84,182,183]. Molecular tests may be used to supplement the malignancy risk assessment, instead of directly proceeding to surgery [84,223]. Newer versions of commercial molecular tests show promising diagnostic accuracy for the prediction of malignancy and for determining the optimal management of FN/SFN nodules [228,229]. Molecular tests are increasingly being used and have gained widespread acceptance for determining the need for diagnostic surgery in FN/SFN nodules [84,223]. However, the added clinical value of molecular tests may be controversial for the management of indeterminate nodules

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[230,231]. US surveillance instead of immediate surgery can be considered if molecular tests suggest that the nodule is benign. In the absence of clinical, pathological, or US risk factors, US surveillance may also be considered for selected small (≤ 2 cm) nodules after consideration of clinical features and patient preferences [170,172].

Suspicious for Malignancy Cytology

Surgery is recommended for nodules with cytology suspicious for malignancy [84,182,183]. If a nodule has a low suspicion or benign US pattern, repeat FNA may be considered before surgery to exclude the possibility of false-positive cytology results in nodules without suspicious US features [232].

Malignant Cytology

Surgery is recommended for nodules with malignant cytology. Active surveillance with follow-up US should be considered as an alternative to immediate surgery for adults with low-risk PTMC without high-risk features such as LN or distant metastasis, suspected gross ETE to the trachea or RLN, worrisome tumor locations (such as attachment to the trachea or posteromedial capsule along the course of RLN), or high-grade malignancy [175,178]. Frequent US follow-up may be preferable to immediate surgery in patients with a high surgical risk due to comorbidities or a short life expectancy.

Role of CT in Thyroid Cancer Diagnosis

Thyroid CT Protocol

CT with an optimized dedicated protocol should be performed to diagnose thyroid cancer. The recommended protocol is summarized in Table 7. In patients with thyroid cancer, pre- and post-contrast CT scans are preferred. Pre-contrast CT scans are useful for the detection of calcifications and ectopic thyroid tissues and for differentiating tumor recurrence from remnant thyroid tissue after thyroidectomy [21,233]. A contrast-enhanced CT is mandatory to assess LN metastases, which are seen as areas of strong or heterogeneous enhancement and cystic changes [21,234]. Based on studies of iodine retention, contrast media is not contraindicated in patients with thyroid cancer. Recent studies have suggested that delaying radioactive iodine therapy after contrast-enhanced CT scans is not necessary [235] because the iodine clears within 4–8 weeks. Body iodine content is not essential for radioactive iodine therapy [236,237]. The CT scan range should extend from the skull base to the superior mediastinum in the anteroposterior window to evaluate upper mediastinal LNs and anatomic variations such as the aberrant right subclavian artery [21,234,238].

Table 7. Recommended CT Protocol for Patients with Thyroid Cancer*

Items	Parameters
kVp, mAs	Manufacturer's recommended settings
Collimation, mm	64 x 0.5–0.625
Section thickness/increment, mm	0.5–1/0.5–1 (no overlap)
Scan range	Skull base to AP window
Scan direction	Craniocaudal direction
IV route	Right arm preferred†
Scan delay, sec	25–40 (using fixed scan delay)
Injection rate of contrast media, mL/sec	3.0–3.5
Concentration of contrast media, mg/mL	300
Amount of contrast media, mL	75–90
Volume of saline used for flushing, mL	Approximately 30
Reconstruction parameters	
Slice thickness, mm	2–3
dFOV, mm	220–230
Matrix	512 x 512
Kernel (filter/algorithm)	Manufacturer's recommended settings (usually standard or smooth Kernel)

*This protocol is for multidetector CT scanners with 64 or more channels, †Right arm is preferred for IV access to avoid venous reflux of contrast media due to possible physiological compression of the left innominate vein. AP = aortopulmonary, dFOV = display field of view, IV = intravenous

Acquisition of enhanced scans at an accurate time point is essential to appreciate the hypervascular LN metastasis seen in most thyroid cancers. Compared to venous phase scans, early (arterial) phase scans (25–40-second delay) depict early strong enhancement of metastatic LNs [239-241], when the contrast is injected at a rate of 3.0–3.5 mL/sec (total contrast: 75–90 mL). It accurately differentiates them from benign LNs [239,240,242]. Thin reconstruction (slice thickness: 2–3 mm) is recommended for patients with thyroid cancer. Image reconstruction should include unenhanced axial, enhanced axial, and coronal reformatted images. Sagittal reconstruction can be used to evaluate nodules in the isthmus or pyramidal

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Table 8. CT-Based Risk Stratification for Cervical Lymph Node Metastasis in Patients with Thyroid Carcinomas

Category	Imaging Features
Suspicious*	Any of the three suspicious features
	Cystic change
	Calcification
	Strong (focal/diffuse) or heterogeneous enhancement
Indeterminate†	Loss of hilar fat and vessel enhancement, with no suspicious CT features
Probably benign‡	Presence of hilar fat or vessel enhancement and no suspicious CT features

*Lymph nodes with any suspicious imaging feature are included in this category, regardless of the presence of any imaging feature of probably benign or indeterminate lymph nodes, †Lymph nodes that are not included in suspicious or probably benign categories, ‡Lymph nodes with imaging features of hilar fat or vessel are considered probably benign, if there are no suspicious imaging features. US = ultrasonography

lobe, LNs located anterior to the common carotid artery or internal jugular vein, and Delphian LNs.

CT image quality in the lower neck is frequently reduced by noise and streak artifacts from the shoulder girdle and stagnated contrast media in the subclavian vein. In patients with thyroid cancer, several strategies can be used to minimize noise and artifacts, including the shoulder-down position [243-245], flushing with sufficient amounts of saline [239,246,247], scanning in a craniocaudal direction, use of automatic tube current modulation [243], and iterative reconstruction [248].

Risk Stratification of Cervical Lymph Nodes on CT Scans

Cervical LNs are classified into three categories based on their malignancy risk: suspicious, indeterminate, and probably benign (Table 8). Suspicious LNs are defined as LNs that show cystic changes, calcifications, strong (focal/

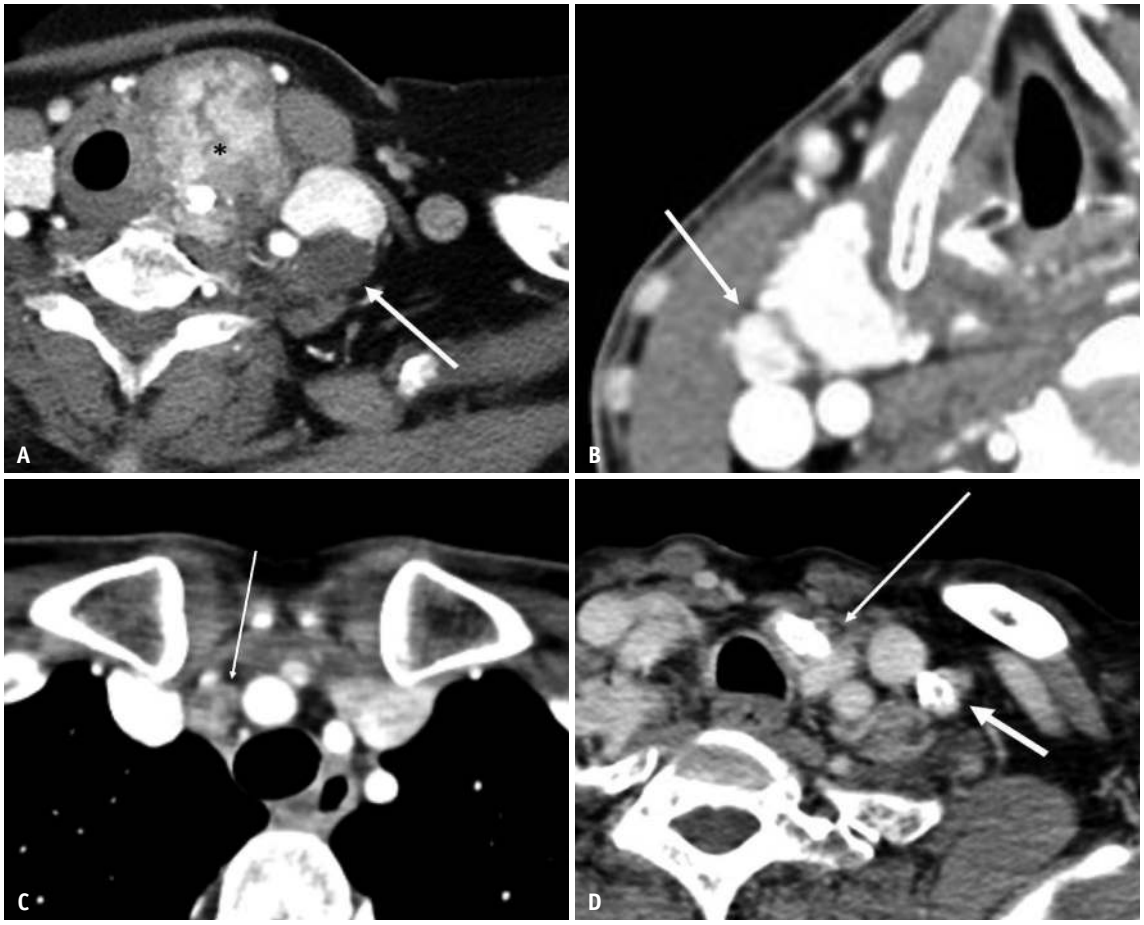

Fig. 10. Suspicious lymph nodes on CT.
A. Non-enhancing cystic lymph node (arrow). Primary cancer demonstrating heterogeneous enhancement and calcifications, seen in the left thyroid gland (asterisk). **B.** Diffuse strong enhancement of the lymph node (arrow). **C.** Heterogeneous, mild enhancement of lymph node (arrow). **D.** Calcification in an enhancing lymph node (short arrow). Primary cancer with macrocalcifications is seen in the left thyroid gland (long arrow). Diagnosis: metastatic papillary thyroid carcinomas **(A-D)**.

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diffuse), or heterogeneous enhancement (Fig. 10). The CT criteria for suspicious LNs have a high specificity (70%–90%) and PPV (70%–82%) for the diagnosis of metastasis [241,249,250]. Probably benign LNs are defined as LNs that do not have imaging features of suspicious LNs and show CT features typical of benign nodes. This includes hilar fat or vessel enhancement, regardless of their eccentricity (Supplementary Fig. 5). Indeterminate LNs are defined as LNs that do not have imaging features of suspicious or benign LNs (Supplementary Fig. 6).

Several studies have reported that the addition of CT scans to US improves the detection of LN metastasis in both the central and lateral neck compartments [241,249-253]. CT scans also identify metastasis in LNs that appear indeterminate or benign on US [254]. Additionally, CT scans can detect LN metastasis in compartments missed by US (e.g., in the mediastinum or retropharyngeal area), and may affect decisions regarding patient management, even in small thyroid cancers [241,255,256].

Preoperative Evaluation of Invasive Thyroid Cancer

Invasive cancer occurs in 13%–15% of patients with differentiated thyroid cancers [257]. For these patients, CT can assist in accurately delineating the extent of involvement of the aerodigestive tract and vessels [84,234,258]. MRI may have a similar degree of accuracy in the evaluation of invasive thyroid cancers [259-261]. However, MRI requires a relatively long time to perform, and the image quality may be degraded due to motion artifacts in the lower neck associated with respiration, swallowing, and pulsation. Therefore, MRI may be considered a second-line imaging modality. It is appropriate for patients with contraindications to the use of iodine-based contrast media or ionizing radiation and for some patients with advanced thyroid cancers.

Postoperative Evaluation of Recurrent Thyroid Cancer

CT may be useful in cases of suspected recurrent disease that are not delineated on US, or when the suspected recurrent disease involves the aerodigestive tract. CT may also be used in cases where US may not adequately visualize disease recurrence, especially in those patients with high serum Tg or Tg antibodies and negative US [21,84,234]. A recent study demonstrated the added value of CT to US for the detection of thyroid cancer recurrence [262]. Before revision surgery or image-guided intervention, target lesions should be accurately identified using both US and CT [21].

Future Perspectives

K-TIRADS is a pattern-based RSS that has the advantage of easy categorization of nodules during real-time US examination. In the revised 2021 K-TIRADS, the US lexicon, risk stratification, and imaging-based management of thyroid nodules have been updated for easy clinical use. The cutoff size for biopsy in the 2021 K-TIRADS was revised to reduce unnecessary biopsies while maintaining adequate sensitivity for the detection of malignancy according to the nodule size. Future studies should evaluate the interobserver variability of US features and classified risk categories defined by the 2021 K-TIRADS, and investigate the potential use of artificial intelligence for the risk stratification of nodules. We plan to revise the K-TIRADS and imaging-based recommendations for the management of thyroid nodules periodically. This revision will be based on new evidence and the results of international collaborative work.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0713.

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

Dong Gyu Na, Jung Hwan Baek, Ji-hoon Kim, Jeong Hyun Lee, Jung Hee Shin who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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