



A Narrative Review of the 2023 Korean Thyroid Association Management Guideline for Patients with Thyroid Nodules

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The 2023 Korean Thyroid Association (KTA) Management Guideline for Patients with Thyroid Nodules constitute an update of the 2016 KTA guideline for thyroid nodules and cancers that focuses specifically on nodules. The 2023 guideline aim to offer updated guidance based on new evidence that reflects the changes in clinical practice since the 2016 KTA guideline. To update the 2023 guideline, a comprehensive literature search was conducted from January 2022 to May 2022. The literature search included studies, reviews, and other evidence involving human subjects that were published in English in MEDLINE (PubMed), Embase, and other relevant databases. Additional significant clinical trials and research studies published up to April 2023 were also reviewed. The limitations of the current evidence are discussed, and suggestions for areas in need of further research are identified. The purpose of this review is to provide a summary of the 2023 KTA guideline for the management of thyroid nodules released in May 2023 and to give a balanced insight with comparison of recent guidelines from other societies.

Keywords: Thyroid nodule; Guideline; Diagnosis; Treatment

INTRODUCTION

Thyroid nodules are a common endocrine disorder, typically with a favorable prognosis. The diagnostic approach of ultrasonography (US) followed by fine-needle aspiration (FNA) is well-established as the gold standard [1]. The incorporation of molecular pathology tests based on high-throughput sequencing

techniques has improved the accuracy of preoperative diagnosis. Furthermore, a novel clinical strategy termed active surveillance (AS) involves postponing treatment from the time of diagnosis until disease progression.

These changes have led to a paradigm shift in the diagnosis and management of thyroid nodules, marked by the emergence of more surgical and/or non-surgical options for thyroid cancer

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and new drugs for advanced thyroid cancer cases. In response, the members of the Guideline Development Committee of the Korean Thyroid Association (KTA) agreed on the need to update the guideline and decided to develop separate guideline for thyroid nodules instead of a single guideline covering both thyroid nodules and cancers.

The 2023 guideline updated the research base for each topic covered by the 2016 guideline and added new topics, including the role of pathological and molecular marker tests in diagnosis, the noninvasive treatment of benign thyroid nodules, and special considerations for pregnant women. In this update, the major changes are (1) the definition of high-risk groups for thyroid cancer screening; (2) the application of the revised Korean Thyroid Imaging Reporting and Data System (K-TIRADS) and 2023 World Health Organization classification of thyroid neoplasms; (3) the addition of the role of core needle biopsy (CNB) and molecular marker tests; (4) the application of AS in low-risk papillary thyroid microcarcinoma (PTMC); and (5) updated indications for the non-surgical treatment of benign thyroid nodules. This review provides an overview of the 2023 KTA Management Guideline for Patients with Thyroid Nodules, with an emphasis on updates.

DEVELOPMENT PROCESS OF THE 2023 GUIDELINE

A comprehensive literature search was conducted between January 2022 and May 2022, which included studies, reviews, and other forms of evidence related to human subjects and published in English. The databases searched were MEDLINE (PubMed), Embase, and other pertinent sources. Additionally, relevant clinical trials and research studies published up to April 2023 were considered. The manuscript and its specific recommendations were crafted by integrating the best available research evidence

with the panelists' knowledge and clinical experience. This process was grounded in a systematic review, assessment of related evidence, consideration of principles of care, and reasoned inferences.

The recommendations were graded using a modified version of the American College of Physicians guideline methodology [2], which has also been adopted in previous KTA guidelines, to facilitate comparison with the previous version and to maintain consistency among the guidelines (Table 1) [3]. The customary KTA classifications of levels 1, 2, and 3 are used in Table 2 to summarize both the evidence and expert opinion and to provide final recommendations for patient assessment and therapy. Given the inherent challenges in generating evidence for certain aspects of thyroid nodule or cancer management, some level 1 recommendations are based on the judgment that there is a significant net benefit from the recommended behavior, even when the evidence is low quality or scarce [4].

The draft of the manuscript was revised after receiving comments from KTA members at a public hearing, and the revised draft was sent to the Advisory Board for additional feedback and then posted on the KTA website for 4 weeks for critical evaluation by the KTA members. Six related societies have endorsed the clinical practice guideline: the Korean Endocrine Society, the Korean Association of Endocrine Surgeons, the Korean Society of Head and Neck Surgery, the Korean Society of Thyroid Radiology, the Korean Society of Nuclear Medicine, and the Endocrine Pathology Study Group of the Korean Society of Pathologists. All proposed changes and comments were considered by the guideline task force, and the resulting changes were incorporated into the final document, which was published in the *International Journal of Thyroidology* in May 2023, after approval by the KTA Board of Directors [5]. The recommendations for the management of thyroid nodules are summarized in Table 2.

Table 1. Korean Thyroid Association Recommendation Levels for Clinical Strategies, Diagnostic Testing, or Treatment in Patient Care

Recommendation level	Definition	Meaning
1	Strong recommendation	There is sufficient objective evidence and/or general agreement of significant health benefit or harm from the recommended behavior.
2	Conditional recommendation	There is objective evidence of significant health benefits or harms from the recommended behavior, but the evidence is not clear or sufficient to make a strong recommendation.
3	Expert consensus	There is insufficient objective evidence but beneficial based on the patient's situation and expert consensus.
4	Inconclusive	There is no evidence of significant health benefits or harms from taking the recommended action, or there is much disagreement, so there is neither support for nor opposition to taking the action.

Table 2. Summary of 2023 Korean Thyroid Association Guideline Statements for Thyroid Nodules**Section 1: Thyroid cancer screening in high-risk groups**

- 1.A. Screening family members with three or more cases of differentiated thyroid cancer in the family may lead to an earlier diagnosis, but there is no evidence supporting that doing so reduces morbidity and mortality; therefore, ultrasonography (US) screening for this purpose is not recommended. Recommendation level 4
- 1.B. Family members of patients with familial thyroid cancer or hereditary tumor syndromes should receive genetic counseling and be offered screening and treatment based on their genetic mutation status. Recommendation level 2
- 1.C. US screening for thyroid cancer is not usually recommended for patients with Graves' disease, Hashimoto's thyroiditis, or hyperparathyroidism. Recommendation level 4
- 1.D. US screening should be considered for those in 1A–C with the following features: suspected thyroid nodules, asymmetric thyroid goiter, or lymph node enlargement on physical examination. Recommendation level 2

Section 2: Diagnostic evaluation of incidental or clinically detected thyroid nodules

- 2.A. Thyroid function tests, including thyroid stimulating hormone (TSH), should be performed as part of the initial work-up for thyroid nodules, and a thyroid scan should be performed if the TSH level is below the normal range. Recommendation level 1
- 2.B. Routine serum thyroglobulin measurements for all thyroid nodules are not recommended. Recommendation level 1
- 2.C. Measurement of serum calcitonin may be considered before the surgical or non-surgical treatment of thyroid nodules. Recommendation level 2
- 2.D. Incidental focal uptake lesions in the thyroid on ¹⁸F-FDG PET/CT are highly suggestive of thyroid cancer and should undergo pathological evaluation in conjunction with the US findings. In patients with diffuse uptake on ¹⁸F-FDG PET/CT with US and clinical findings consistent with chronic lymphocytic thyroiditis, no further imaging or pathological testing is recommended. Recommendation level 1
- 2.E. Thyroid US, including a cervical lymph node evaluation, is recommended in all patients with known or suspected thyroid nodules. Recommendation level 1

Section 3: The pathological diagnosis of thyroid nodules

- 3.1. Role of pathological tests and molecular markers
- 3.1.A. Fine needle aspiration (FNA) is the gold standard for the pathological diagnosis of thyroid nodules. Recommendation level 1
- 3.1.B. FNA results of thyroid nodules should be reported according to the diagnostic categories of the Bethesda system. Recommendation level 1
- 3.1.C. Core needle biopsy (CNB) results of thyroid nodules should be reported according to the diagnostic categories of the Korean Thyroid Association pathological diagnosis recommendations. Recommendation level 2
- 3.1.D. Molecular marker testing can be performed based on the pathological category to help assess malignancy risk and decide whether to perform surgical resection, considering clinical risk factors, US findings, and patient preferences. Recommendation level 3
- 3.2. Management strategies according to pathological diagnosis
- 3.2.1. Nondiagnostic
- 3.2.1.A. Nondiagnostic nodules on initial FNA should be reevaluated with a US-guided pathological examination. Recommendation level 1
- 3.2.1.B. Cystic nodules that remain nondiagnostic on a repeated pathological examination (without US features highly suggestive of malignancy) may require careful surveillance or surgical excision. Recommendation level 3
- 3.2.1.C. Diagnostic surgical resection should be considered if a repeated pathological examination is nondiagnostic, if US findings strongly suggest malignancy, if there is a 20% or greater increase in size during follow-up, or if there is a clinically suspected risk of malignancy. Recommendation level 3
- 3.2.2. Benign
- 3.2.2.A. A benign nodule on pathological examination does not require immediate further investigation or treatment. Recommendation level 1
- 3.2.3. Atypia of unknown significance (AUS)
- 3.2.3.A. For pathological category 3 (AUS) nodules, US surveillance, repeated FNA, CNB, or molecular marker testing may be performed to assess malignancy risk and guide decision-making regarding diagnostic surgery, considering clinical risk factors, US findings, patient preferences, and feasibility. Recommendation level 3
- 3.2.3.B. If repeated FNA, CNB, or molecular marker testing is not performed or is inconclusive, US surveillance or diagnostic surgery may be performed considering clinical risk factors, US findings, and patient preferences. Recommendation level 2
- 3.2.4. Follicular neoplasm

(Continued to the next page)

Table 2. Continued

- 3.2.4.A. Tumors larger than 2 cm diagnosed as follicular neoplasms should be considered for surgery, as the risk of malignancy increases with size. For tumors of 2 cm or smaller, malignancy risk still exists, and diagnostic surgery may be considered based on clinical judgment. Recommendation level 2
- 3.2.4.B. Based on clinical and US findings, US surveillance can be pursued or molecular marker testing can be performed to assess malignancy risk and surgical suitability. Clinical decisions should be based on patient preferences and feasibility. Recommendation level 3
- 3.2.5. Suspicious for malignancy
- 3.2.5.A. If the pathological diagnosis is suspicious for papillary thyroid carcinoma (PTC) suspicious for malignancy, surgical resection should be performed as if it is malignant, with consideration of clinical risk factors, US features, and patient preferences. Recommendation level 2
- 3.2.5.B. Molecular marker testing may be considered if the results could influence the decision-making process regarding whether to proceed with surgery, with consideration of clinical risk factors, US features, and patient preference. Recommendation level 3
- 3.2.6. Malignancy
- 3.2.6.A. If the pathological diagnosis is malignant, surgery is generally recommended. Recommendation level 1
- 3.2.6.B. Active surveillance (AS) may be considered in low-risk adult patients with papillary thyroid microcarcinoma (PTMC) confirmed on pathology and imaging such as US, if there are no high-risk features including high-risk histology (aggressive cellular subtype), adjacent tissue invasions (e.g., airways or nerves), and cervical lymph node or distant metastases. Recommendation level 2

Section 4: Long-term follow-up of thyroid nodules

- 4.1. Follow-up of pathologically confirmed benign thyroid nodules
- 4.1.A. High suspicion (K-TIRADS 5): Perform US within 12 months and a repeated pathological examination if there is no reduction in size. Recommendation level 1
- 4.1.B. Low or intermediate suspicion (K-TIRADS 3 or 4): Perform US within 12–24 months. If the US examination shows an increase in nodule size (greater than 2 mm in at least two dimensions with a diameter increase of 20% or greater, or a volume increase of 50% or greater) or new suspicious features, consider a pathological evaluation or continue surveillance until a further increase in size before a pathological evaluation. Recommendation level 3
- 4.1.C. Benign (K-TIRADS 2): If a pathological evaluation is performed due to an increase in nodule size or for treatment planning, and the nodule is subsequently confirmed as benign, no further surveillance US is necessary to assess the risk of malignancy. Recommendation level 2
- 4.1.D. Benign on repeated pathological examination: If a nodule is confirmed to be benign on a repeated pathological examination during follow-up and shows no malignant changes in US, further pathological examination is not necessary. Recommendation level 1
- 4.2. Follow-up of thyroid nodules that do not meet the indications for a pathological examination.
- 4.2.A. Highly suspicion (K-TIRADS 5): Repeat US every 6–12 months for the first 1–2 years, then every year thereafter if there is no increase in size. Recommendation level 2
- 4.2.B. Low-risk or intermediate suspicion (K-TIRADS 3 or 4): Consider repeating surveillance US at 1–2-years intervals or longer. For nodules measuring 1 cm or smaller with low-risk US features, surveillance US may be repeated every 2–5 years. Recommendation level 3
- 4.2.C. Benign (K-TIRADS 2): Surveillance US is not required, but may be considered after 2–5 years based on the size of the nodule and clinical assessment. Recommendation level 3

Section 5: Treatment of thyroid nodules

- 5.A. Routine thyroid hormone suppression for benign thyroid nodules is not recommended. There may be a treatment response, but the potential harm outweighs the benefit of suppressive therapy. Recommendation level 1
- 5.B. Periodic surveillance is recommended for nodules with increasing size that are nonetheless confirmed benign on cytology. Surveillance without treatment is recommended for most asymptomatic nodules with a slight increase in size. Recommendation level 2
- 5.C. There is no evidence supporting thyroid hormone suppression for benign nodules that increase in size. Recommendation level 4
- 5.D. If a thyroid nodule is diagnosed as benign on repeated pathological examinations, treatment may be considered for pressure symptoms, cosmetic concerns, or an autonomous nodule. Treatment options including surgery, radioiodine therapy, and non-surgical ablation (ethanol, radiofrequency and laser), should be chosen based on clinical characteristics, comorbidities, treatment advantages and disadvantages, patient preferences, and feasibility. Recommendation level 3
- 5.E. Nodules larger than 4 cm that continue to increase in size may be considered for surgery if there are significant compressive symptoms or clinical concerns of malignancy. Recommendation level 3
- 5.F. Benign solid thyroid nodules with normal thyroid function may be considered for surgery or non-surgical intervention if there are pressure symptoms or cosmetic concerns. Recommendation level 2

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Table 2. Continued

- 5.G. Radiofrequency or laser ablation is recommended as a non-surgical treatment for benign solid nodules. Recommendation level 2
- 5.H. For recurrent benign cystic nodules, ethanol ablation is recommended as the first-line treatment if there are pressure symptoms or cosmetic concerns. Recommendation level 1
- 5.I. For overt hyperfunctioning thyroid nodules, radioactive iodine or surgery should be considered as the first-line treatment. Recommendation level 1

Section 6: Thyroid nodules in pregnant women

- 6.1. If a thyroid nodule is found in a pregnant woman, consider FNA based on the US features as in nonpregnant women. If serum TSH is persistently low after the first trimester, defer the pathological evaluation until after delivery, when a thyroid scan can be performed to assess the function of the nodule. Recommendation level 1
- 6.2. Thyroid cancer diagnosed in the first trimester requires US surveillance, and surgery should be considered if there is significant growth (greater than 2 mm in at least two dimensions with a diameter increase of 20% or greater, or a volume increase of 50% or greater) by 24 weeks of gestation or if cervical lymph node metastases are detected. However, surgery may be performed after delivery if there is no change in size by the second trimester or if the cancer is first diagnosed in the second trimester. For advanced thyroid cancer, surgery is preferably performed during the second trimester. Recommendation level 3

FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; K-TIRADS, Korean Thyroid Imaging Reporting and Data System.

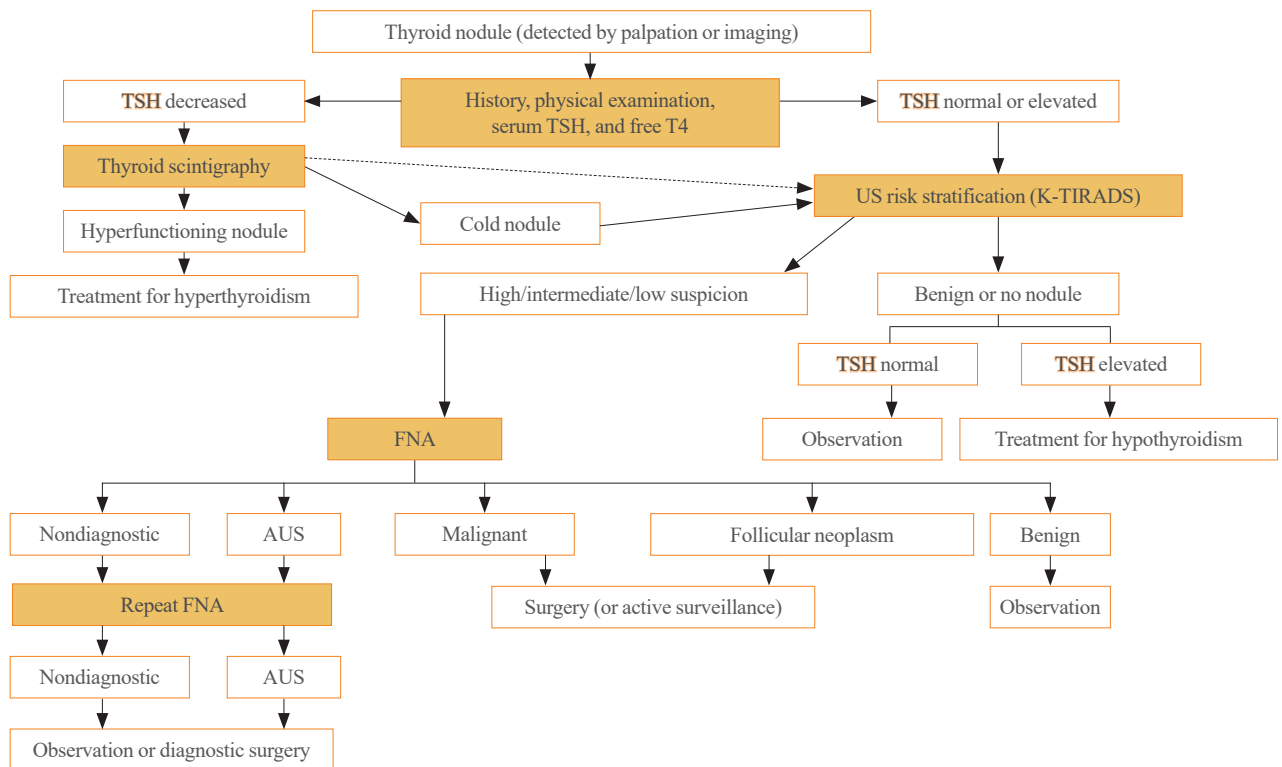


Fig. 1. Initial evaluation for the diagnosis of thyroid nodules. TSH, thyroid stimulating hormone; T4, thyroxine; US, ultrasonography; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; FNA, fine-needle aspiration; AUS, atypia of undetermined significance.

SECTION 1. DEFINITION OF HIGH-RISK GROUPS FOR THYROID CANCER SCREENING

When considering candidates for thyroid cancer screening within the context of hereditary syndromes, it is important to consid-

er factors such as the benefit of early detection. Conditions such as multiple endocrine neoplasia syndrome and hereditary medullary thyroid cancer (MTC) syndrome are examples where oncologic outcomes may be improved through screening [6,7]. While individuals with Graves' disease [8,9], Hashimoto's thyroiditis [10], and primary hyperparathyroidism [11-13] have a

relatively similar or even higher risk of thyroid cancer compared to individuals without those diseases, their prognosis may not significantly differ. Familial non-MTC, defined as three or more affected thyroid cancer patients in a family, has not demonstrated a poorer prognosis compared to a control group [14-16]. Consequently, routine thyroid cancer screening is not indicated for this particular group in the 2023 guideline.

However, specific populations, such as childhood cancer survivors, require careful consideration for thyroid cancer screening. For these individuals, screening should begin after the successful treatment of the primary cancer. It is recommended that they undergo annual or biannual physical examinations, accompanied by thyroid US every 5 years [7,17,18].

Staying up to date with the latest medical guidelines is crucial, and consulting with a multidisciplinary team of healthcare professionals—including endocrinologists, surgeons, radiologists, nuclear medicine physicians, and pathologists—will help

determine the most appropriate and evidence-based screening strategies for individuals with hereditary syndromes and related conditions.

SECTION 2. DIAGNOSTIC EVALUATION OF INCIDENTAL OR CLINICALLY DETECTED THYROID NODULES

The initial evaluation of thyroid nodules includes thyroid function test (TFT) (thyroid stimulating hormone [TSH] and free thyroxine). Routine measurements of serum thyroglobulin or calcitonin are not recommended because of their low specificity [7,19]. However, calcitonin testing is recommended in certain situations—specifically, for thyroid nodules suspicious for MTC, patients with a family history of MTC, and before surgery [7]. The algorithm for the diagnostic evaluation of thyroid nodules is presented in Fig. 1. For incidentalomas detected by

Table 3. US Patterns and Malignancy Risk of Thyroid Nodules and Biopsy Size Thresholds in the 2021 K-TIRADS^a

Category	US patterns	Suggested malignancy risk, %	Nodule size threshold for biopsy, cm ^b
High suspicion (K-TIRADS 5)	Solid hypoechoic nodule with any of the three suspicious US features ^c	>60	>1 ^d
Intermediate suspicion (K-TIRADS 4) ^e	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 ^f	10–40	>1–1.5 ^g
Low suspicion (K-TIRADS 3)	Partially cystic or iso-/hyperechoic nodule without any of the three suspicious US features	3–10	>2
Benign (K-TIRADS 2) ^h	1) Iso-/hyperechoic spongiform 2) Partially cystic nodule with intracystic echogenic foci and comet-tail artifact 3) Pure cyst	3	Not indicated ⁱ
No nodule (K-TIRADS 1)	-	-	-

Modified from Ha et al. [1].

US, ultrasonography; K-TIRADS, Korean Thyroid Imaging Reporting and Data System.

^aBiopsy should be performed regardless of the size of the most suspicious nodule in cases with poor prognostic 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; ^bFine-needle aspiration (FNA) is the primary pathology test and core needle biopsy can be performed as an adjunctive pathology test to FNA; it should be performed by a trained operator [11,47]; ^cSuspicious US features of thyroid nodule: punctate echogenic foci, nonparallel orientation, and irregular margins; ^dBiopsy is recommended for small (>0.5 and ≤1 cm) high suspicion (K-TIRADS 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 and ≤1 cm) K-TIRADS 5 nodules without high-risk features to decide the management plan in adults. In children, biopsy should be considered for small K-TIRADS 5 nodules (>0.5 and ≤1 cm) to decide the management plan considering the clinical context; ^eExtensive parenchymal punctate echogenic foci (microcalcifications) without discrete nodules (suspicious for diffuse sclerosing variant of papillary thyroid carcinoma) and diffusely infiltrative lesions (suspicious for infiltrative malignancy, such as metastasis or lymphoma) are considered to be intermediate suspicion suspicion (K-TIRADS 4) nodules; ^fEntirely calcified nodules with complete posterior acoustic shadowing, with no soft tissue component identified due to dense shadowing on US (isolated macrocalcification); ^gCutoff size for biopsy should be determined within the range of 1 and 1.5 cm, based on the US features, nodule location, clinical risk factors, and patient factors (age, comorbidities, and preferences); ^hRegardless of coexisting suspicious US features (punctate echogenic foci, nonparallel orientation, or irregular margin); ⁱAlthough 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.

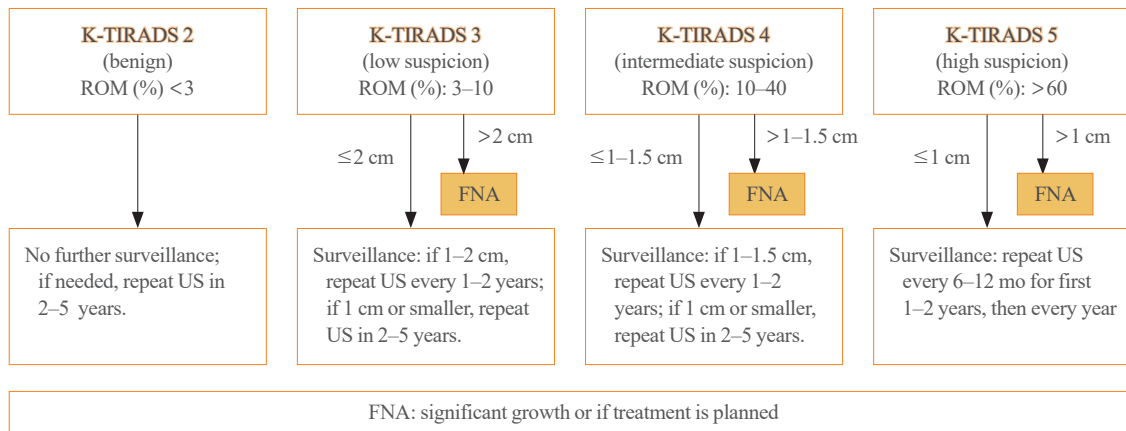


Fig. 2. Diagnostic work-up algorithm based on ultrasonography (US) features (Korean Thyroid Imaging Reporting and Data System [K-TIRADS]). A significant growth is defined as a diameter increase of 20% or more that is greater than 2 mm in at least two dimensions, or a volume increase of 50% or more. ROM, risk of malignancy; FNA, fine-needle aspiration.

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography, a pathological evaluation should be considered, guided by a US-based risk stratification [20].

Thyroid US is a noninvasive imaging test that is both safe and highly sensitive and accurate. Some groups have proposed US-based risk stratification, and the KTA has adopted the K-TIRADS. The 2021 K-TIRADS has been incorporated into the 2023 guideline [1]. K-TIRADS classifies US findings into five categories (high, intermediate, low suspicion, benign, and no nodule) (Table 3). Compared to the 2016 guideline, the 2023 guideline suggest a larger cut-off size for recommending a pathological diagnosis of thyroid nodules and extend the intervals between surveillance to minimize unnecessary procedures or operations (Fig. 2).

SECTION 3. THE PATHOLOGICAL DIAGNOSIS OF THYROID NODULES

The management of thyroid nodules should be based on US findings and a pathologic diagnosis. The combined use of US-based risk stratification and the Bethesda system after FNA may allow the early detection of thyroid cancer and assist in making optimal management decisions (Table 4) [1].

The 2023 guideline has adopted the recently updated third edition of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [5]. The third TBSRTC, which was released in 2023, has the goal of enhancing diagnostic clarity by discontinuing the use of several terms. In the previous edition, diagnostic categories I, III, and IV had interchangeable terms, which sometimes caused confusion [21]. The 3rd TBSRTC has

Table 4. The 2023 Bethesda System for Reporting Thyroid Cytopathology with Implied ROM

Diagnostic category	ROM in adults, % (range)	ROM in children, % (range)	Estimated final ROM if excluding NIFTP
I. Nondiagnostic	13 (5–20)	14 (0–33)	12
II. Benign	4 (2–7)	6 (0–27)	2
III. Atypia of undetermined significance	22 (13–30)	28 (11–54)	16
IV. Follicular neoplasm	30 (23–34)	50 (28–100)	23
V. Suspicious for malignancy	74 (67–83)	81 (40–100)	65
VI. Malignant	97 (97–100)	98 (86–100)	94

Modified from Ali et al. [21], with permission from Mary Ann Liebert, Inc.

ROM, risk of malignancy; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

streamlined the terminology by adopting a single, distinct name for each category to eliminate ambiguity. Category I is now called “nondiagnostic,” emphasizing the lack of diagnostic information due to inadequacy in the specimen’s cellular or colloid content. Category III is now solely referred to as “atypia of undetermined significance (AUS),” providing a clearer definition of the category’s nature. Similarly, category IV now exclusively uses “follicular neoplasm” to clarify the diagnostic category. An important development in the 3rd TBSRTC is the introduction of a two-level classification system within AUS: “nuclear” (previously “cytologic”) and “other.” This distinction is critical because AUS cases with nuclear atypia have a signifi-

Table 5. Diagnostic Frequency and Implied ROM according to the Diagnostic Category of Thyroid CNB

CNB diagnostic category	Diagnostic frequency, %	ROM based on final diagnosis from clinical and/or surgical follow-up, %	Change in ROM due to NIFTP
I. Nondiagnostic or unsatisfactory	2 (2–3)	33 (18–50)	No significant change
II. Benign	46 (40–52)	4 (2–6)	No significant change
III. Indeterminate	10 (7–14)	39 (32–45)	24% decrease (24–34)
IV. Follicular neoplasm	7 (5–9)	52 (46–57)	20% decrease (37–45)
V. Suspicious for malignancy	2 (2–3)	98 (96–100)	No significant change
VI. Malignant	28 (23–34)	100	No significant change

Modified from Jung [24].

ROM, risk of malignancy; CNB, core needle biopsy; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

cantly higher risk of malignancy than those with other patterns, such as architectural or oncocytic atypia. In addition, the TB-SRTC has been effectively adopted for use in pediatric thyroid cytopathology. Reflecting recent research, the risk of malignancy values for the six diagnostic categories have been specifically calculated for pediatric cases (Table 4).

FNA is the main procedure used to determine whether a nodule requires excision by categorizing nodules according to their risk of malignancy, with minimal complications [22]. However, 2% to 3% of nodules yield nondiagnostic results (Bethesda I), and 7% to 14% are classified as indeterminate nodules (Bethesda III) [21]. In such cases, the necessity of a 3-month waiting period is questionable. A shorter waiting period might be justified, particularly when clinical or imaging findings are suggestive of malignancy.

In nodules with nondiagnostic FNA results, repeating the FNA leads to nondiagnostic outcomes in 28.1% to 40.0% of cases. In contrast, CNB results in nondiagnostic findings in only 1.1% to 3.8% of cases. This suggests that CNB may be more effective in reducing the rate of nondiagnostic results compared to FNA. The pathologic classification of CNB, along with its advantages and potential risks, was introduced in the 2023 guideline. The pathologic diagnosis from CNB is categorized into six groups, similarly to the classification system used for FNA (Table 5). CNB is particularly valuable as it may yield more conclusive diagnostic outcomes for AUS nodules than subsequent FNA [23,24].

CNB is recommended as a second-line procedure only if FNA yields nondiagnostic results after at least one attempt, according to the European Thyroid Association (ETA), or two attempts, as per the French Society of Endocrinology (SFE). This cautious approach is due to potential complications such as bleeding from CNB and the lack of established diagnostic pathology cri-

teria in various countries. However, the risk of bleeding from CNB is only 2.5% to 4.9% [25,26]. Additionally, CNB offers the benefit of facilitating histological evaluation for a preoperative diagnosis using immunohistochemical (IHC) markers. IHC staining proves particularly useful in cases where poorly differentiated, anaplastic, or medullary thyroid carcinoma, differentiated high-grade thyroid carcinoma, or lymphoma are suspected. In Korea, where the application of molecular testing is limited by high costs, CNB has been included in the 2023 guideline. It is valued for its ability to provide critical information that aids in distinguishing malignant from benign thyroid nodules.

The role of molecular testing is similar to that described in the previous 2016 guideline [3]. The high specificity of *BRAF* mutation for papillary thyroid carcinoma (PTC) has been updated in detail based on data from Asia, where the *BRAF* mutation is prevalent. The prognostic significance of molecular markers is substantial when a *TERT* promoter mutation co-occurs with other driver mutations (*RAS*, *BRAF*, etc.). A next-generation sequencing multi-gene panel is newly recommended in the 2023 guideline as an option with higher diagnostic accuracy and different malignancy risks depending on the region and population. Therefore, the 2023 guideline advised that molecular marker testing should be considered based on clinical risk factors, the risk of malignancy based on cytology and US findings, the feasibility of the procedures, and patient preference.

SECTION 4. LONG-TERM FOLLOW-UP OF THYROID NODULES

Follow-up surveillance is necessary even if a nodule is determined to be benign, because pathology tests for nodules have a false-negative rate of about 5%. Thyroid US should be performed to determine clinically meaningful size changes. Signifi-

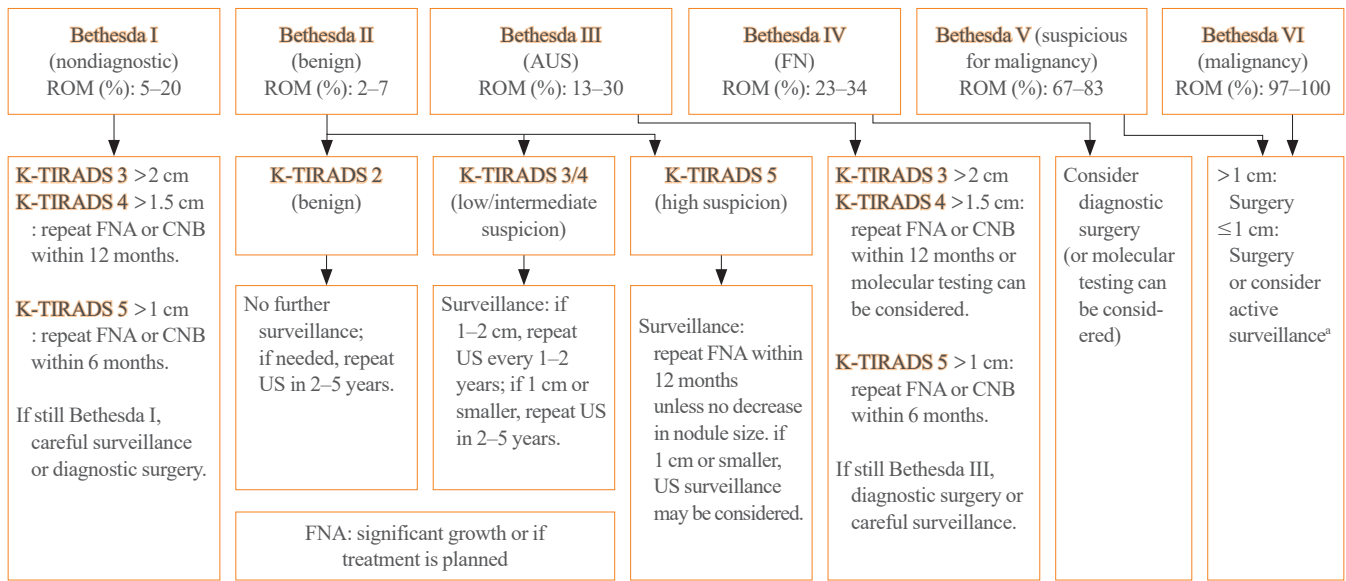


Fig. 3. Follow-up algorithm based on pathological and radiologic assessment. Reproduced from Ha et al. [1]. ROM, risk of malignancy; AUS, atypia of undetermined significance; FN, follicular neoplasm; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; FNA, fine-needle aspiration; CNB, core needle biopsy; US, ultrasonography. ^aActive surveillance instead of immediate surgery can be considered for adults with probable or proven low-risk papillary microcarcinoma.

cant nodule growth is defined as a diameter increase of 20% or more that is greater than 2 mm in at least two dimensions, or a volume increase of 50% or more.

The 2023 guideline described the follow-up strategies for two groups of thyroid nodules: pathologically confirmed benign nodules and those for which FNA is not indicated (Fig. 3). For biopsy-proven benign nodules, those identified as high suspicion on US should be followed with US surveillance within 12 months, and repeated FNA should be performed if they do not shrink. In the 2022 French consensus, US-suspicious thyroid nodules (European Thyroid Imaging Reporting and Data System [EU-TIRADS] 5) with a benign FNA result (Bethesda II) should be monitored every 1–2 years for 5 years after detection, and then monitoring should be discontinued if the nodules are stable [7]. The ETA recommends repeating FNA for US-suspicious thyroid nodules with benign FNA results if the nodule size is > 10 mm [19].

Regarding low to intermediate suspicion nodules on US, the 2023 KTA guideline recommend surveillance after 12 to 24 months and repeated FNA if significant nodule growth is observed [5]. The SFE recommends conducting surveillance after 1 to 2 years and repeating FNA only if the nodule characteristics warrant it [7]. The ETA recommends re-evaluating nodules (> 20 mm for EU-TIRADS 3 or > 15 mm for EU-TIRADS 4) in 3 to 5 years [19].

For nodules that are not recommended for biopsy, the surveil-

lance intervals have been extended compared to the 2016 guideline. The follow-up period for high suspicion nodules has increased from 6–12 to 12 months, and for low suspicion nodules, the recommendation has shifted from 1–2 years to no further surveillance. The ETA has based these surveillance intervals on the EU-TIRADS classification and the size of the nodules. Specifically, for EU-TIRADS 2–3 nodules that are less than 1 cm, no further evaluation is advised, whereas nodules larger than 1 cm should be reevaluated. For EU-TIRADS 4 nodules, the ETA suggests reevaluation after 1 year, and for EU-TIRADS 5 nodules, a follow-up is recommended within 6 to 12 months.

The 2023 guideline now included AS as an alternative strategy for low-risk PTMC. If the pathological diagnosis is malignant, surgical treatment is usually indicated. However, AS may be considered in the following cases.

- (1) Very low-risk tumors (e.g., PTMC that is clinically free of metastases and local invasion and has no cytologic evidence of aggressive disease).
- (2) Patients at high-risk for surgery due to other comorbidities.
- (3) Patients expected to have a short life expectancy (e.g., those with severe cardiovascular disease, other malignancies, and advanced age).
- (4) Patients with concomitant medical or surgical comorbidities that need to be treated prior to thyroid surgery.

SECTION 5. TREATMENT OF THYROID NODULES

In general, benign thyroid nodules do not require treatment. However, treatment may be considered if there are pressure symptoms, cosmetic concerns, or if the nodule exhibits autonomous functioning. When pressure symptoms or cosmetic concerns are present, imaging studies should be conducted to confirm that these symptoms are associated with a thyroid nodule, thereby distinguishing them from nonspecific symptoms.

Benign thyroid nodules eligible for non-surgical treatment include: (1) those with two or more benign FNA or CNB results; (2) nodules with low suspicion (K-TIRADS 2) and autonomously functioning thyroid nodules that are expected to yield a benign FNA result; and (3) pure cysts classified as nondiagnostic by FNA. The 2022 SFE Consensus further recommends performing two FNAs for nodules classified as EU-TIRADS 3 and 4, and a single FNA for EU-TIRADS 2 nodules. However, the ETA does not specify non-surgical treatment as an indication.

The treatment options for benign thyroid nodules include non-surgical ablation (ethanol, radiofrequency, laser ablation), radioactive iodine treatment, and surgery. The choice of treatment is determined by clinical characteristics, comorbidities, the advantages and disadvantages of each treatment modality, patient preference, and feasibility. Ethanol injection is typically the first-line treatment for cystic nodules that recur following aspiration, while thermal ablation, using either radiofrequency or laser, is preferred for solid nodules.

CNB is recommended as a mandatory pathological test before non-surgical ablation, because CNB has a high diagnostic sensitivity for follicular neoplasms. Patients with two FNA results or a single CNB result indicating follicular neoplasm or malignancy, as well as those with high suspicion nodules (K-TIRADS 5) based on US are not candidates for non-surgical treatment. If a nodule increases in size or becomes symptomatic at follow-up after non-surgical treatment, a repeated pathological evaluation of the nodule is warranted.

SECTION 6. THYROID NODULES IN PREGNANT WOMEN

The size of the thyroid gland and nodules may increase during pregnancy due to the thyrotrophic effects of human chorionic gonadotropin and TSH stimulation, which occurs as a result of iodine store depletion, particularly in regions with low iodine intake [27,28]. However, pregnancy does not affect maternal or

neonatal outcomes or cancer-specific survival [27]. Therefore, the approach to evaluating thyroid nodules in pregnant women is the same as in nonpregnant women. The clinical importance of thyroid nodules in pregnancy is primarily associated with two scenarios: toxic adenoma that causes hyperthyroidism, and thyroid cancer that carries a high-risk of recurrence and mortality [29].

Evaluation of thyroid nodules during pregnancy involves TFT and US imaging. If the serum TSH level remains low without an associated rise in anti-TSH receptor antibodies beyond the first trimester, a functional thyroid nodule may be suspected. In such cases, a definitive pathological diagnosis can be postponed until after delivery.

Based on the US findings (K-TIRADS), FNA could be performed starting in the second trimester, depending on the patient's preference. However, there was no difference in recurrence and survival rates of thyroid cancer when surgery was performed during pregnancy compared to after delivery [30]. Another retrospective study indicated that delaying treatment for up to 1 year after a thyroid cancer diagnosis did not negatively impact patient outcomes [31]. In a Korean study, 19 pregnant women diagnosed with PTC just before or during pregnancy were monitored without surgery; the mean tumor size at diagnosis was 0.91 cm (interquartile range, 0.61 to 1.11), and the mean tumor size at 9.5 months post-diagnosis was 0.98 cm (interquartile range, 0.72 to 1.12). The change in tumor size by trimester was not significant, and there were no occurrences of new thyroid cancers or lymph node metastases during the follow-up period [32]. Therefore, the 2023 guideline suggests that surgery may be deferred until after delivery if there is no change in size by the second trimester or if the thyroid cancer is first diagnosed in the second trimester.

CONCLUSIONS

Although thyroid nodules have a high prevalence, most are benign and have favorable outcomes. Nevertheless, the approach to diagnosing and managing these nodules can be significantly affected by socioeconomic factors, including healthcare costs. The 2023 guideline synthesizes expert consensus to ensure that individuals at high-risk are appropriately screened and that those requiring diagnosis receive timely and appropriate treatment. It also offers comprehensive guidance on the diagnosis and classification of thyroid nodules and will be updated to include specific action plans covering the continuum from diagnosis to follow-up, based on a review of the evidence. Further-

more, we anticipate that well-designed prospective studies will be conducted to address several key questions: (1) which patients should undergo screening for thyroid cancer; (2) the appropriate tests and intervals for monitoring non-cancerous nodules that are growing or symptomatic; (3) the use of molecular markers or IHC staining following core biopsy for nodules with indeterminate cytology; (4) the most cost-effective treatment strategies for patients with unique considerations (such as those in high-risk groups, pregnant women, and children); and (5) the development of shared decision-making processes that incorporate patient preferences.

CONFLICTS OF INTEREST

Young Joo Park is an editor-in-chief and Eun Kyung Lee is an associate editor of the journal. But they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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