

Review Article

Ten Key Questions on the 2023 Bethesda “AUS” Category: Practical Guidance for Surgeons, Endocrinologists, and Pathologists

Dez Questões-Chave sobre a Categoria “AUS” do Bethesda 2023: Orientações Práticas para Cirurgiões, Endocrinologistas e Patologistas

Sule Canberk^{1*}, Mariana Simplício¹, Massimo Bongiovanni², Elisabete Rodrigues³, João Capela⁴

1. Department of Pathology, Faculty of Medicine, RISE-Health, University of Porto, Porto, Portugal
2. Department of Pathology and Cytology, UNILABS, Lausanne, Switzerland
3. Department of Endocrinologia, H. S. João, Porto, Portugal
4. Endocrine and Cervical Surgery Service H. S. João, Porto, Portugal

Corresponding Author/Autor Correspondente:

Sule Canberk [sulecanberk@med.up.pt]

Faculdade de Medicina da Universidade do Porto/Faculty of Medicine of the University of Porto
Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

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ABSTRACT

The 2023 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) redefines *Atypia of Undetermined Significance* (AUS) by introducing subclassification into AUS with nuclear atypia and AUS-other. This change reflects growing evidence that the risk of malignancy is subtype-dependent. For endocrine surgeons, this means that cytology can no longer be interpreted in isolation: AUS subtypes must be integrated with ultrasound patterns and, when appropriate, molecular data to guide individualized management.

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This review distils the 2023 TBSRTC update, the 2023 ETA guidelines, the 2025 ATA Guidelines, and recent multicenter studies into a practical framework that aims to avoid both overtreatment and missed malignancy in AUS cases.

Keywords: Biopsy; Fine-Needle; Endocrine Surgical Procedures; Thyroid Neoplasms/pathology; Thyroid Neoplasms/surgery; Thyroid Nodule/pathology

RESUMO

O Sistema de Bethesda de 2023 para Comunicação de Citopatologia da Tiroide (TBSRTC) redefine a Atipia de Significado Indeterminado (AUS) através da introdução de subclassificação em AUS com atipia nuclear e AUS-outro. Esta alteração reflete evidência crescente de que o risco de malignidade é dependente do subtipo. Para os cirurgiões endócrinos, isto significa que a citologia já não pode ser interpretada isoladamente: os subtipos de AUS devem ser integrados com os padrões ecográficos e, quando apropriado, com dados moleculares para orientar a gestão individualizada. Esta revisão sintetiza a atualização do TBSRTC de 2023, as diretrizes da ETA de 2023, as Diretrizes da ATA de 2025 e estudos multicêntricos recentes num enquadramento prático que visa evitar tanto o sobretratamento como a malignidade não diagnosticada nos casos de AUS.

Palavras-chave: Biopsia por Agulha Fina; Neoplasias da Tiroide/cirurgia; Neoplasias da Tiroide/patologia; Nódulo da Tiroide/patologia

INTRODUCTION

For more than a decade, AUS functioned as a "catch-all" cytology category, applied when follicular cells showed atypia insufficient for a definitive diagnosis of follicular neoplasm, suspicious for malignancy, or malignant, yet exceeding what would be confidently attributed to benign change. This ambiguity posed persistent challenges for surgeons, since AUS neither excluded malignancy nor provided clear next steps regarding surveillance, repeat FNA, molecular testing, or surgery.¹

The 2023 TBSRTC¹ represents a paradigm shift by subdividing AUS into biologically and clinically distinct subgroups: AUS with nuclear atypia and AUS-other (AUS-other includes architectural, oncocytic, inflammatory, and not otherwise specified patterns. This subtype-based approach improves risk stratification, clarifies expected malignancy rates, and directly informs surgical planning.^{1,2}

For surgeons, AUS is no longer a black box. The updated framework transforms an indeterminate label into actionable information: when paired with ultrasound and, if needed, molecular testing, it can guide whether to repeat FNA, monitor, or proceed to lobectomy or thyroidectomy. The goal of this guide is to translate TBSRTC 2023¹ from cytologic terminology into practical, evidence-based decision-making for endocrine surgical practice.^{1,3}

Q1. WHAT EXACTLY CHANGED ABOUT AUS IN THE 2023 TBSRTC?

First edition of TBSRTC advised that AUS should be used sparingly, ideally in no more than 7% of thyroid FNAs.⁴ Because this target proved difficult to achieve, the 2nd edition⁵ raised the acceptable threshold to 10%, a figure that remains in the 2023 update.¹ This limit is not rigid but emphasizes that AUS should reflect genuine diagnostic uncertainty, not serve as a default for borderline cases.

The 2023 TBSRTC¹ introduces a major structural revision: AUS is now divided into two overarching patterns *AUS-with nuclear atypia* and *AUS-other*. The former applies when nuclear changes (enlargement, grooves, irregular contours, chromatin pallor) raise concern for papillary thyroid carcinoma but are insufficient for a definitive diagnosis. The latter encompasses non-nuclear atypias, including architectural atypia, oncocytic (Hurtle) cell change without nuclear features, inflammatory/reactive atypia, and cases not otherwise specified (NOS) (Table 1).

This reorganization replaces the older "FLUS" terminology and narrows the category into biologically meaningful subgroups. The intent is to improve interobserver agreement, align AUS subtypes with differing risks of malignancy, and guide individualized management. Although not formally mandatory, the 2023 TBSRTC edition strongly encourages reporting the AUS subtype to optimize subsequent decisions regarding repeat FNA, molecular testing, or surgery.^{1,6-9}



Table 1 – AUS Subtypes (Bethesda III, 2023): Morphology, Risk Of Malignancy (ROM), and Suggested Clinical Action

AUS Subtype	Cytologic Features	Estimated ROM	Suggested Action
AUS – Nuclear atypia ^{7,10,11}	Focal/partial nuclear enlargement, grooves, chromatin pallor; insufficient for Bethesda V	36%–48%	Repeat FNA, molecular testing, or surgery depending on imaging and clinical context
AUS – Other (Architectural) ^{7,10,11}	Microfollicular/trabecular pattern without nuclear features	10%–20%	Repeat FNA; observe if imaging low risk
AUS – Other (Oncocytic) ^{7,15–17}	Predominantly oncocytic (Hürthle) cells without papillary-type nuclei	5.6% (without nuclear atypia); ~48% (with nuclear atypia)	Repeat FNA or surveillance if no nuclear features; escalate if nuclear atypia present
AUS – Other (NOS) ¹	Indeterminate atypia not fitting nuclear, architectural, or oncocytic patterns	~10%–20% (variable)	Consider repeat FNA or second opinion

Q2. WHY IS "AUS" NOT THE SAME AS "NON-DIAGNOSTIC"?

Despite occasional confusion among clinicians, AUS and non-diagnostic (ND) represent entirely distinct TBSRTC categories with different definitions, cytologic thresholds, and clinical implications¹ (Fig. 1).

- AUS is used only when a sample contains low cellularity, even non-diagnostic samples, but the observed atypical

features do not clearly meet criteria for benign, suspicious, or malignant categories. It implies that true cytologic atypia is present, but it is qualitatively or quantitatively insufficient for definitive classification.

- In contrast, ND applies to inadequate samples, typically due to scant cellularity, obscuring artifacts (e.g., blood or air-drying), or poor follicular content. ND does not presume the presence of atypia; it reflects technical or sampling failure.

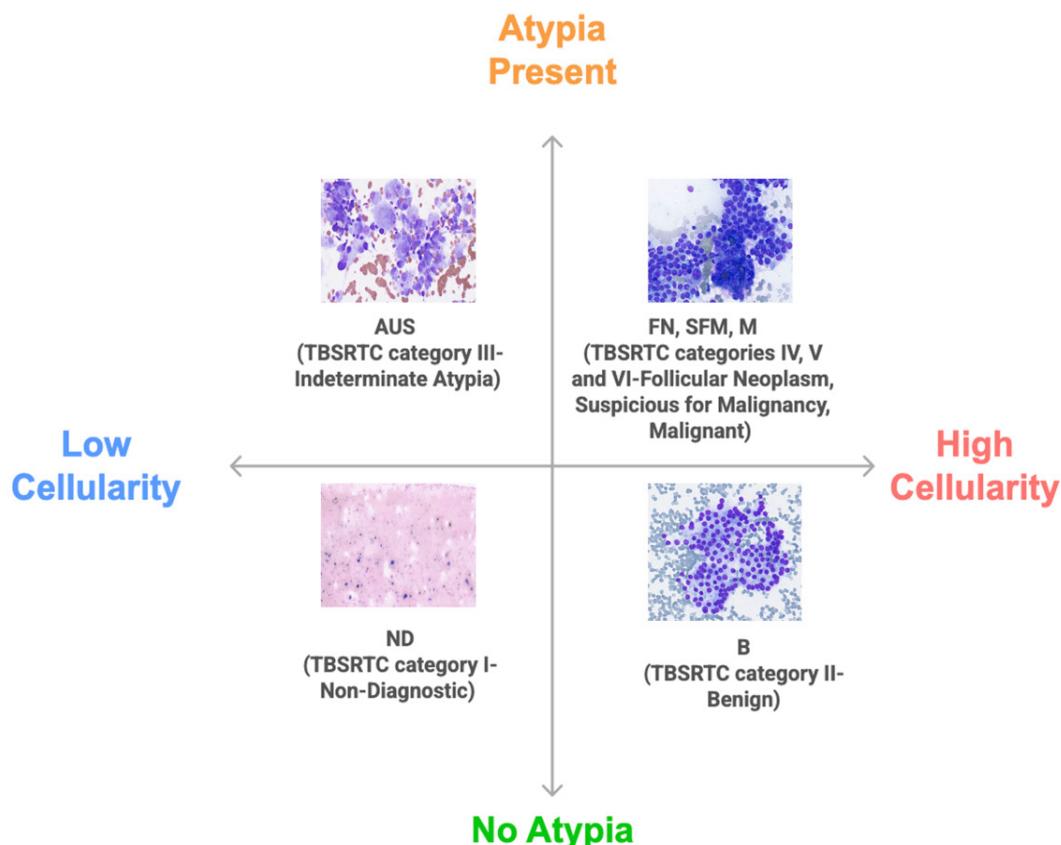


Figure 1 – Thyroid FNA Diagnostic Categories by Atypia and Specimen Adequacy (TBSRTC, 3rd Edition, 2023).

This distinction carries direct consequences for clinical management. A non-diagnostic result typically leads to repeat FNA, often within a few months, without further risk stratification. An AUS diagnosis, however, triggers a more layered pathway involving AUS subtyping (nuclear versus other), ultrasound stratification, and potentially molecular testing.^{1,3}

The 2023 TBSRTC further clarifies that inadequate samples with clearly atypical cells should not be reported as ND. If scant but morphologically evaluable atypical groups are present – even if the material does not meet adequacy criteria – AUS may still be justified, provided nuclear or architectural details are interpretable.¹

Misinterpreting AUS as ND can lead to inappropriate de-escalation, with false reassurance and delayed risk-based evaluation. For surgeons, the distinction is not semantic: AUS implies atypia and should prompt thoughtful evaluation of risk, particularly when nuclear features or high-risk ultrasound findings coexist.^{1,3,10}

Q3. WHAT SHOULD I DO IF THE REPORT JUST SAYS "AUS" WITHOUT SUBTYPE?

A cytology report stating only "AUS" without indicating a morphologic subtype does not meet the reporting standards outlined in the 2023 TBSRTC. The updated edition clearly states that all AUS cases recommended to be qualified by specific cytologic features, most commonly as *AUS-with nuclear atypia* or *AUS-other*, based on the dominant atypia identified.¹ This structural revision reflects a growing consensus that the ROM varies significantly depending on the type of atypia present, and that this variation must be explicitly reported to support appropriate clinical decision-making.

Most studies consistently show that nuclear atypia within the AUS category conveys a higher malignancy risk than other atypical patterns. In the pre-2023 TBSRTC literature, Gan *et al* (in 2017) reported a ROM of 36.8% for AUS with nuclear atypia versus 14.7% for AUS with architectural atypia.¹¹ Glass *et al* (in 2021), in a reappraisal of 510 AUS cases, found ROMs of 44.1% for nuclear atypia, 26.3% for combined nuclear and architectural atypia, 13.4% for architectural atypia, and 13.8% for oncocytic AUS.⁸ These studies used the older second edition of TBSRTC terminology, but their findings support the 2023 revision.

In the post- 2023 TBSRTC era, where AUS is formally subclassified as either *AUS-with nuclear atypia* or *AUS-Other*,

multicenter series continue to show the same pattern. Bagis *et al* (in 2024) demonstrated malignancy rates of 48.2% for AUS with nuclear atypia versus 13.9% for AUS-Other.⁷ Słowińska-Klencka *et al* (2025) reported a twofold higher ROM for nuclear atypia (10%-29%) compared with other subtypes (2%-12%), even when borderline tumors and ultrasound categories were considered.¹⁰ Saharti & Samargandy (2024) further confirmed this, with a ROM of 71% for nuclear atypia versus 12.5% for AUS-Other.¹²

Taken together, these studies-before and after the 2023 TBSRTC update, consistently demonstrate that AUS-with nuclear atypia carries the highest risk, while architectural, oncocytic, and NOS patterns, now grouped under AUS-Other, are significantly lower risk.

By contrast, Guerreiro *et al* (2023) reported a different distribution. In their series of 79 AUS cases with surgical follow-up, only 15% were classified as AUS- with nuclear atypia, while the majority (85%) were AUS-other, most with architectural atypia.⁶ Unexpectedly, architectural atypia carried a ROM of 48%, nearly equal to the 50% observed for AUS-with nuclear atypia. This divergence likely reflects the small size of the AUS-with nuclear atypia subgroup, selection bias from a surgically enriched cohort, and the predominance of follicular-subtype papillary thyroid carcinoma among architectural cases.

The clinical relevance of this classification is clear. The 2025 ATA Guidelines³ recommend that AUS reports specify the cytologic subtype (nuclear versus other) and that this information be integrated into management algorithms. Risk stratification is based on the subtype in combination with sonographic scoring systems (e.g., EU-TIRADS, ACR-TIRADS)^{13,14} and, when appropriate, molecular testing, to guide whether repeat aspiration, surveillance, lobectomy, or total thyroidectomy is most appropriate. A report that simply states "AUS" without qualification impairs this workflow and is considered incomplete under current standards.

The recommended response to an unqualified AUS report is pragmatic: request clarification from the reporting cytopathologist or pursue a second opinion/slide re-review, particularly when treatment decisions are pending. This step ensures alignment with the 2023 TBSRTC and ATA 2025 guidance and supports individualized, evidence-based patient management.

In modern practice, an AUS report without subtype is incomplete; accurate management depends on distinguishing



AUS-with nuclear atypia from AUS-other and integrating this with imaging and, when appropriate, molecular data.

Q4. WHAT'S THE CLINICAL MEANING OF "ONCOCYTIC AUS"? SHOULD I WORRY?

In the 2023 Bethesda System,¹ aspirates composed predominantly of oncocytic (Hürthle) cells fall under AUS-Other, unless there are concurrent nuclear features suggestive of papillary thyroid carcinoma. Purely oncocytic aspirates are a common source of diagnostic difficulty because oncocytic change occurs not only in oncocytic neoplasms but also in Hashimoto thyroiditis, multinodular goiter, and reactive settings. For this reason, the 2023 TBSRTC places these cases under AUS-Other to emphasize their generally lower risk of malignancy. However, if nuclear atypia is also present (nuclear enlargement, chromatin clearing, grooves, irregular contours), the case is no longer "oncocytic AUS" but should instead be classified as AUS with nuclear atypia, since the malignancy risk profile then aligns with papillary carcinoma-type changes rather than oncocytic cytology alone.

In the large surgical cohort of Bagis *et al*,⁷ oncocytic AUS without nuclear atypia showed a ROM of only 5.6%, the lowest of all AUS subtypes, while cases with concomitant nuclear atypia had a ROM of 48.2%, essentially the same as AUS-with nuclear atypia. Other series, such as Zhao *et al*¹⁵ and Kroll-Wheeler *et al*,¹⁶ confirm the variability of Oncocytic cell-predominant AUS, with ROM estimates ranging from 10% to 25% depending on case mix and surgical selection. Beyond numerical risk, Lametti *et al*¹⁷ emphasized the morphologic overlap between oncocytic AUS and oncocytic follicular neoplasms, which may lack the classic papillary-type nuclei but still behave as follicular-patterned carcinomas, underscoring why oncocytic AUS must be interpreted cautiously and in the clinical context.

The 2025 ATA Guidelines³ adopt the 2023 TBSRTC framework.¹ They recommend that AUS be subtyped and managed in a risk-adapted fashion, integrating cytologic pattern, ultrasound features (EU-TIRADS or ACR-TIRADS), molecular results, and clinical context. For oncocytic AUS without nuclear atypia, particularly in nodules with low-suspicion ultrasound findings, repeat FNA or surveillance is often appropriate. If nuclear atypia is present or the ultrasound pattern is high-risk, molecular testing or diagnostic lobectomy should be considered. ATA 2025³ also notes that molecular classifiers are less informative in oncocytic lesions, as their mitochondrial-rich transcriptome and distinctive genomic profile frequently yield indeterminate or "suspicious" results;

these should never override the cytologic and sonographic context.

For surgeons, the practical meaning is straightforward: oncocytic AUS alone is low risk and belongs under AUS-Other, but the addition of nuclear atypia escalates the risk and shifts the case into AUS-nuclear, warranting more aggressive management.^{1,7,10,12}

Q5. HOW MANY TIMES SHOULD A THYROID FNA WITH AN AUS RESULT BE REPEATED, AND WHAT IS THE OPTIMAL INTERVAL BETWEEN ASPIRATIONS?

The 2023 TBSRTC lists repeat FNA, molecular testing, diagnostic lobectomy, or surveillance as options but does not require a fixed interval or multiple repeats.¹

A single repeat, US-guided FNA is standard; if cytology remains AUS, the risk of malignancy rises to about 30% (TBSRTC category IV range) and further FNAs are discouraged, proceed to molecular testing or diagnostic lobectomy.¹

The 2023 ETA² guideline also recommends one repeat FNA for the AUS category regardless of EU-TIRADS score and notes that adequacy is not interval-dependent; if AUS persists, management should be risk-adapted (EU-TIRADS 3: re-evaluate, consider molecular testing or surgery; EU-TIRADS 4 and 5: surgery or active surveillance with or without molecular testing).

The 2025 ATA³ differentiated thyroid cancer guideline integrates the 2023 TBSRTC with ultrasound and molecular risk but does not add any new rule on the number or timing of repeat FNAs.

Based on the authors' long-term clinical and cytopathology experience, most nodules initially classified as AUS prove benign when re-aspirated, regardless of whether they were reported as AUS with nuclear atypia or AUS-Other. In daily practice, more than one repeat FNA rarely adds diagnostic value; after a second AUS result the risk of malignancy is already about 30%, and performing a third FNA seldom changes management and only delays definitive diagnosis. The timing of the repeat aspiration may also be influenced by nodule size: very small nodules (<2 cm) tend to undergo more post-biopsy haemorrhage or degeneration, which can compromise the cellular yield and interpretation of an early second FNA, whereas larger nodules (≥ 3 cm) more often yield adequate and diagnostically reliable material on

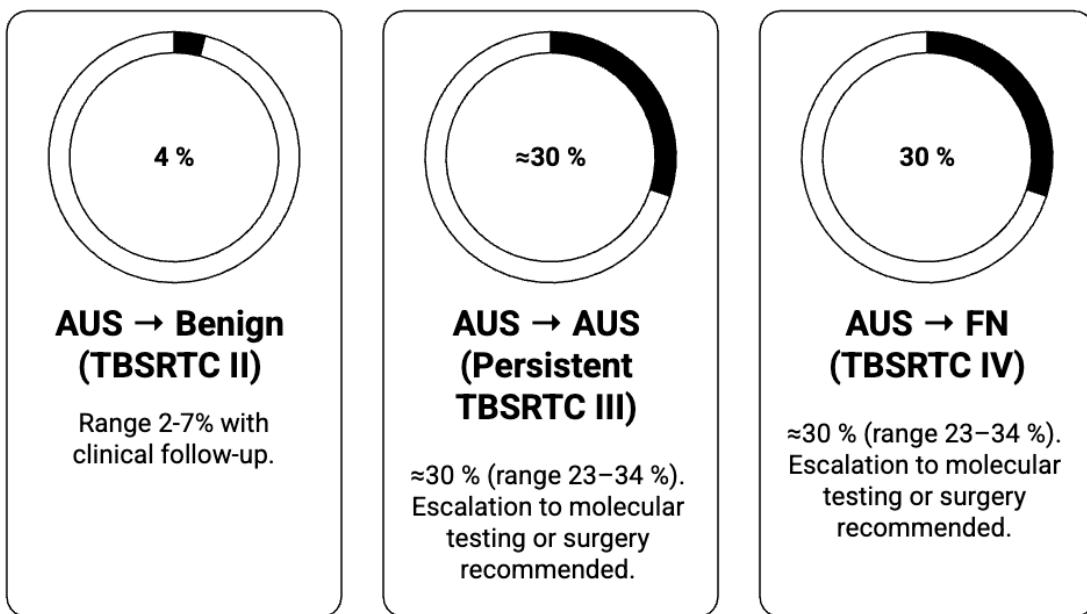


Figure 2 – Reported ROMs of Repeat FNA After an Initial AUS diagnosis.^{1,18,19}

repeat sampling. For this reason, while a single, well-timed repeat FNA is reasonable, especially for AUS-Other, routine multiple re-aspirations are not recommended, and subtype-driven AUS management strategies still require validation in prospective multi-institutional studies before universal adoption. However, the repeat FNA may be performed earlier when ultrasound features indicate higher suspicion (e.g., EU-TIRADS 4–5), since the probability of malignancy is greater and earlier reassessment can facilitate timely management.

Q6. WHEN IS REPEAT FNA ENOUGH, AND WHEN SHOULD I GO TO SURGERY?

According to TBSRTC 3rd edition,¹ repeat FNA is the preferred initial step in most AUS cases, since many nodules resolve to a more definitive diagnosis on re-aspiration, while 10%-30% remain AUS. The 2023 TBSRTC¹ also notes that malignancy risk differs by subtype, being higher for AUS with nuclear atypia (36%–44%) than for AUS-Other (15%–23%). Decisions regarding surgery versus continued observation are not dictated by Bethesda alone but should be based on the integration of cytologic findings with imaging, molecular results, and clinical context. The ATA guidelines³ further specify that surgery is favored when AUS coexists with high-risk ultrasound features, concerning clinical history (such as prior radiation exposure or family history), or significant clinical symptoms.

Q7. IS AUS WITH NUCLEAR ATYPIA BASICALLY PTC-LITE?

No. AUS with nuclear atypia is not papillary carcinoma, but it represents the highest-risk indeterminate cytology subgroup. The 2023 TBSRTC¹ defines it as aspirates showing limited or focal nuclear changes, such as enlargement, chromatin clearing, grooves, or contour irregularities, that raise concern for PTC but fall short of “suspicious for malignancy.” These changes can also appear in benign contexts, including Hashimoto thyroiditis, cyst lining cells, or reactive epithelium, and therefore cannot alone establish a diagnosis of carcinoma. The clinical relevance lies in its higher risk of malignancy compared with other AUS patterns, which justifies closer scrutiny. ATA 2025³ recommends managing AUS with nuclear atypia through an integrated approach: careful ultrasound reassessment, consideration of molecular testing if repeat FNA again shows nuclear atypia, and surgical consultation when cytology, imaging, or clinical features point to significant risk. Thus, AUS with nuclear atypia signals a high-risk gray zone diagnosis, not “PTC-lite,” and requires thoughtful triage rather than automatic progression to surgery.

Q8. CAN A AUS DIAGNOSIS BE WRONGLY USED IN CASE OF HASHIMOTO’S THYROIDITIS?

Yes. Hashimoto’s is one of the most frequent sources of false-positive AUS. Reactive follicular cells in a lymphocytic



background often show nuclear enlargement, chromatin clearing, grooves, and widespread oncocytic change that mimic AUS-nuclear or AUS-other (due to the oncocytic morphology). According to the 2023 TBSRTC, these cases should be reported as chronic lymphocytic thyroiditis rather than AUS when atypia is patchy, lacks true pseudoinclusions, and occurs in a clear inflammatory background.

For surgeons, the pitfall is twofold: overcalling AUS in Hashimoto's can trigger unnecessary repeat FNAs, molecular testing, and surgery; but undercalling carries risk too, since several studies (Lee *et al*, Jankovic *et al*, Loh *et al*, Canberk *et al*) have reported that papillary thyroid carcinoma may coexist with Hashimoto's thyroiditis, with prevalence varying across series.²⁰⁻²² Ultrasound correlation (diffuse hypoechoic, heterogeneous parenchyma, pseudonodules) and antibody testing should be integrated with cytology. Communication between clinician and cytopathologist is critical to avoid both overtreatment and missed malignancy.¹⁹

Q9. SHOULD I ALWAYS ORDER MOLECULAR TESTING AFTER AUS?

No. Molecular testing is not required for every AUS case. In Europe, including ETA 2023 guideline,² the first-line approach remains repeat FNA and careful ultrasound correlation, reserving molecular analysis for select situations. Its utility depends strongly on subtype:

- **AUS –with nuclear atypia** carries the highest ROM (>30%–40%), and molecular testing may be considered when repeat aspiration is indeterminate and ultrasound is not clearly high or low risk.¹
- **AUS-Other:**
 - **AUS with architectural atypia** generally shows lower ROM (~10%–15%), and repeat FNA is usually sufficient. Molecular tests here rarely change management.¹
 - **Oncocytic AUS** is particularly challenging: molecular classifiers are unreliable due to the mitochondrial-rich background, often producing indeterminate or inconclusive results.
 - **AUS-NOS** should be clarified by repeat aspiration before molecular testing is considered.

ATA 2025³ leans more heavily on molecular testing as a triage tool, but in Europe,² the approach is more conservative, supported by ETA 2023²: repeat FNA, ultrasound, and multidisciplinary assessment remain the backbone of management.

Molecular data, when used, should only supplement – not replace – cytology and imaging. A negative test cannot rule out surgery if clinical, radiologic, or cytologic features are worrisome.

Q10. HOW CAN SURGEONS AVOID COMMON MISSTEPS AFTER AN AUS DIAGNOSIS?

The 2023 TBSRTC¹ and ATA 2025³ frameworks highlight that AUS is not a uniform risk category, and missteps usually arise when its heterogeneity is overlooked. The key is to avoid managing AUS as a one-size-fits-all entity.

Potential pitfalls include:

- **Skipping subclassification:** AUS with nuclear atypia carries higher risk than AUS-Other, and this distinction should always guide management.
- **Assuming repeat FNA is unnecessary:** Many architectural or oncocytic AUS cases resolve on re-aspiration, whereas persistence of nuclear atypia warrants escalation.
- **Overvaluing molecular tests:** Classifiers may be useful in AUS-nuclear but often yield inconclusive results in oncocytic or architectural atypia; they should never replace cytology and ultrasound.
- **Neglecting ultrasound correlation:** Imaging risk (e.g., EU-TIRADS 2 vs 5) fundamentally alters the interpretation of an AUS result.

A structured, layered approach-subtype identification, ultrasound stratification, selective molecular testing, and repeat sampling when appropriate-helps surgeons avoid both overtreatment and delayed diagnosis (Table 1).

CONCLUSION

AUS is not a final diagnosis but a triage category. The 2023 TBSRTC¹ update clarifies its role by requiring subclassification into AUS with nuclear atypia and AUS-Other, thereby linking cytology more directly to malignancy risk and management. For surgeons, the value of an AUS report depends on three elements: (1) the specified subtype, (2) the cytologic reasoning behind the interpretation, and (3) integration with ultrasound and clinical context. Without this information, the pathway to repeat FNA, molecular testing, or surgery becomes uncertain and prone to error. Accurate subclassification and clear reporting transform AUS from a diagnostic "gray zone" into a clinically actionable step in patient management, aligning pathology with evidence-based surgical decision-making.

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All authors contributed to the design, analysis, and writing of the manuscript, contributed to the final manuscript, and approved the final version.

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Todos os autores contribuíram para a conceção, análise, redação do manuscrito e contribuíram para o manuscrito final e aprovaram a versão final.

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