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A comparative review of pre-operative fine-needle aspiration cytology and post-operative histopathological findings in thyroid swellings

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Abstract
Background: Thyroid swellings, especially thyroid nodules, are common and the primary clinical goal is to detect malignancy accurately and to avoid unnecessary surgery. Usually reported by the Bethesda System, FNAC or Fine needle aspiration cytology is the first line diagnostic test. Whereas, post-operative histopathology is the gold standard for definitive diagnosis. In the nondiagnosis and indeterminate categories, discordance between FNAC and histopathology is most common; which may lead to overtreatment and delayed diagnosis.
Aim: To evaluate pre-operative FNAC findings with post-operative histopathological result of thyroid swellings and to evaluate the factors and adjuncts (ultrasound risk systems, repeat sampling/core-needle biopsy, and molecular testing) impacting cytology-histology correlation.
Methods: We employed a PRISMA-style narrative review framework. Information from the major guideline and evidence-based sources on reporting thyroid cytology (Bethesda), ultrasound risk stratification (ACR TI-RADS/EU-TIRADS), and problem-solving strategies for nondiagnostic or indeterminate FNAC (repeat FNAC, core-needle biopsy and molecular classifiers such as Afirma and ThyroSeq) were synthesised. The study aimed to obtain cytology-histology concordance patterns by Bethesda category and malignancy risk trends and common causes of false-negative/false-positive FNAC.
Key findings: Overall high concordance between cytology and histology is seen at the extremes. Most resected lesions with an FNAC diagnosis of benign (Bethesda II) correlate with benign histology. Malignant FNAC (Bethesda VI) shows very strong correlation with carcinoma on histopathology. Most clinically meaningful discordance occurs in Bethesda category I, which are nondiagnostic cases, and in Bethesda categories III and IV, which are the AUS/FLUS and follicular-patterned lesions, respectively. These mismatches are caused by sampling limitations, interpretive variability and the fact that cytology cannot assess capsular or vascular invasion. Risk stratification by ultrasound increases pre-test probability and facilitates triaging of discordant cases; core-needle biopsy reduces nondiagnostic results and may give more definitive information about tissue architecture in selected nodules; molecular testing refines risk stratification and may obviate the need for diagnostic surgery in appropriately selected indeterminate nodules. The risk of malignancy estimates were centred around NIFTPs, therefore the impact of this reclassification must be evaluated for historical ROM values.
Conclusion: When interpreted with the Bethesda categories and integrated with ultrasound risk stratification, FNAC is effective in the preoperative triage of thyroid swellings. Nonetheless, the main contributors of discrepancies between cytology and histology occur owing these categories. Using the TI-RADS/EU-TIRADS score in conjunction with selective repeat sampling/CNB and molecular testing will improve histo-pathological agreement for post-operative diagnosis and allow for more tailor made conservative surgery decision making.

Keywords: Thyroid nodule, thyroid swelling, FNAC, Bethesda System, histopathology, cytology-histology correlation, TI-RADS, EU-TIRADS, core-needle biopsy, molecular testing

1. Introduction
Swelling of thyroid indicates a wide clinical spectrum, which includes diffuse goiter, multinodular goiter, inflammatory enlargement (e.g. thyroiditis), discrete thyroid nodule. Most thyroid nodules are benign, therefore the practical and clinical priority is not the detection of nodules but the reliable identification of the small malignant subset while minimizing unnecessary invasive procedures. Fine-needle aspiration cytology (FNAC) is, in

modern practice, the important first-line test for risk triage because of its speed, minimal invasiveness, low cost and generally high accuracy when performed and interpreted under optimal conditions. However, the histopathological analysis of surgically resected specimens is still considered the gold standard in providing evidence of malignancy and allowing for sub-typing, staging inputs and other test if required 7, and 1-3.

Standardized reporting protocols contributed significantly to the increased consistency of diagnosis in thyroid cytology. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is a structured six-tier diagnostic system (Categories I-VI), which are linked to a suggested risk of being malignant and recommended management to enhance communication between cytopathologists, endocrinologists, surgeons and radiologists and interobserver reproducibility.

Simultaneously, the role of ultrasound of the thyroid has changed from descriptive to structured risk stratification. The ACR TI-RADS and EU-TIRADS systems are formalized systems that provide sonographic predictors of malignancy (such as echogenicity, margins, microcalcifications and shape) and help determine which nodules need FNAC, appropriate size thresholds for sampling and intensity of follow-up for nodules that do not meet biopsy criteria [4-6]. These ultrasound frameworks aim to improve the detection of clinically significant cancers by refinement of pre-test probability and to reduce unnecessary FNAC.

Even with these advancements, FNAC and final histopathology disagree and is clinically relevant. When FNAC returns negative (benign) results but clinical suspicion for malignancy is still high, then definitive treatment may be delayed owing to false-negative FNAC result, which would allow the cancer to progress or metastasize before surgery is undertaken. On the other hand, a false-positive or overcalled indeterminate cytology can raise the rates of diagnostic or therapeutic thyroidectomy performed for lesions that eventually end up being benign, and thus expose patients to surgical risk, as well as the long-term burden of lifelong thyroid hormone replacement. Discordance has many reasons. These include sampling limitations (non-representative aspirates, cystic change, heterogeneous nodules), interpretative challenges in borderline follicular-patterned lesions, overlapping cytomorphology of benign and malignant entities, and variable institutional thresholds to determine indeterminate categories.

This review collates information about the cytology-histology correlation across Bethesda categories, focusing on mismatch patterns and their clinical implications. The reclassification of some tumors as NIFTP (noninvasive follicular thyroid neoplasm with papillary-like nuclear features) has altered estimates of malignancy risk and therapeutic approaches. In the end, it assesses other strategies meant to increase concordance, such as ultrasound risk systems, core-needle biopsy (CNB), and molecular testing, and in particular with respect to indeterminate FNAC, where the foremost aims are to avoid unnecessary surgery and ensure timely diagnosis of cancer.

2. Methods

2.1 Protocol and reporting approach

An organized review methodology based on PRISMA implementation was employed to organize the review workflow within the following steps, including a literature identification, screening, eligibility assessment and synthesis (figure 1 is the PRISMA-flow using a standard template [18]). The review question was designed as follows: How much accurate is the pre-operative FNAC reporting under Bethesda/TBSRTC indicated in post-operative histopathology of thyroid swellings, and which adjuncts (ultrasound risk systems, CNB and molecular testing) magnify it? The overall approach complied with best-practice guidance for the systematic evidence synthesis of diagnostic test accuracy research; it specified transparent eligibility criteria, a reproducible search logic, and structured extraction of diagnostic performance outcomes [18, 19].

2.2 Data sources and search strategy

A thorough electronic search strategy was developed to identify studies in the relevant biomedical databases that are used for thyroid diagnostic studies, namely PubMed/MEDLINE, Embase, Scopus and Cochrane Library. We built search strings using Boolean combinations of controlled vocabulary (when applicable) and free-text terms. The core words with which the authors searched were (i) thyroid nodule/swellings, e.g., thyroid nodule, thyroid swelling, goiter, (ii) FNAC/FNA, e.g., fine needle aspiration, FNAC, FNA, (iii) standardized cytology reporting, e.g., Bethesda, TBSRTC, and (iv) reference diagnosis and correlation, e.g., histopathology, surgical pathology, cytology histology correlation [1-3]. Other terms were added to help capture evidence on adjuncts that may improve cytology-histology agreement, such as ultrasound risk stratification systems (TI-RADS, EU-TIRADS, ACR TI-RADS), core-needle biopsy (core needle biopsy, CNB), and molecular testing (e.g., molecular testing, Afirma, ThyroSeq, genomic classifier) [4-6, 9, 10, 12, 15-17]. The reference lists of included articles and key reviews were also screened for additional studies.

2.3 Eligibility criteria (PICOTS)

A PICOTS framework was used to define eligibility. The study involved patients assessed for thyroid nodules or thyroid enlargement who underwent FNAC. The FNAC from the index test was reported using Bethesda/TBSRTC categories or set of results clearly mappable to Bethesda categories [1-3]. The Comparator was histopathology of resected thyroid specimens post-operatively; where no surgery was done, only studies with strong follow-up defining benignity were acceptable. The outcomes were malignancy rates by Bethesda category, diagnostic performance measures (sensitivity, specificity, PPV, NPV), cytology-histology discordance rates, and incremental value of add-ons (such as ultrasound risk stratification, CNB, molecular classifiers) [4-6, 9, 10, 12, 15-17]. The use of timing setting refers to a preoperative outpatient or hospital-based routine diagnosis pathway.

2.4 Study selection and data extraction

The study selection process typically involved a two-step screening: (i) title/abstract screening, and (ii) full-text assessment against the inclusion criteria, with differences resolved through discussion. The selected variables taken from previous studies were study design and setting; sample size; criteria for nodule selection; FNAC technique (palpation-guided vs ultrasound-guided); distribution of

Bethesda categories; patterns for the selection of surgery (to assess selection bias); histopathological end points, and diagnostic accuracy parameters reported. [1-3, 18, 19]

2.5 Quality assessment

The QUADAS-2 domains (patient selection, conduct/interpretation of the index test, reference standard validity, and flow/timing) were used to assess methodological quality and risk of bias [19]. Results synthesis was expected to show heterogeneity due to differences in the rates of ultrasound guidance, cytopathologist expertise, institutional surgery thresholds in Bethesda III/IV nodules, and use of other testing pathways (CNB and molecular testing) [4-6, 9, 10, 12, 15-17].

3. Results

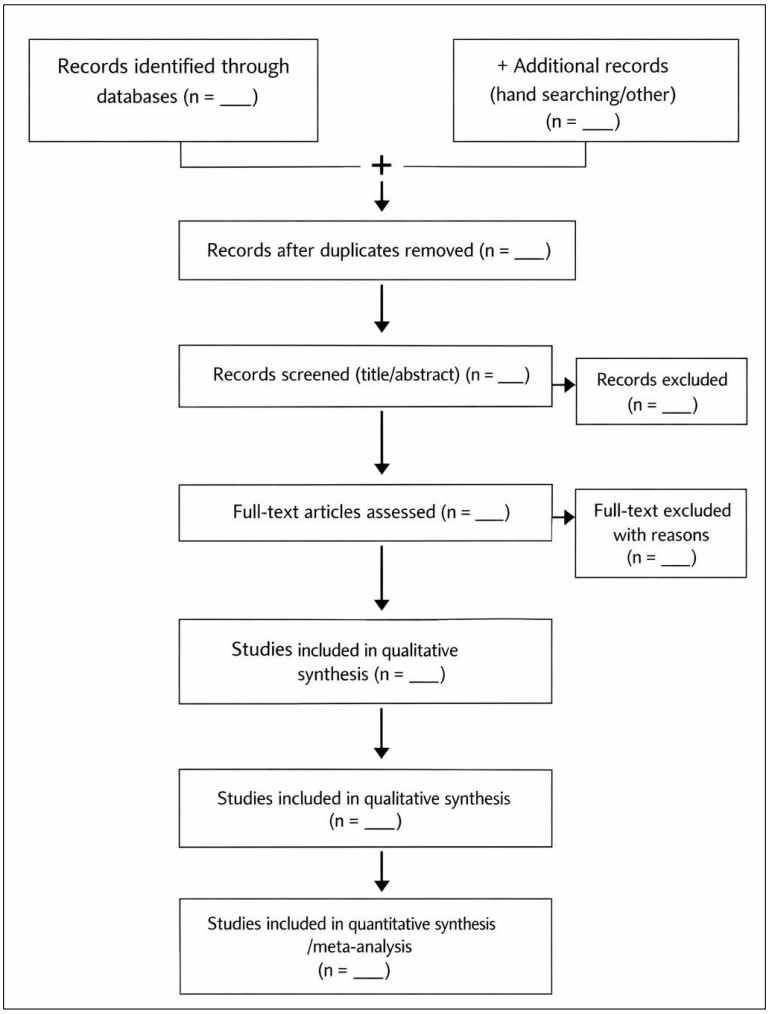

Fig 1: PRISMA-style flow diagram

3.1 Study characteristics

Many correlation investigations originate from tertiary centers and are retrospective cohorts. Surgical histology is predominantly accessible for nodules chosen for surgery, leading to verification bias (it is less likely for benign FNAC cases to get surgery). Higher-level estimates across settings are provided by systematic reviews and meta-analyses [8, 13, 14, 16, 17, 26].

Table 1: Study characteristics

Study	Country/Setting	Design	N (patients / nodules)	FNAC guidance	Reporting system	Reference standard	Key outcomes reported
Bongiovanni *et al*., 2012 (m4.ti.ch)	Multicenter (meta-analysis)	Systematic review & meta-analysis	25,445 FNAs; 6,362 surgical follow-ups	Mixed (included studies)	Bethesda categories (meta-analysis of TBSRTC performance)	Surgical histology (where available)	Pooled malignancy risks by Bethesda category; category distribution; ROM estimates
Lan *et al*., 2020 (PMC)	Multicenter (systematic review)	Systematic review & meta-analysis	10,078 patients; 10,842 nodules	Ultrasound-guided (per included studies)	Cytology (FNA) vs histologic assessment (CNB) across studies	Surgical histology as gold standard (in inclusion criteria)	Sensitivity/specificity of FNA vs CNB; PLR/NLR; AUC comparison; overall diagnostic accuracy
Woliński *et al*., 2016/2017 (PMC meta-analysis) (PMC)	Multicenter	Systematic review & meta-analysis	11 studies included (comparative CNB vs FNAB)	Ultrasound-guided required for inclusion	Bethesda used to define diagnostic vs nondiagnostic results	Study-dependent (comparative diagnostic yield focus)	RR of nondiagnostic results (CNB vs FNAB); heterogeneity; diagnostic yield improvement
Tessler *et al*., 2017 (ACR TI-	USA (radiology guideline)	Guideline/white paper	N/A (not a primary cohort	Ultrasound-based risk	ACR TI-RADS	N/A	US feature scoring; thresholds for FNA vs follow-up; risk

RADS) (PubMed)			study)	stratification			categories
Russ *et al*., 2017 (EU-TIRADS) (PubMed)	Europe (thyroid guideline)	Guideline	N/A	Ultrasound-based risk stratification	EU-TIRADS	N/A	EU-TIRADS pattern-based categories; FNA thresholds; malignancy risk stratification
Cibas & Ali, 2017 (Bethesda 2017 update) (PubMed)	International cytopathology standard	Reporting system update	N/A	Applies to FNA specimens	TBSRTC (2017)	N/A	Updated diagnostic criteria, implied ROM by category, standardized reporting for cyto-histo audit

3.2 FNAC reporting systems and expected histologic correlation

TBSRTC relates cytology categories to associated risk of malignancy and management recommendations [1-3]. In general.

- The term Bethesda II, which is benign, most likely to correlate with benign histology in the majority of all resected cases; false negatives occur most often due to sampling limitations or interpretive pitfalls.
- Bethesda VI represents malignant nodules with a high correlation to papillary thyroid carcinoma on histopathology.
- The majority of the inconsistencies and uncertainties arise from Bethesda I/III/IV, prompting repeat sampling, CNB, or molecular testing.

Table 2: Bethesda categories: typical correlation patterns with histopathology

Bethesda category	Cytology meaning	Typical histology among resected cases	Main discordance drivers
I	Nondiagnostic/unsatisfactory	Benign nodules common; occasional malignancy	Poor cellularity, cystic change, technique issues
II	Benign	Colloid nodules, thyroiditis, benign hyperplasia	Sampling miss of focal carcinoma; cystic PTC
III	AUS/FLUS	Mix of benign hyperplasia/thyroiditis and follicular-pattern lesions	Interobserver variability; borderline nuclear atypia; NIFTP effect
IV	Follicular neoplasm/SFN	Follicular adenoma vs follicular carcinoma; Hurthle lesions	FNA cannot assess capsular/vascular invasion
V	Suspicious for malignancy	PTC and variants common	Threshold effects; NIFTP reclassification; mimic lesions
VI	Malignant	PTC predominant; medullary/anaplastic less frequent	Rare overcalls; unusual variants

Evidence from a meta-analysis suggests that Bethesda can be useful for risk stratification. However, the rates of malignancy for the three indeterminate categories show significant variability across institutions. This variability is driven by case-mix, threshold for calling AUS/FLUS, and the surgical indication [8].

3.3 Ultrasound risk stratification improves pre-test probability

Ultrasound systems standardize features for assessing risk (composition, echo, shape, margin, echo foci) The frameworks EU-TIRADS and ACR TI-RADS are widely used [5, 4]. Studies show that ultrasound can stratify malignancy risk sufficiently; however, performance differs by system and threshold [13, 14, 26]. The EU-TIRADS meta-analysis supports its use for stratifying malignancy risk [14]. According to the Bethesda categories, it is most valuable for borderline scenarios.

Related Practical Integration Examples.

- Such low TI-RADS suggest that the lesion may be observed.
- A repeat sampling or Core Needle Biopsy (CNB) or molecular testingis preferred for Bethesda III with a high TI-RADS.
- Surgery is more likely in cases of Bethesda IV with moderate/high TI-RADS, but molecular testing may prevent avoidable thyroidectomy in selected patients.

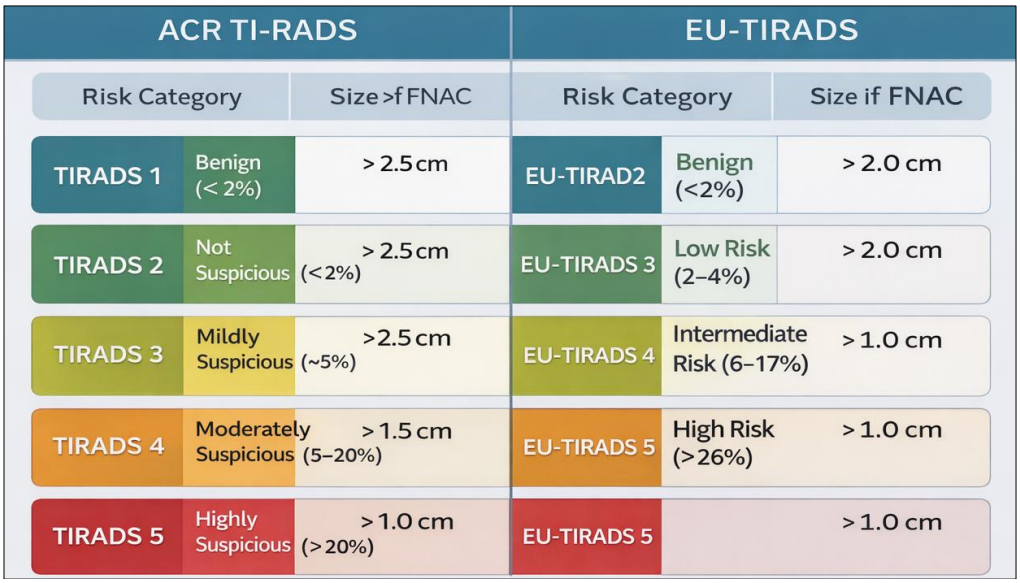

Fig 2: Ultrasound Risk Stratification Systems Comparison

3.4 Core-needle biopsy (CNB) as a problem-solving tool

When FNAC is multiple times nondiagnostic or still indeterminate, CNB is utilized. According to a meta-analysis often cited in the literature involving 34 studies, the overall pooled risk ratio (RR) for nondiagnostic result was around 0.27 (with 95% CI 0.17-0.41), favoring CNB.

Consensus recommendations and systematic reviews also endorse CNB for inconclusive cytology and chosen nodules [15-17]. Somatic CNB may improve depiction of architectural patterns and allow ancillary studies, although it does not completely resolve capsular/vascular invasion in follicular-patterned neoplasms (a histologic criterion).

When CNB brings value.

- Despite ultrasound guidance, Bethesda I was repeated.
- Recurrent Bethesda III: suspect ultrasound features.
- Ultrasound results in discordance with cytology.

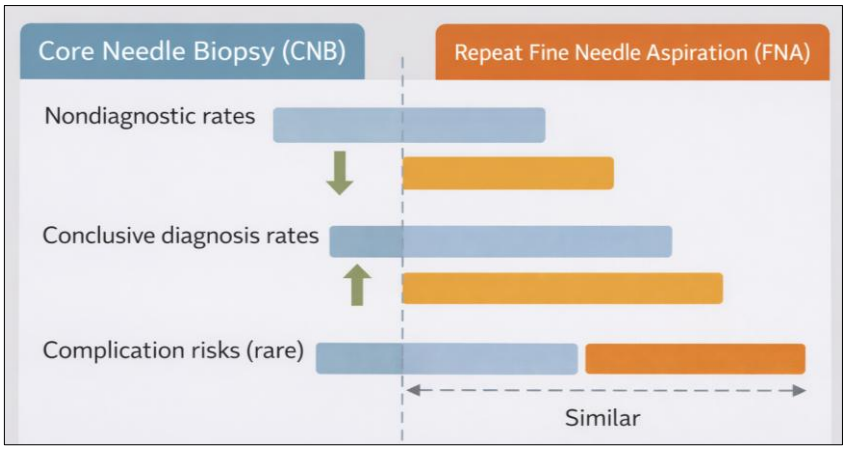

Fig 3: CNB vs repeat FNA evidence graphic

3.5 Molecular testing reduces diagnostic surgery in indeterminate nodules

Depending on the platform and population, molecular tests have a high NPV to rule out and high PPV to rule. Studies of the Afirma gene expression classifier and later classifiers have shown the ability to identify nodules that are likely benign [9, 10].These classifiers could help reduce diagnostic surgery for Bethesda III/IV nodules. The validation data of ThyroSeq v3 for indeterminate FNAC contexts has been published and can be found via PubMed. The review in Cancer Cytopathology also provides the clinical validation evidence along with its DOI.

Since performance is dependent on prevalence and institutional case-mix, real-world outcomes should be interpreted locally, and in combination with ultrasound risk and clinical factors.

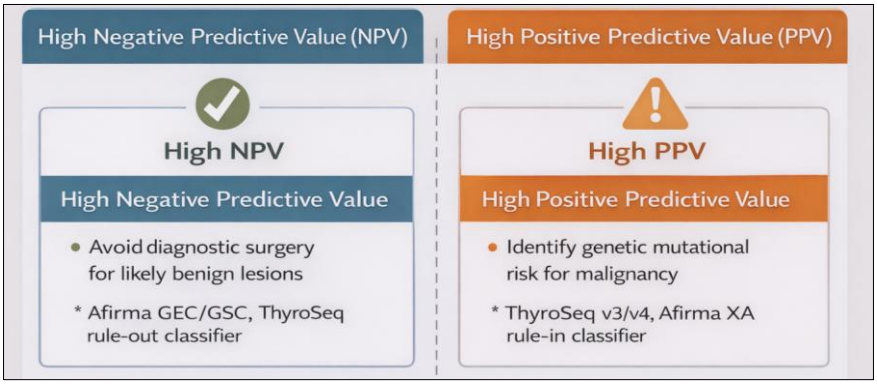

Fig 4: Molecular testing role

3.6 NIFTP and shifting malignancy-risk estimates

The new classification of encapsulated follicular variant of papillary thyroid carcinoma as NIFTP has changed estimated malignancy rates for Bethesda III-V categories and affects interpretation of "malignancy" as an outcome [11, 30-32]. A major reason older ROM tables from Bethesda may not fit the current institutional experience.

4. Discussion

4.1 What cytology-histology correlation means clinically

It is better to interpret cytology-histology correlation as clinical triage accuracy, not as the perfect category agreement on an exact one-to-one basis. A correlation is more robust at the extremes of the Bethesda/TBSRTC framework, Bethesda II (benign lesions) and Bethesda VI (malignant lesions), because the cytomorphologic criteria are more definitive and the management pathways are more straightforward [1-3]. In contrast, correlation becomes weaker in intermediate or workflow-limited categories Bethseda I (nondiagnostic) and Bethesda III/IV (AUS/FLUS; FN/SFN), where sampling limits, borderline atypia, and biologic ambiguity often limit certainty [1-3]. As per Clinical, the goal is not perfect agreement, but rather the correct triage: (i) avoid missing clinically significant malignancy, (ii) reduce the number of surgeries for benign disease, which are potentially avoidable, and (iii) choose the correct extent of surgery (lobectomy vs total thyroidectomy) when operative

management is necessary and appropriate based on imaging-based risk, staging, and guideline-directed planning [6].

4.2 Major causes of discordance and mitigation

A key factor responsible for discordance is sampling limitations. Aspirates may fail to yield a diagnosis or may suggest that the lesion is benign even though malignant foci exist with cystic degeneration, dense calcification, deep/postsieror nodules and very small lesions. Techniques for preventive action such as ultrasound-guided fineneedle aspiration cytology (FNAC), targeting of solid areas and suspicious areas on ultrasound, and if possible, on-site adequacy assessment to reduce the incidence of nondiagnostic cytology by allowing additional passes on the spot [2, 10].

The issue of interpretation being open to variability is of considerable relevance for Bethesda III (AUS/FLUS), especially where "borderline" nuclear or architectural atypia are concerned. Further, such atypias are often interpreted differently by different observers and at different institutions. The quantity and expertise of the cases may alter diagnostic distribution According to the evidence, low-volume pathologists may assign atypia diagnoses more often and benign diagnoses less often, resulting in increased indeterminate rates and driving downstream diagnostic surgery [5]. This raises an important systems-level issue. There will be biological discordance but behind this is also an operational discordance that is influenced by training, workload, and institutional thresholds for indeterminate calls.

Biological limitations of FNAC further limit the correlation. FNAC of follicular patterned lesions cannot reliably separate Foll. adenoma from Foll. carcinoma since capsular and/or vascular invasion, which define malignancy, are defined histologically. When used in conjunction, ACR TI-RADS, or their European equivalents, can reduce rates of discordance between cytology and pathology. In selected indeterminate cases, the use of adjuncts, such as core-needle biopsy (CNB) and/or molecular testing, can allow for more accurate risk stratification, and help to avoid unnecessary surgery without oncological safety issues.

Table 3: Common pitfalls causing FNAC-histology mismatch

Problem	Typical effect	Example settings	Mitigation
Low cellularity / cystic aspirate	Bethesda I or false benign	cystic PTC, hemorrhagic nodules	repeat US-guided FNAC; sample solid component
Borderline nuclear atypia	Bethesda III variability	thyroiditis, repair changes	strict Bethesda criteria; second review
Follicular-pattern lesions	Indeterminate cytology	Bethesda IV	lobectomy vs molecular/CNB based on risk
NIFTP reclassification	ROM shifts	Bethesda III-V	report outcomes with/without NIFTP
Ultrasound-cytology discordance	Under/over-treatment	high TI-RADS + benign FNAC	repeat FNAC/CNB; multidisciplinary review

4.3 Suggested integrated diagnostic pathway

A well-defined integrated pathway incorporates first ultrasound risk stratification that defines pre-test probability and biopsy thresholds [2, 3]. FNAC results are then interpreted using the Bethesda classification but the management should remain risk integrated i.e. (i) the cytological category; (ii) ultrasound risk level; and (iii) patient related factors such as age, co-morbidities, compressive symptoms, preferences and local resource availability. Sometimes Bethesda III/IV nodules must undergo repeated ultrasound-guided aspirate, core needle biopsy (because of indeterminate/nondiagnostic repeated results), and/or molecular testing that can importantly refine risk, improve cytology-histology correlation, and reduce diagnostic thyroidectomy when the risk of malignancy is low to moderate. [7-9]

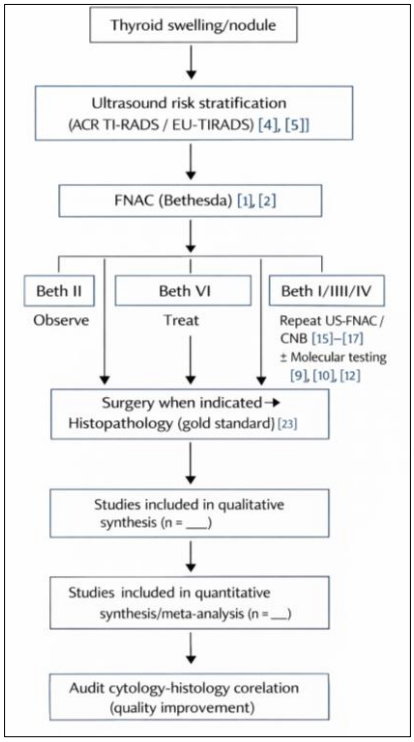

Fig 5: Integrated pathway: clinical + ultrasound + FNAC → escalation → histology

4.4 Practical recommendations

According to Bethesda I, if FNAC is nondiagnostic but ultrasound shows suspicious findings, consider repeat FNAC or CNB. According to Bethesda II, correlate with TI-RADS/EU-TIRADS and repeat sampling only when high-suspicion features, significant growth or clinical discordance is present [2, 3] For Bethesda Category III, incorporate ultrasound assessment of risk, repeat FNAC or CNB when necessary, and use molecular testing where available to prevent unnecessary operations, and ensure the procedure is safe. For Bethesda IV, surgery is often necessary for definitive invasion assessment, although CNB/molecular testing may support selected decision-making when operative risk is high or imaging is of low suspicion (7)-(9). Management of Bethesda V/VI should follow guideline-based pathways with surgical planning guided by staging and imaging [6]. The reclassification of NIFTP might allow unlabeling of malignancy to certain indolent encapsulated follicular-variant tumors and reduce apparent ROM estimates in the indeterminate categories which allows for a conservative and risk-calibrated approach where possible.

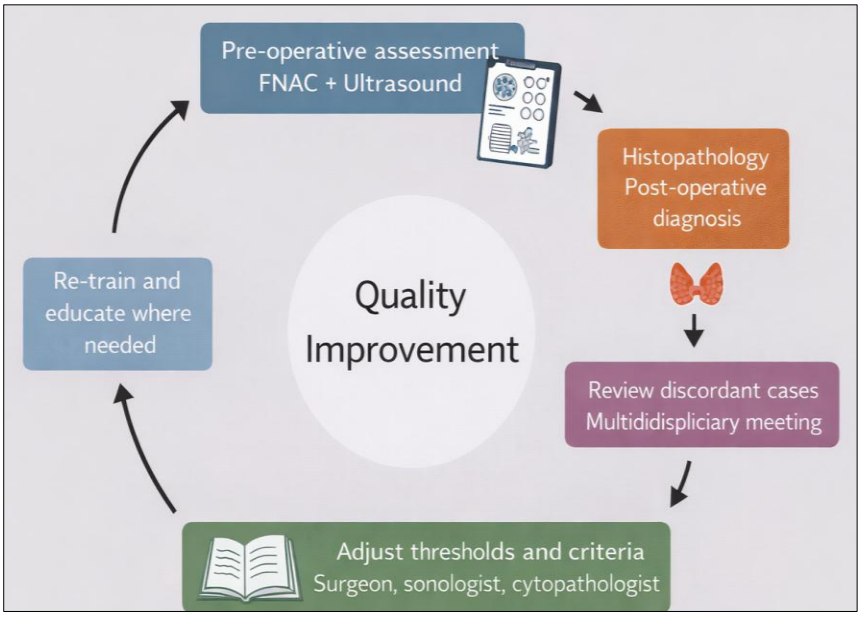

Fig 6: Audit loop

5. Limitations

There are a number of limitations in this review that must be taken into account. Initially, there is verification (work-up) bias from many correlation studies. Only a limited subset of patients goes on to surgery and thus gets a reference standard histopathology.

Consequently, malignancy rates and diagnostic performance estimate which is for indeterminate categories may be inflated or distorted compared to the population risk (the truth) [1-3]. The studies vary in a lot of aspects like acquisition and expertise level amongst others. There is variation in applying ultrasound risk systems, including differences in deciding whether FNAC will be performed on a nodule. This can affect case mix and influence observed Bethesda distributions and cancer rates [4-6]. In the third instance, the histopathologic classification is evolving with the acceptance of NIFTP which is changing the calculation of final histology malignant and therefore risk-of-malignancy (ROM) calculation, which is especially important in Bethesda III/IV categories where follicular-patterned lesions are common [4]. The practicality and influence of adjunct strategies differ among health systems. Because core-needle biopsy (CNB) and molecular testing may not be universally available, cost-prohibitive, and show variable cost-effectiveness depending on baseline cancer prevalence, local surgical thresholds and test platform [7-9]. Ultimately, the ways in which hospitals differ when it comes to training cyto-pathologists, volume of cases, assessing adequacy and making surgery decisions can lead to meaningful local variation in ROM. Subsequently, the authors stress that "published ROM" is likely not generalizable [1-3].

6. Conclusion

FNAC continues to be the mainstay of evaluation of thyroid swelling because it is practical and easily available. FNAC still has a good clinical utility when the result is standardized by Bethesda categories and integrated with ultrasound risk stratification [1-6]. The most clinically meaningful discordance between cytology and histopathology arises in nondiagnostic catregory (Bethesda I) and indeterminate category (Bethesda III/IV), where sampling limitations, interpretive variability and biologic constraints are maximal [1-3]. Using a risk-integrated approach to decision making can lead to better outcomes when managing a thyroid nodule. Therapies include ultrasound-guided FNAC to repeat a nodule with a sampling error, selective use of a CNB for repeatedly nondiagnostic or indeterminate nodules, and molecular testing where available and appropriate to refine a nodule's malignancy risk and reduce the risk of potentially avoidable diagnostic surgery without jeopardizing oncologic safety [4-9]. Importantly, the permanent institutional audit of cytology-histology correlation at a single institution which uses uniform histologic endpoints and captures NIFTP explicitly allows for better accurate local ROM estimation, improved patient counseling, and optimized pathways that balance early cancer diagnosis with the harm of unnecessary thyroidectomy and lifelong therapy [1-6].

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