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Review

Reporting Thyroid Cytology in a Globalized World

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Abstract: The Italian SIAPEC-AIT 2014 classification, the 2017 Bethesda System for Reporting Thyroid Cytology (TBSRTC), the 2016 UK Royal College of Pathologists (RCPath) thyroid reporting system, and the 2019 Japanese reporting system for thyroid aspiration cytology (JRSTAC2019) represent the most widely used reporting systems among clinicians and pathologists for the purpose of cytologically diagnosing, estimating the potential risk of malignancy (ROM), and defining the most appropriate treatment for a patient with a thyroid nodule. Although all the systems use overlapping diagnostic categories and morphologic criteria, they differ on the basis of the criteria for inclusion in the cytologic categories, which may, in turn, affect the ROM of a given category and the clinical management of the patient, particularly with regard to the "indeterminate" categories. The aim of this review is to analyze the main differences that emerge between the systems and to propose possible solutions for a comprehensive reporting system that integrates and harmonizes all the criteria of the Italian classification and the Bethesda system, also taking into account the impact that the new tumor entity NIFTP (non-invasive follicular tumor with papillary-like nuclear features) that has, in many instances, replaced the non-invasive form of the follicular variant of papillary carcinoma, has had on the modification of malignancy risks.

Keywords: thyroid reporting systems; indeterminate category; thyroid cytology

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1. Introduction

The diagnosis of thyroid nodules represents an important problem for clinicians and pathologists, especially regarding the diagnostic framing and the choice of the most appropriate treatment. More than 50% of the general population may have a thyroid nodule, detected by instrumental diagnostic methods such as ultrasonography, but only 5% of them present malignant characteristics and behavior [1–3].

In addition to clinical and ultrasonographic examination, the study of thyroid nodules is performed by fine needle aspiration (FNA) or needle aspiration, a rapid, effective, safe, and cost-effective procedure. This technique allows, through fine needle aspiration under ultrasound guidance, to prepare cytological preparations and study the morphology of the cells of the lesion [4]. However, between 15% and 25% of lesions are cytologically indeterminate, i.e., they present a morphological picture that does not allow them to be identified with certainty as benign or malignant [3].

In order to distinguish nodules to be sent for surgical treatment from those to be observed over time with clinical and ultrasonographic examinations, classifications (or reporting systems) based on cytological criteria have been drawn up.

Among the reporting systems, the Italian SIAPeC-AIT classification, in its latest version updated in 2014/(CI14) and *The Bethesda System for Reporting Thyroid Cytopathology*, proposed in 2007 and updated in 2017 (TBSRTC) are among the most widely used in the world [5,6] together with the *Guidance On The Reporting Of Thyroid Cytology Specimens* from The UK Royal College Of Pathologists [7] and *The Japanese reporting system for thyroid aspiration cytology* [8].

Although the morphologic parameters used by these systems are very similar, there are, however, differences in the criteria for inclusion in cytologic categories (see below) that affect the recommendations for the clinical management of patients. The purpose of this review is to discuss these differences in order to propose a common reporting system that can be used for all patients with thyroid nodules.

2. Italian 2014 and Bethesda 2017 Classifications: Common Issues

Both reporting systems identify six categories, respectively, non-diagnostic, non-neoplastic/benign, indeterminate (two categories for each system), suspected of malignancy, and diagnostic for malignancy (Table 1). For each of these categories, a risk of malignancy (ROM) is also defined, i.e., the estimated risk that a lesion may be malignant on histologic examination, which represents the main difference between the two systems (see below).

Table 1. Comparison between 2014 Italian SIAPEC-AIT classification, 2017 Bethesda and 2016 UK RCPath reporting system for thyroid cytology.

2014 Italian SIAPEC-AIT Reporting System	2017 Bethesda Reporting System for Thyroid Cytology	2016 UK Royal College of Pathologists System
TIR 1 Non-diagnostic **TIR 1C** Non-diagnostic—cystic	**I**. Non-diagnostic	**Thy1:** Non-diagnostic **Thy1c:** Non-diagnostic—cystic
TIR 2 Benign	**II.** Benign	**Thy2:** Non neoplastic **Thy2c:** Non neoplastic—cystic
TIR 3A Low-risk indeterminate lesion	**III.** Atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS)	**Thy3a:** Neoplastic possible, atypia/non diagnostic
TIR 3B High-risk indeterminate lesion (oncocytic lesions included)	**IV.** Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) (oncocytic lesion FNHCT/SFNHCT included)	**Thy3f:** Neoplastic possible, suggesting follicular neoplasm
TIR 4 Suspicious of malignancy	**V.** Suspicious of malignancy	**Thy4:** Suspicious of malignancy
TIR 5 Malignant	**VI.** Malignant	**Thy5:** Malignant

The SIAPEC-AIT and the Bethesda system use overlapping morphological criteria such as the degree of cellular atypia and architectural atypia to determine the correct inclusion of thyroid nodules in the various categories, especially for nodules with indeterminate features.

Architectural atypia is defined by the amount of microfollicles in the cytologic preparation while cytologic atypia consists in the identification of irregularities of the follicular cell nuclei (elongation, clarification, nuclear grooves).

The probability that a nodule presenting cytologic atypia may be malignant appears to be higher in the literature than that of a nodule presenting only architectural atypia: in some works, cytologic atypia indicates 50% of the ROM compared with 24% of architectural atypia [9], while in others this difference is even higher (33.3% versus 7.7%) [10].

In both systems the risk of malignancy for benign nodules is very low (less than 3% in both systems) [6,11] and for those suspected to be malignant (79–89%) [11,12] and malignant (more than 97%) [11,12], the risk is significantly high, and this finding is of fundamental importance to determine the therapeutic strategy (i.e., follow-up in the former and surgery in the latter). For indeterminate lesions, the estimated ROM is variable between the two systems, but an estimated risk of malignancy greater than 15% for indeterminate

categories that are candidates for clinical and ultrasonographic follow-up (TIR 3A in CI14 and AUS/FLUS in TBSRTC) may create management problems for the clinician and the patient. In the Italian classification, the low-risk category (TIR 3A) has an expected ROM between 12 and 22% [13], whereas the high-risk category (TIR 3B) has an expected ROM between 40 and 55% [13]. In contrast to the 2008 TBSRTC, in which the ROMs were similar to those of the 2014 Italian classification, those of the 2017 edition are higher. In fact, AUS/FLUS results in a ROM estimated between 10 and 30% and the FN/SFN category is in a range between 25 and 40% [11], creating doubts regarding the choice of patient management between conservative therapy (expected for AUS/FLUS lesions) and surgical therapy (expected for FN/SFN lesions).

The recognition in the recent edition of the *WHO classification of Endocrine Tumors* (2017) of a new nosological entity, NIFTP (non-invasive follicular tumor with papillary-like nuclear features—see below) should result in a reduction of ROMs, especially in the indeterminate categories of both classification systems [3].

3. Indeterminate Diagnoses in the Italian Classification 2014

The 2014 Italian classification analyzes the morphologic characteristics of thyroid nodule cells to place them in the most appropriate diagnostic category. It was recently observed that the ROM for indeterminate lesions was slightly higher than estimated, reporting a value of 17% for the TIR3A category and 47% for the TIR3B category [13]. However, similar to the ROM observed in other reporting systems, this parameter for the low-risk indeterminate categories (TIR3A and AUS/FLUS) is affected by the fact that the majority of nodules with this diagnosis are not referred for surgery [14].

3.1. Indeterminate Low-Risk Lesions (TIR 3A)

CI14 defines TIR 3A as a lesion of increased cellularity with numerous microfollicular structures in a colloid-poor context, or rare clusters of microfollicular structure cells that may also present with oncocytic metaplasia [6].

In the assessment of ROM, the TIR3A includes lesions presenting mainly architectural atypia while excluding those presenting cytological atypia above the mild grade; therefore, the estimated risk of malignancy in low-risk indeterminate lesions is lower than in the Bethesda classification [3,6]. The introduction of NIFTP reduces the ROM of this category in a non-significant way (from 15.9% to 14% according to Straccia et al. [14]).

Treatment for TIR3A type lesions is conservative with follow-up and repeat aspiration 6 months after the first one. Surgical option (lobectomy) should be considered if clinical or ultrasound parameters worsen [6].

3.2. Indeterminate High-Risk Lesions (TIR 3B)

TIR 3B corresponds to a high cellularity lesion with microfollicular/trabecular structure, containing little colloid and with presence of moderate to severe cytological atypia. Also included in this category are Hürthle cell or oncocytic cell lesions, thyrocyte-derived cells that exhibit abundant finely granulated cytoplasm, reflecting an excess of mitochondria, often associated with a core polymorphism and prominent nucleoli [6].

The TIR 3B category, with surgical option as the treatment of first choice [6], includes all lesions presenting moderate to severe cytologic atypia, with progressive stratification of malignancy risk [13], and oncocytic lesions. However, a recent study observed a significant difference in ROM in this category between follicular cell and Hürthle cell lesions, showing a ROM of 59% for the former group and 9% for the latter, respectively [14]. The latter finding suggests that Hürthle cell lesions, of which a considerable proportion are non-neoplastic forms, should be included in the indeterminate low-risk category (TIR 3A) to reduce the amount of inappropriate surgery.

4. Indeterminate Diagnoses in the 2017 Bethesda Classification

The recent 2017 version of the Bethesda Classification (TBSRTC), following analysis of recent literature and meta-analysis, presents a reassessment of the risk of malignancy of AUS/FLUS and FN/SFN lesions increased to 10–30% (compared with 5–15% in the previous version) and 25–40%, respectively, compared with 15–30% in 2008 [3,15].

4.1. AUS/FLUS

Bethesda defines an AUS/FLUS as a nodular lesion that exhibits a degree of atypia, primarily nuclear and/or architectural that does not allow the lesion to be associated with a suspected neoplastic lesion or suspected of malignancy [16].

The extremely heterogeneous picture of AUS/FLUS lesions and the remodelling of a higher ROM than the previous Bethesda edition has led some authors to propose a sub-classification of nodules based on morphological atypia, with a higher ROM for nodules presenting nuclear atypia than those with only architectural atypia, the presence of oncocytic features presenting a lower ROM, and atypia not otherwise specified [9]. In this way, it is possible to distinguish nodules that will be treated with a conservative approach, with a repeat FNA within 3–6 months [17], from those that will be sent for surgery.

Recently, the use of molecular tests for mutations, in particular BRAF V600E, N-RAS and TERT, such as Afirma-GEC and ThyroSeq assay is being implemented in clinical practice in order to distinguish among the various AUS nodules those that will go to surgery [18], but routine use is limited by a suboptimal cost–benefit ratio [19] and variability in test performance [18].

4.2. FN/SFN Follicular Neoplasms; FNHCT/SFNHCT Oncocytic Neoplasms

FN/SFN refers to a thyroid aspirate comprising follicular cells, many of which exhibit architectural alteration characterized by cell crowding or microfollicular formation, and mild cytologic atypia such as nuclei enlargement, nuclear membrane alteration, and mild chromatin shedding [16]; presenting histologic counterpart including a wide range of clinical entities such as follicular adenoma, Hürtle cell lesion, NIFTP, and others.

In Bethesda, a particular category is represented by Hürthle cell (oncocytic) neoplasms (and suspected neoplasms) Some laboratories prefer the use of the term SFNHCT because many needle aspirates diagnosed as oncocytic neoplasms result on histologic examination as hyperplastic lesions with a predominant oncocytic component (15–26%) [20].

Both FN/SFN and FNHCT/SFNHCT lesions are treated surgically with lobectomy [17].

5. British and Japanese Reporting Systems for Thyroid Cytology

In addition to the Italian classification and the Bethesda system, other thyroid cytology reporting systems frequently used by pathologists are *The Guidance On The Reporting Of Thyroid Cytology Specimens* from The UK Royal College Of Pathologists proposed in 2009 and revised in 2016 [7] and *The Japanese reporting system for thyroid aspiration cytology* proposed by the Japanese Thyroid Association in 2019 [8].

Both the British and the Japanese systems use similar morphologic criteria as the Italian classification and the Bethesda system such as the presence of architectural atypia and cytologic atypia but differ from the latter based on the classification of the indeterminate category and therapeutic recommendations for patient management.

The UK system divides the indeterminate category into two groups: Thy3a and Thy3f [7,21].

Thy3a (neoplasm possible-atypical/non-diagnostic) defines a lesion that has atypical features but nevertheless insufficient to allow inclusion in the other categories. Often this category includes suboptimal specimens.

Thy3f (possible follicular neoplasm) defines a lesion suspected of follicular neoplasm that cannot be excluded by morphologic examination alone; oncocytic lesions are included in this category.

Recent studies have shown a ROM of 25% for the Thy3a category and 31% for the Thy3f category [21].

The management of the patient, once a "possible neoplasm" has been established, is entrusted to a multidisciplinary team whose members include the surgeon, the endocrinologist, and the nuclear medicine physician who, on the basis of mainly clinical criteria, collegially choose the best possible treatment between conservative and surgical approaches [22].

The 2019 Japanese classification gathers all the indeterminate lesions in one category of "Undetermined Significance" [8], unlike the previous classification that subdivided them in two categories based on their follicular or non-follicular architecture [23].

The "Undetermined Significance" category includes different type of lesions whose cytological or architectural atypia is not sufficient for being classified in the follicular, suspect for malignancies or malignant categories, or lesions for which a papillary carcinoma cannot be excluded, or lesions that features follicular, lymphoid or other atypical cells. The ROM for the "Undetermined Significance" category results to be around 13% [8].

In the Japanese system, nodules classified as FN undergo a series of examinations for the purpose of discriminating nodules that will be treated with a conservative approach from those that will undergo surgery if certain clinicopathologic features are present such as cytologic or ultrasonographic atypia, nuclei with large size, plasma thyroglobulin >1000 ng/mL, nodules extending into the mediastinum, and independently functioning nodules [8]. The subclassification of nodules has resulted in a reduction in unnecessary thyroidectomies also in view of the tendency of Japanese clinicians to treat most nodules with a conservative approach [8,24].

6. Remodeling the Risk of Malignancy: The NIFTP

NIFTP (non-invasive follicular tumor with papillary-like nuclear features) is defined as a thyroid neoplasm diagnosed using strict histologic criteria including the presence of tumor encapsulation or clear demarcation, a follicular growth pattern without papillary structures, less than a 30% trabecular or insular growth pattern, and the absence of psammoma bodies. Nuclear features of papillary thyroid carcinoma are present (enlargement, crowding/overlapping, elongation, irregular contours, grooves, chromatin clearing), whereas capsular or vascular invasion, tumor necrosis (not associated with FNA) and increased number of mitoses are absent. The molecular phenotype of NIFTP is different from the classical type papillary thyroid carcinoma, since it is typically a RAS mutated tumor rather than a BRAF V600E mutated one.

In the 2017 WHO classification, the term NIFTP was proposed to replace the term "non-invasive variant follicular capsular papillary carcinoma" to emphasize the non-invasive feature of the neoplasm for whose treatment lobectomy followed by follow-up is recommended [25,26].

A recent meta-analysis about the distribution of cytological findings associated with NIFTP over the Bethesda categories showed a prevalence of diagnosis of these features in the AUS/FLUS class (30%), followed by the SM class (24%) and by the FN/SFN class (21%) [27].

The introduction of NIFTP resulted in a re-evaluation of ROM in the various classification categories. Initial studies initially estimated a significant reduction in ROM in the various diagnostic classes (45% in AUS/FLUS, 18% in FN/SFN and 48% in suspected malignancy) [28]. Recently, studies on the impact of NIFTP on thyroid cytology diagnostics showed, after revision of the criteria in 2018 [29], a smaller ROM reduction in the various diagnostic classes of TBSRTC. Kopczynski et al. [30] observed a statistically nonsignificant reduction of 0.7% for the FN/SFN category, 4.2% for the SUSP category, 0.5% for the MAL category, and no reduction in ROM for the AUS/FLUS category. In another study, Ventura et al. [31] observed a reduction in ROM of 15.2% for AUS/FLUS, 7.6% for FN/SFN, and 14.2% for SFN.

However, it is noted that the percentage of NIFTP diagnosis and ROM is different among western and Asian studies. This is due to several factors as a higher rate of FVPTC diagnosis in western countries, which might affect the rate of NIFTP, or the higher resection rate of the thyroid nodules in the western practice compared to the conservative strategy management of the Asian one [32].

Therefore, it can be stated that the impact of NIFTP on the efficacy of thyroid cytology diagnostics, especially in the Bethesda system, is less than initially expected.

7. Discussion

The Italian 2014 and Bethesda 2017 classifications as well as the 2016 RCPath and the 2019 JTA reporting systems have allowed the introduction of rigorous diagnostic criteria such as to allow cytopathologists to report a thyroid lesion in a homogeneous way and accessible to all (clinicians and patients).

The "indeterminate" category, although with small differences between the classifications, gathers cytologic features of difficult interpretation. A recent metanalysis showed that the Italian classification demonstrate an increased rate of ROM from low- to high-risk category, compared to the other systems [12]. It is the ambiguous nature of this category that causes the main differences in the clinical management of the patients between the reporting systems. Where the Italian [6] and the Bethesda [17] classifications propose a surgical approach, the British [7] system suggests a multidisciplinary assessment and the Japanese [8] system prompt to a more conservative method (Table 2).

Table 2. "Indeterminate" diagnostic categories; comparison of risk of malignancy (ROM) and clinical management between Italian, Bethesda, British and Japanese classification.

2014 Italian SIAPEC-AIT		**2017 Bethesda**		**2016 RCPath Classification**		**2019 JRSTAC**	
Diagnostic Category *(ROM %)*	Management	Diagnostic Category *(ROM %)*	Management	Diagnostic Category *(ROM %)*	Management	Diagnostic Category *(ROM %)*	Management
TIR 3A Low-risk indeterminate lesion (*12–22%*) [13]	Clinical follow up/Repeat FNA	**III.** AUS/FLUS (*10–30%*) [11]	Repeat FNA/Molecular testing or lobectomy	**Thy 3a** Neoplasm possible – atypia/nondiagnostic (*25%*) [21]	Multidisciplinary assessment	**Undetermined Significance** (*13%*) [8]	Conservative approach/Surgery (if suspicious ultrasound or cytologic features of atypia, nodules extending to the mediastinum, high serum thyroglobulin are present)
TIR 3B High-risk indeterminate lesion (*30–55%*) [13]	Surgery	**IV.** FN/suspicious FN (*25–40%*) [11]	Molecular testing, lobectomy	**Thy 3f** Neoplasm possible, suggesting follicular neoplasm (*31%*) [21]			

In order to unify the reporting in one global system, preserving the common criteria and harmonizing the different ones, a possible suggestion is the subdivision of indeterminate lesions in two groups: low-risk indeterminate lesions and high-risk indeterminate lesions.

The first group includes lesions that present mainly architectural atypia but only mild cytological atypia and, in addition, lesions with oncocytic cells. The second group includes those morphological pictures presenting moderate and severe cytological atypia, independently from the identification of any architectural atypia.

A more rigorous grading of cytological atypia with the inclusion of moderate–severe ones in the highest risk category would result in keeping the ROM for low-risk indeterminate nodules below 15%, justifying the surgical choice only for those at high risk (ROM of 15–40%).

When operationally evaluating the criteria for inclusion of a case in one of the indeterminate categories, the possibility that a NIFTP may be diagnosed on histologic examination should be considered [33]. Since this tumor entity does not show invasive and metastasizing capacity, it should not be considered as a malignant neoplasm and therefore the risk of malignancy in the indeterminate categories is estimated to be lower than reported in the literature until 2016. This factor will contribute to a further reduction in ROM for indeterminate categories that would approach the 10% level for low-risk categories and return to the 15–30% level of the first version of Bethesda in high-risk indeterminate lesions.

Regarding the possibility of better stratifying patients with cytologically indeterminate nodules, especially those at low risk who are not candidates for surgery who do not present

a family history of thyroid cancer or exposure to ionizing radiations, immunohistochemical evaluation of the expression of malignancy markers such as HBME-1 and Galectin-3 could be a useful aid in identifying potentially malignant lesions [34]. More sophisticated molecular tests to search for BRAF V600E and TERT promoter mutations and for molecular profiling of indeterminate lesions (Afirma, ThyroSeq) represent an additional and more specific tool, compared to the immunohistochemical analysis, for the correct identification of those nodules that are clinically and cytologically indeterminate, but with high risk of malignant evolution, which could benefit from conservative surgery that is often resolving (Table 3).

Table 3. Proposal of an integrated global reporting system.

Diagnostic Categories	Recommended Actions
Non-diagnostic	Repeat FNA within 3 months.
Benign	Clinical follow-up. Repeat FNA in case of local mininvasive surgery.
Low-risk indeterminate lesion	Repeat FNA within 6 months (rule-out chronic thyroiditis). Molecular and immunohistochemical tests. Possibly lobectomy in familial thyroid cancers or exposure to ionizing radiation.
High-risk indeterminate lesion	Lobectomy, molecular and immunohistochemical tests.
Suspicious of malignancy	Lobectomy or total thyroidectomy.
Malignant	Lobectomy or total thyroidectomy.

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References

1. Hossein, G. Changind Trends in Thyroid Practice: Understanding Nodular Thyroid Disease. *Endocr Pract.* **2004**, *10*, 31–39.
2. Ross, D.S. Editorial: Nonpalpable thyroid nodules–Managing an epidemic. *J. Clin. Endocrinol. Metab.* **2002**, *87*, 1938–1940.
3. Poller, D.N.; Baloch, Z.W.; Fadda, G.; Johnson, S.J.; Bongiovanni, M.; Pontecorvi, A.; Cochand-Priollet, B. Thyroid FNA: New classifications and new interpretations. *Cancer Cytopathol.* **2016**, *124*, 457–466. [CrossRef]
4. Straccia, P.; Rossi, E.; Bizzarro, T.; Brunelli, C.; Cianfrini, F.; Damiani, D.; Fadda, G. A meta-analytic review of the Bethesda System for Reporting Thyroid Cytopathology: Has the rate of malignancy in indeterminate lesions been underestimated? *Cancer Cytopathol.* **2015**, *123*, 713–722. [CrossRef]
5. Pusztaszeri, M.; Rossi, E.; Auger, M.; Baloch, Z.; Bishop, J.; Bongiovanni, M.; Chandra, A.; Cochand-Priollet, B.; Fadda, G.; Hirokawa, M.; et al. The Bethesda System for Reporting Thyroid Cytopathology: Proposed Modifications and Updates for the Second Edition from an International Panel. *Acta Cytol.* **2016**, *60*, 399–405. [CrossRef] [PubMed]
6. Nardi, F.; Basolo, F.; Crescenzi, A.; Fadda, G.; Frasoldati, A.; Orlandi, F.; Palombini, L.; Papini, E.; Zini, M.; Pontecorvi, A.; et al. Italian consensus for the classification and reporting of thyroid cytology. *J. Endocrinol. Investig.* **2014**, *37*, 593–599. [CrossRef]
7. Cross, P.; Chandra, A.; Giles, T.; Johnson, S.; Kocjan, G.; Poller, D.; Stephenson, T. Guidance on the Reporting of Thyroid Cytology Specimens. January 2016. Available online: http://www.ukeps.com/docs/thyroidfna.pdf (accessed on 1 August 2021).

8. Hirokawa, M.; Suzuki, A.; Higuchi, M.; Hayashi, T.; Kuma, S.; Ito, Y.; Miyauchi, A. The Japanese reporting system for thyroid aspiration cytology 2019 (JRSTAC2019). *Gland Surg.* **2020**, *9*, 1653–1662. [CrossRef]
9. Vanderlaan, P.A.; Marqusee, E.; Krane, J.F. Usefulness of Diagnostic Qualifiers for Thyroid Fine-Needle Aspirations with Atypia of Undetermined Significance. *Am. J. Clin. Pathol.* **2011**, *136*, 572–577. [CrossRef]
10. Johnson, D.N.; Cavallo, A.B.; Uraizee, I.; Tanager, K.; Lastra, R.R.; Antic, T.; A Cipriani, N. A Proposal for Separation of Nuclear Atypia and Architectural Atypia in Bethesda Category III (AUS/FLUS) Based on Differing Rates of Thyroid Malignancy. *Am. J. Clin. Pathol.* **2019**, *151*, 86–94. [CrossRef]
11. Vuong, H.G.; Ngo, H.T.T.; Bychkov, A.; Jung, C.K.; Vu, T.H.; Lu, K.B.; Kakudo, K.; Kondo, T. Differences in surgical resection rate and risk of malignancy in thyroid cytopathology practice between Western and Asian countries: A systematic review and meta-analysis. *Cancer Cytopathol.* **2020**, *128*, 238–249. [CrossRef]
12. Trimboli, P.; Fulciniti, F.; Paone, G.; Barizzi, J.; Piccardo, A.; Merlo, E.; Mazzucchelli, L.; Giovanella, L. Risk of Malignancy (ROM) of Thyroid FNA Diagnosed as Suspicious for Malignancy or Malignant: An Institutional Experience with Systematic Review and Meta-Analysis of Literature. *Endocr. Pathol.* **2020**, *31*, 52–56. [CrossRef] [PubMed]
13. Trimboli, P.; Crescenzi, A.; Castellana, M.; Giorgino, F.; Giovanella, L.; Bongiovanni, M. Italian consensus for the classification and reporting of thyroid cytology: The risk of malignancy between indeterminate lesions at low or high risk. A systematic review and meta-analysis. *Endocrine* **2019**, *63*, 430–438. [CrossRef] [PubMed]
14. Straccia, P.; Santoro, A.; Rossi, E.D.; Brunelli, C.; Mosseri, C.; Musarra, T.; Pontecorvi, A.; Lombardi, C.P.; Fadda, G. Incidence, malignancy rates of diagnoses and cyto-histological correlations in the new Italian Reporting System for Thyroid Cytology: An institutional experience. *Cytopathology* **2017**, *28*, 503–508. [CrossRef]
15. Cibas, E.S.; Ali, S.Z. The Bethesda system for reporting thyroid cytopathology. *Am. J. Clin. Pathol.* **2009**, *132*, 658–665. [CrossRef]
16. Ali, S.Z. *The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria and Explanatory Notes*; Springer: Cham, Switzerland, 2018.
17. Haugen, B.R.; Sawka, A.M.; Alexander, E.K.; Bible, K.C.; Caturegli, P.; Doherty, G.M.; Mandel, S.J.; Morris, J.C.; Nassar, A.; Pacini, F.; et al. American Thyroid Association Guidelines on the Management of Thyroid Nodules and Differentiated Thyroid Cancer Task Force Review and Recommendation on the Proposed Renaming of Encapsulated Follicular Variant Papillary Thyroid Carcinoma without Invasion to. *Thyroid* **2017**, *27*, 481–483. [CrossRef]
18. Sahli, Z.T.; Smith, P.W.; Umbricht, C.B.; Zeiger, M.A. Preoperative Molecular Markers in Thyroid Nodules. *Front. Endocrinol.* **2018**, *9*, 179. [CrossRef] [PubMed]
19. Nicholson, K.; Roberts, M.S.; McCoy, K.L.; Carty, S.E.; Yip, L. Molecular Testing Versus Diagnostic Lobectomy in Bethesda III/IV Thyroid Nodules: A Cost-Effectiveness Analysis. *Thyroid* **2019**, *29*, 1237–1243. [CrossRef] [PubMed]
20. Giorgadze, T.; Rossi, E.D.; Fadda, G.; Gupta, P.K.; Livolsi, V.A.; Baloch, Z. Does the fine-needle aspiration diagnosis of "hürthle-cell neoplasm/follicular neoplasm with oncocytic features" denote increased risk of malignancy? *Diagn. Cytopathol.* **2004**, *31*, 307–312. [CrossRef]
21. Poller, D.N.; Bongiovanni, M.; Trimboli, P. Risk of malignancy in the various categories of the UK Royal College of Pathologists Thy terminology for thyroid FNA cytology: A systematic review and meta-analysis. *Cancer Cytopathol.* **2020**, *128*, 36–42. [CrossRef]
22. Mitchell, A.L.; Gandhi, A.; Scott-Coombes, D.; Perros, P. Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. *J. Laryngol. Otol.* **2016**, *130*, S150–S160. [CrossRef]
23. Kakudo, K.; Kameyama, K.; Miyauchi, A.; Nakamura, H. Introducing the reporting system for thyroid fine-needle aspiration cytology according to the new guidelines of the Japan Thyroid Association. *Endocr. J.* **2014**, *61*, 539–552. [CrossRef]
24. Kakudo, K.; Kameyama, K.; Hirokawa, M.; Katoh, R.; Nakamura, H. Subclassification of Follicular Neoplasms Recommended by the Japan Thyroid Association Reporting System of Thyroid Cytology. *Int. J. Endocrinol.* **2015**, *2015*, 938305. [CrossRef]
25. Nikiforov, Y.E.; Seethala, R.R.; Tallini, G.; Baloch, Z.W.; Basolo, F.; Thompson, L.D.R.; Barletta, J.A.; Wenig, B.M.; Ghuzlan, A.A.; Kakudo, K.; et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors Yuri. *JAMA Oncol.* **2016**, *2*, 1023–1029. [CrossRef]
26. Haugen, B.R.; Alexander, E.K.; Bible, K.C.; Doherty, G.M.; Mandel, S.J.; Nikiforov, Y.E.; Pacini, F.; Randolph, G.W.; Sawka, A.M.; Schlumberger, M.; et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **2016**, *26*, 1–133. [CrossRef] [PubMed]
27. Bongiovanni, M.; Giovanella, L.; Romanelli, F.; Trimboli, P. Cytological Diagnoses Associated with Noninvasive Follicular Thyroid Neoplasms with Papillary-Like Nuclear Features According to the Bethesda System for Reporting Thyroid Cytopathology: A Systematic Review and Meta-Analysis. *Thyroid* **2019**, *29*, 222–228. [CrossRef] [PubMed]
28. Strickland, K.C.; Howitt, B.E.; Marqusee, E.; Alexander, E.K.; Cibas, E.S.; Krane, J.F.; Barletta, J.A. The Impact of Non-Invasive Follicular Variant of Papillary Thyroid Carcinoma on Rates of Malignancy for Fine Needle Aspiration Diagnostic Categories. *Thyroid* **2015**, *25*, 987–992. [CrossRef]
29. Parente, D.N.; Kluijfhout, W.P.; Bongers, P.J.; Verzijl, R.; Devon, K.M.; Rotstein, L.E.; Goldstein, D.P.; Asa, S.; Mete, O.; Pasternak, J.D. Clinical Safety of Renaming Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: Is NIFTP Truly Benign? *World J. Surg.* **2018**, *42*, 321–326. [CrossRef]
30. Kopczyński, J.; Suligowska, A.; Niemyska, K.; Palyga, I.; Walczyk, A.; Gąsior-Perczak, D.; Kowalik, A.; Hińcza, K.; Mężyk, R.; Góźdź, S.; et al. Did Introducing a New Category of Thyroid Tumors (Non-invasive Follicular Thyroid Neoplasm with Papillary-

like Nuclear Features) Decrease the Risk of Malignancy for the Diagnostic Categories in the Bethesda System for Reporting Thyroid Cytopathology? *Endocr. Pathol.* **2020**, *31*, 143–149. [CrossRef] [PubMed]
31. Ventura, M.; Melo, M.; Fernandes, G.; Carrilho, F. Risk of Malignancy in Thyroid Cytology: The Impact of the Reclassification of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP). *Endocr. Pract.* **2019**, *25*, 642–647. [CrossRef] [PubMed]
32. Vuong, H.G.; Tran, T.T.; Bychkov, A.Y.; Jung, C.K.; Nakazawa, T.; Kakudo, K.; Katoh, R.Y.; Kondo, T. Clinical Impact of Non-Invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features on the Risk of Malignancy in the Bethesda System for Reporting Thyroid Cytopathology: A Meta-Analysis of 14,153 Resected Thyroid Nodules. *Endocr. Pract.* **2019**, *25*, 491–502. [CrossRef]
33. Lloyd, R.V.; Osamura, R.Y.; Klöppel, G.R.J. *WHO Classification of Tumours of Endocrine Organs*; WHO: Lyon, France, 2017.
34. Fadda, G.; Rossi, E.D.; Raffaelli, M.; Pontecorvi, A.; Sioletic, S.; Morassi, F.; Lombardi, C.P.; Zannoni, G.F.; Rindi, G. Follicular thyroid neoplasms can be classified as low- and high-risk according to HBME-1 and Galectin-3 expression on liquid-based fine-needle cytology. *Eur. J. Endocrinol.* **2011**, *165*, 447–453. [CrossRef]