Non-Neoplastic and Indeterminate Thyroid Lesions

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3.1 Non-Neoplastic Thyroid Lesions

3.1.1 Nondiagnostic Cytology

In approximately 15% of cases, fine-needle aspiration cytology (FNAC) results in a cytologically inadequate specimen. Nondiagnostic (or unsatisfactory) smears have an inadequate number of cells to allow a diagnosis, due to cystic fluid without cells, bloody smears or improper techniques in preparing slides. This category also includes thyroid cystic lesions, which are a frequent cause of inadequate results [1, 2].

The risk of malignancy for a nodule with nondiagnostic cytology is 1–4% [1].

In the case of an initial nondiagnostic cytology result, FNAC should be repeated with ultrasound (US) guidance and, if available, on-site cytologic evaluation. If the result is still nondiagnostic, close observation or diagnostic surgery may be considered [3].

Surgery is recommended if the nodule has clinical risk factors for malignancy, highly suspicious US features, growth >20% (in two dimensions, detected during US surveillance), or based on compressive symptoms and cosmetic concerns [3].

Percutaneous ethanol injection may be considered in cystic nodules with no suspicion of malignancy [3].

3.1.2 Benign Cytology

Benign diagnosis represents the most frequent result following FNAC, with a rate of 70%. The most common benign lesions are macrofollicular or adenomatoid/

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hyperplastic nodules, colloid adenomas, nodular goiter, lymphocytic and granulomatous thyroiditis [1, 2]. The risk of malignancy in this category is 0–3% [1].

In nodules with benign cytology, further immediate diagnostic evaluations or treatment are not required. The follow-up of these lesions is mainly determined on the basis of the US features and secondarily according to the nodule growth [3]. In benign nodules with highly suspicious US characteristics, US and FNAC should be repeated within 12 months [3]. In lesions with low or intermediate suspicious US features, repeat US is recommended at 12–24 months. In the case of US evidence of new suspicious characteristics or growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume), FNAC may be performed or follow-up may be continued with US, repeating FNAC only in the case of continued growth [3]. In nodules with very low suspicion US features, the utility of follow-up with US in order to assess the nodule growth, as an indicator for the repetition of FNAC, is limited. In these cases, if US is repeated, it should be performed at 24 months or more [3]. Follow-up is no longer indicated for a nodule undergoing repeat FNAC with a second benign cytology result [3].

Regarding therapy, routine TSH suppression treatment is not recommended. Surgery may be indicated for growing nodules that are benign after repeat FNAC if they are larger than 4 cm, in the case of structural or compressive symptoms or on the basis of clinical concern [3].

3.2 Indeterminate Thyroid Lesions

In approximately 20–25% of cases, FNAC leads to the diagnosis of indeterminate thyroid nodule. This result represents a clinical issue, since malignancy, although relatively low (up to 30%), cannot be ruled out with certainty. In this context, surgery, when indicated, has a diagnostic rather than therapeutic purpose, with almost 80% of surgical procedures being unnecessary [1–3].

The inability to assess any vascular or capsular invasion, which is the cornerstone of the diagnosis of differentiated thyroid carcinoma, is the main limitation of FNAC, which decreases its overall diagnostic accuracy [1, 2].

In order to solve the problem of unnecessary surgery without missing potentially malignant nodules, in the Bethesda System for Reporting Thyroid Cytology (BSRTC), proposed by the United States National Cancer Institute (NCI), indeterminate lesions were divided into category III or AUS/FLUS (atypia of undetermined significance or follicular lesion of undetermined significance) and category IV or FN/SFN (follicular neoplasms or suspicious for a follicular neoplasm), with different expected malignancy rates and therefore different management options [1].

The FLUS/AUS category is represented by lesions with focal architecture or nuclear atypia whose significance cannot be further determined and specimens that are limited due to poor fixation or obscuring blood [1]. The FN/SFN category includes cellular aspirates composed of follicular cells arranged in an altered architectural pattern characterized by cell crowding and/or microfollicle formation and

lacking nuclear features of papillary carcinoma or composed almost exclusively of oncocytic (Hürthle) cells [1].

The risk of malignancy is 5–15% for the AUS/FLUS category and 15–30% for the FN/ SFN category [1].

In the case of AUS/FLUS cytology, repeat FNA or molecular testing can be considered in order to integrate the malignancy risk evaluation. If either of them is not performed or inconclusive, on the basis of clinical risk factors, US features and patient preference, either surveillance or diagnostic surgery may be indicated [3].

Diagnostic surgery represents the long-established standard of care for nodules with FN/SFN cytology. However, after the consideration of clinical risk factors and US characteristics, molecular testing may be utilized to integrate the evaluation of malignancy risk [3].

The classification and malignancy rate of indeterminate nodules according to the BSRTC and the management recommended by the 2015 American Thyroid Association guidelines are summarized in Table 3.1.

As regards surgery, patients with thyroid nodular disease with indeterminate cytology may be subjected to total thyroidectomy or hemithyroidectomy. The choice between these two procedures depends on several factors: familial history of differentiated thyroid carcinoma, nodule size greater than 4 cm, highly suspicious US characteristics, previous radiation exposure and positivity for known molecular alterations specific for differentiated thyroid carcinoma. Furthermore, all these factors must be further associated with the possible coexistence of hyperthyroidism, the presence of bilateral nodules, the patient's medical comorbidities and the patient's preference [3].

If an intermediate or high-risk differentiated thyroid carcinoma is diagnosed after hemithyroidectomy, through final histopathological examination, it is recommended to perform a completion thyroidectomy, as hemithyroidectomy is considered oncologically inadequate in these cases [3].

It is important to emphasize that, even in the most experienced hands and in high-volume centers, thyroidectomy can lead to serious complications, including hypoparathyroidism, recurrent laryngeal nerve injury and postoperative cervical hematoma. These complications lead to a reduction in the quality of life of the patients and increased costs for healthcare systems [4]. For these reasons, there is an

Table 3.1 Indeterminate thyroid lesions: classification[a], malignancy rate[a], and management[b]

Bethesda category	Diagnostic category	Malignancy rate	Management
III	Atypia of undetermined significance or follicular lesion of undetermined significance	5–15%	Repeat FNAC Molecular testing Surveillance/surgery
IV	Follicular neoplasms or suspicious for a follicular neoplasm	15–30%	Surgery (molecular testing)

FNAC fine-needle aspiration cytology

[a] According to the Bethesda System for Reporting Thyroid Cytopathology

[b] Recommended by the 2015 American Thyroid Association guidelines

increased emphasis on assessing the risk of malignancy of indeterminate nodules in order to minimize unnecessary surgical procedures.

As already mentioned, the application of molecular testing on cytological samples can provide a more precise assessment of the risk of malignancy in indeterminate nodules and a more accurate preoperative estimation of the aggressiveness of the neoplasm. Thus, these tests can help to avoid unnecessary surgery for benign nodules and distinguish more aggressive thyroid cancers that need to undergo total thyroidectomy rather than hemithyroidectomy. However, none of the available tests can decisively confirm the presence of malignancy, nor precisely establish its aggressiveness [5].

Recent progress in omics approaches (genomics, transcriptomics, proteomics and metabolomics) is improving the understanding of molecular alterations associated with thyroid cancer initiation and progression, allowing the detection of new biomarkers of malignancy that are useful for the management of indeterminate nodules [6–9]. In this context, a growing body of evidence is accumulating on the use of liquid biopsy for the diagnosis of thyroid carcinoma, as already occurs in many other tumor types (e.g., lung cancer). It represents a noninvasive approach that analyses biomarkers released by cancer cells (e.g., circulating free nucleic acids, proteins or metabolites) and detectable in body fluids (e.g., serum, saliva or urine) [9–13].

Finally, the development of modern techniques of artificial intelligence allows the elaboration of complex diagnostic algorithms to improve the accuracy of preoperative diagnosis. Also this approach, integrating clinical (e.g., age, sex and familial history), laboratory (e.g., serum thyroglobulin and thyroid autoantibodies), US, cytological and molecular features may help to differentiate between malignant and benign thyroid nodules in the case of indeterminate cytology [14, 15].

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