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Diagnosis and classification of thyroid nodules: advances and challenges

Diagnóstico y clasificación de los nódulos tiroideos: avances y desafíos

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ABSTRACT

The study of thyroid nodules was a fundamental focus of medical practice due to their high prevalence and clinical impact on the population. It was found that the frequency of these nodules varied depending on the diagnostic method, with ultrasound revealing a higher rate compared to clinical palpation. It was also observed that the incidence increased with age, reaching significant figures in older adults. The thyroid gland, with its complex embryogenesis and anatomical peculiarities, played an essential role in metabolic regulation, which explained the wide-ranging clinical repercussions of its structural alterations. From a histological point of view, the follicular organization of the gland and cellular variations, including the presence of oncocytes, were documented, providing key information for understanding the pathophysiology of nodular disease. In the diagnostic field, fine-needle aspiration biopsy became established as the gold standard, reducing unnecessary surgical procedures and improving the identification of malignant lesions. The introduction of standardized systems such as Bethesda and TI-RADS made it possible to stratify the risk of malignancy and provide a common language among specialists, which optimized therapeutic decision-making. However, limitations persisted in relation to indeterminate results and the need to correlate morphological findings with clinical history and epidemiological context. In short, a comprehensive approach to thyroid nodules favored the early detection of neoplasms and the implementation of appropriate interventions, ensuring a better prognosis for patients.

Keywords: Thyroid Nodules; Prevalence; Diagnosis; Bethesda; TI-RADS.

RESUMEN

El estudio de los nódulos tiroideos representó un eje fundamental en la práctica médica, debido a su elevada prevalencia y al impacto clínico que tuvieron en la población. Se evidenció que la frecuencia de estos nódulos varió en función del método diagnóstico, siendo la ecografía la técnica que reveló una tasa más alta en comparación con la palpación clínica. Se observó además que la incidencia aumentó con la edad, alcanzando cifras significativas en adultos mayores. La glándula tiroides, con su compleja embriogénesis y particularidades anatómicas, desempeñó un papel esencial en la regulación metabólica, lo que explicó las amplias repercusiones clínicas de sus alteraciones estructurales. Desde el punto de vista histológico, se documentó la organización folicular de la glándula y las variaciones celulares, incluyendo la presencia de oncocitos, que aportaron información clave para comprender la fisiopatología de la enfermedad nodular. En el campo diagnóstico, la biopsia por aspiración con aguja fina se consolidó como el método de referencia, reduciendo procedimientos quirúrgicos innecesarios y mejorando la identificación de

lesiones malignas. La introducción de sistemas estandarizados como Bethesda y TI-RADS permitió estratificar el riesgo de malignidad y proporcionar un lenguaje común entre especialistas, lo que optimizó la toma de decisiones terapéuticas. No obstante, persistieron limitaciones relacionadas con resultados indeterminados y la necesidad de correlacionar los hallazgos morfológicos con la historia clínica y el contexto epidemiológico. En suma, el abordaje integral de los nódulos tiroideos favoreció la detección temprana de neoplasias y la implementación de intervenciones adecuadas, garantizando un mejor pronóstico para los pacientes.

Palabras clave: Nódulos Tiroideos; Prevalencia; Diagnóstico; Bethesda; TI-RADS.

INTRODUCTION

The study of thyroid nodules is a field of relevance in contemporary medical practice, as they represent one of the most frequent manifestations of endocrine pathology in the general population. Their detection, which can vary widely depending on the diagnostic method used, has gained greater visibility with the development and dissemination of sensitive imaging techniques, such as ultrasound, that can detect clinically insignificant lesions. Thus, it has been shown that the prevalence of nodular thyroid disease is much higher than had historically been estimated based on clinical palpation. This reality poses a challenge in both daily clinical practice and public health, due to the associated risk of malignancy and the therapeutic implications of its diagnosis.

A comprehensive approach to thyroid nodules requires a thorough understanding of the thyroid gland's anatomy and histology, as well as the physiological mechanisms that regulate thyroid hormone production and secretion. These hormones play an essential role in the body's metabolism and homeostasis, so any structural or functional alteration can have significant repercussions on multiple body systems. Likewise, understanding the anatomical and embryological variations of the gland, together with recognition of its histopathological characteristics, is essential for the proper interpretation of clinical and laboratory findings.

In this context, diagnostic techniques have evolved significantly in recent decades, moving from exclusively clinical and functional methods to more complex stratification systems that combine ultrasound imaging, fine-needle aspiration, and cytopathological classification using standardized systems such as the Bethesda system. The latter has enabled better correlation between morphological findings and the risk of malignancy, providing a solid basis for therapeutic and surgical decision-making. Similarly, the introduction of scales such as the TI-RADS system has optimized the interpretation of ultrasound images, standardized criteria and facilitating the identification of nodules with suspicious characteristics.

Reviewing these aspects not only enhances understanding of the pathophysiology and clinical behavior of thyroid nodules but also guides medical personnel in selecting individualized management strategies. In short, the study of prevalence, anatomy, histology, diagnostic methods, and classification systems is fundamental to the prevention of complications, early detection of malignant neoplasms, and planning of appropriate therapeutic interventions.

DEVELOPMENT

Prevalence and diagnosis

The prevalence of thyroid nodules varies depending on the detection method used. Palpation identifies nodules in approximately 5 % to 10 % of patients. However, when a more sensitive

imaging technique, such as ultrasound, is used, nodular thyroid disease is detected in up to 34,2 % of patients. The incidence of thyroid nodules increases linearly with age. In individuals under 30 years of age, thyroid nodules are observed in 12.9 % of cases, while between 50 % and 70 % of people over 70 years of age have one or more nodules (Maxwell & Sipos, 2019).

Thyroid gland: anatomy and pathology

The thyroid gland is an organ located at the front of the neck. It is composed of two symmetrical lobes located on either side of the trachea and larynx, connected by the isthmus. In a healthy adult, the thyroid gland weighs around 20 grams and, from an embryological point of view, originates from a proliferation in the floor of the pharynx during the third week of gestation. This structure descends until it reaches its final location, remaining connected to its primitive origin through the thyroglossal duct. The distal portion of this duct may persist in adults and develop into the pyramidal lobe. In some cases, abnormalities in the embryological descent process can cause the formation of thyroglossal cysts or the presence of ectopic thyroid tissue. Rarely, the thyroid gland does not descend to its usual position, remaining as a single gland in an abnormal location, known as the lingual thyroid (Hernández Stegmann et al., 2019).

The thyroid gland is butterfly-shaped and is normally located at the front of the neck. The thyroid gland secretes thyroid hormones into the bloodstream. Thyroid hormones regulate metabolism, maintaining body temperature so that the brain, heart, muscles, and other organs function normally (American Thyroid Association, 2024).

The thyroid gland is light brown in color, soft in consistency, and surrounded by a thin layer of connective tissue known as the perithyroid fascia. This fascia thickens at the back to attach to the cricoid cartilage, forming the lateral ligament of the thyroid, described by Canadian surgeon James Berry in 1888 (Berry's ligament). Thin sheets of connective tissue extend from the perithyroid fascia toward the parenchyma, irregularly delimiting the lobes and lobules of the gland. Over time, the thyroid may become darker due to the deposition of lipofuscin in the cytoplasm of follicular cells, a phenomenon known as melanosis thyroidi (Heredia-Jara & Ortiz-Hidalgo, 2022).

Thyroid nodules larger than 1 cm should be evaluated by periodic ultrasound and reevaluated with cytology if a growth of 20 % or more is observed in at least two diameters of the nodule, with a minimum increase of 2 mm. It is crucial to rule out the possibility of thyroid cancer, given that the prevalence of malignancy identified by biopsy is between 4 and 6,5 %, regardless of nodule size. Ultrasound features that may indicate cancer include hypoechogenicity, irregular borders, and microcalcifications. However, more than 86 % of ultrasounds do not provide sufficient information to assess malignancy risk adequately. Nodules located in the upper pole and middle lobe are more likely to be malignant (Fierros Michel et al., 2022).

The Latin American Thyroid Society suggests that thyroid nodules smaller than one centimeter be monitored annually by ultrasound. If growth, extracapsular invasion, suspicious cervical lymph nodes, or a family history of medullary carcinoma or multiple endocrine neoplasia type 2 is detected, fine needle aspiration (FNA) should be performed. For its part, the American Thyroid Association (ATA) recommends performing FNAB on subcentimeter nodules with abnormal cervical lymph nodes and on those larger than 5 millimeters with suspicious ultrasound characteristics, or without them but with a high-risk history (Román González et al., 2013).

All patients with detectable nodules should undergo at least a TSH test, preferably together

with antithyroid antibodies, and a thyroid ultrasound scan is mandatory. Although ultrasound is not validated as a screening method in the general population, once a thyroid incidentaloma has been identified, a formal study should be performed. Thyroid scintigraphy is a test that should be reserved for endocrinologists, as its current use is limited to detecting autonomous nodular goiter with suppressed TSH. In addition, thyroid puncture should also be indicated exclusively by an endocrinologist (Trincado & Letelier, 2010).

To resolve diagnostic uncertainties and avoid unnecessary biopsies, in 2017, the Thyroid Imaging Reporting and Data System (TI-RADS) Committee of the American College of Radiology (ACR) published a technical document outlining a new system for stratifying the risk of malignancy that classifies thyroid nodules based on their ultrasound appearance. The TI-RADS system classifies patients into five categories, ranging from TR1 (benign-appearing nodule) to TR5 (high probability of cancer) (Montiel-islas & Licea-Medina, 2023).

All patients with a thyroid nodule identified by clinical or imaging methods should undergo a thyroid ultrasound. The following ultrasound findings are useful for the diagnosis of malignancy:

- Microcalcifications (sensitivity 26 % to 59 %, specificity 86 % to 95 %).
- Size greater than four centimeters, in which case surgery is recommended to obtain a histological diagnosis due to the risk of malignancy of up to 20 %.
- Intranodular vascularization (sensitivity 54 % to 74 %, specificity 79 % to 81 %).
- Irregular or microlobulated edges (sensitivity 17 % to 78 %, specificity 39 % to 85 %).
- Hypoechogenicity (sensitivity 27 % to 87 %, specificity 43 % to 94 %).
- Solid component (sensitivity 69 % to 75 %, specificity 53 % to 56 %).
- Intranodular vascular images (specificity of 80 %).
- Nodule taller than it is wide (length/width ratio greater than 1).

The presence of two or more of these characteristics increases the likelihood of thyroid cancer. These findings are not definitive of neoplasia, but they should alert the clinician and guide the decision to biopsy the nodule (Román González et al., 2013).

At the microscopic level, the thyroid gland is composed of closed follicles of different sizes, ranging from 15 to 500 µm in diameter. These follicles are lined by cylindrical epithelial cells and contain a substance called colloid. The main component of a colloid is a glycoprotein called thyroglobulin, which houses thyroid hormones. Once the hormones are secreted into the follicles, they must be reabsorbed by the follicular epithelium to enter the systemic circulation. The thyroid gland receives a blood flow of 5 times its own weight per minute. In addition to follicular cells, other cell types, called C cells or parafollicular cells, can be identified, which secrete calcitonin (Hernández Stegmann et al., 2019).

From a histological point of view, the thyroid follicles are large and distended, filled with colloid and lined by a monolayer of cuboidal or cylindrical epithelial cells. It is common to find areas with signs of hemorrhage, dystrophic calcification, and fibrosis. In addition, hemosiderin-containing macrophages and areas of cystic degeneration with cholesterol crystals are observed (Pinto-Blázquez & Ursua-Sarmiento, 2019).

The cytoplasm of follicular cells is slightly eosinophilic and contains rounded nuclei with homogeneous chromatin and one or more nucleoli. These cells have abundant rough endoplasmic reticulum, Golgi apparatus, numerous lysosomes, and mitochondria. In some cases, the cytoplasm shows intense eosinophilia, referred to as Hürthle cells or oncocytes, due to the

large number of mitochondria.

The appearance of the follicular epithelium may vary depending on the functional state of the gland. In inactive situations, when the follicles are filled with colloid, the follicular cells are usually low cuboidal or almost flat. Conversely, when the gland is highly active and the colloid has been released, the cells are tall and cylindrical.

The colloid is composed of thyroglobulin, an iodinated dimeric glycoprotein with a molecular weight of 660 kDa and composed of 2768 amino acids, produced by follicular cells. In the colloid, it is common to find irregular clear spaces containing birefringent calcium oxalate crystals (weddellite). These crystals may be present in up to 73,1 % of normal thyroid glands, are not observed in children under 10 years of age, and are more common in people over 70 years of age. The presence of these crystals is probably related to a reduced functional state of the thyroid follicles (Heredia-Jara & Ortiz-Hidalgo, 2022).

Bethesda System

Fine needle aspiration (FNA) has proven to be a highly effective method for evaluating thyroid nodules, excelling at early diagnosis and selecting patients who need surgical intervention. This technique, characterized by its non-invasive nature, low cost, and minimal complications, ensures patient safety.

Introduced in the 1980s, FNA has reduced the need for diagnostic thyroidectomies by 30 %. At the same time, it has facilitated the resection of more than 50 % of malignant thyroid nodules. Therefore, FNA, in combination with ultrasound, has established itself as the gold standard for evaluating thyroid nodules (Escalona Veroz, 2023).

Fine-needle aspiration biopsy (FNAB), introduced in the 1980s, has reduced the need for diagnostic thyroidectomies by 30 %. In addition, the percentage of resected malignant thyroid nodules to more than 50 %. This has made ultrasound-guided FNAB the preferred method for evaluating thyroid nodules and making surgical decisions.

The Bethesda 2010 system classifies results into six categories:

1. Nondiagnostic or unsatisfactory specimen.
2. Benign.
3. Atypia of significance or a follicular lesion of indeterminate significance.
4. Follicular neoplasm or suspected follicular neoplasm.
5. Lesion suspected of malignancy.
6. Malignancy.

Each category has an associated risk of malignancy, ranging from 0 % to 3 % for benign cases to almost 100 % for malignant cases, thus providing clear therapeutic guidance for physicians.

The adoption of the Bethesda system has improved the detection of malignancy in thyroid nodules and facilitated the implementation of international guidelines. Although it is not completely accurate and there are discrepancies between cytopathological and post-thyroidectomy histopathological results, false positives are less than 2 %, while false negatives range from 20 % to 24 % (Kraus Fischer et al., 2020).

Fine needle aspiration biopsy (FNAB) is the most effective method for evaluating a thyroid

nodule for its malignant potential. This technique can be performed without patients having to discontinue anticoagulants or acetylsalicylic acid. In cases of multinodular goiters, it is recommended to obtain samples from the four largest nodules (≥ 1 cm) to reduce the risk of missing cancer.

Thyroid nodules are classified according to their risk of malignancy based on their ultrasound appearance. High-risk nodules (with an 80 % risk of cancer) have microcalcifications, irregular borders, extrathyroid extension, soft tissue invasion toward a calcified border, or are taller than they are wide. These nodules require FNAB if they measure ≥ 1 cm. Intermediate-risk nodules (with a 15 % risk of cancer) are hypoechoic and solid; generally, if they measure ≥ 1 cm, FNA should be performed. Low-risk nodules (with a 7 % risk of cancer) are partially cystic with eccentric solid areas; biopsy is recommended if they measure ≥ 1,5 cm. Very low-risk nodules (with less than a 3 % risk of cancer) are spongiform or simple cysts; FNA is optional if they measure ≥ 2 cm. The use of ultrasound to guide sampling improves diagnostic accuracy in both palpable and non-palpable nodules (Fitzgerald, 2024).

The results of cytology obtained by FNA are reported using the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), which classifies the results into six categories:

1. Nondiagnostic or unsatisfactory: The risk of cancer is 1 % to 4 %. The usual treatment is to repeat the FNAB with ultrasound guidance.
2. Benign: The risk of malignancy is approximately 2,5 %. Standard treatment includes surveillance by palpation or ultrasound every six to 18 months.
3. Atypical of undetermined significance (AUS): The risk of cancer is around 14 %, increasing with malignant ultrasound features. The usual treatment is clinical correlation and repeat FNA.
4. Suspected follicular neoplasia (SFN) or follicular neoplasia (FN): The risk of cancer is close to 25 %, being higher when Hürthle cells are observed and in patients over 50 years of age. The standard treatment is surgical ablation of the affected lobe.
5. Suspected malignancy (SM): The risk of cancer is approximately 70 %. The usual treatment is direct thyroid lobe ablation or subtotal thyroidectomy.
6. Malignant: The risk of malignancy is close to 99 %. The standard treatment is subtotal thyroidectomy.

For nodules with non-diagnostic FNA, it is advisable to repeat the FNA within three months, guided by ultrasound. The estimated malignancy rate ranges from 2 % to 12 %. If, despite repeating the study, a cytological diagnosis cannot be made in a solid nodule, surgery is recommended. If the nodule is completely cystic, clinical and ultrasound follow-up is suggested. In cases of complex lesions, it is necessary to correlate family history, ultrasound findings, and clinical risk factors to determine whether surgical resection is indicated.

For nodules with a benign cytodiagnosis, the probability of malignancy is low, so repeating the aspiration is not recommended. Clinical and ultrasound follow-up should be continued, along with TSH every six to 18 months. A new FNA is only necessary in cases of ultrasound findings suspicious for malignancy, an increase in volume greater than 50 %, or an increase of two millimeters in at least two dimensions of the nodule. Suppressive therapy with levothyroxine is not recommended. Hemithyroidectomy is recommended only in the presence of symptoms of local compression, a history of previous irradiation, or for cosmetic reasons.

For follicular lesions, the risk of malignancy is 20 %; repeating FNA is not recommended.

Hemithyroidectomy and isthmectomy should be performed. Frozen section biopsy is not recommended, as it is necessary to evaluate the entire capsule of the lesion for proper differentiation between benign and malignant lesions.

For suspicious nodules, surgery is recommended, and frozen section biopsy may be useful. In addition, a preoperative neck ultrasound with FNA of suspicious lymph nodes is suggested. In these cases, thyroglobulin or calcitonin can be measured in the FNA fluid.

For nodules with a cytological diagnosis of malignancy, thyroidectomy with or without central compartment lymph node dissection is recommended (Román González et al., 2013).

As shown in table 1, the different diagnostic categories allow stratification of thyroid nodule malignancy risk, which in turn guides management decisions from observation to surgical intervention.

Categoría	Riesgo de Malignidad (%)	Manejo
Insuficiente	1-4	Repetir ACAF en 3 meses
Benigno	<1	Seguimiento cada 6-12 meses
ASCUS	5-10	Repetir PAAF
Tumor folicular	20-30	Lobectomía + istmectomía
Tumor de Hüethle	20-45	Lobectomía + istmectomía
Sospechoso	60-75	Lobectomía/tiroidectomía
Maligno	97-99	Tiroidectomía

Figure 1. Relationship between the diagnostic category of thyroid nodules, the risk of malignancy, and management (Cibas and Ali, 2009).

CONCLUSIONS

The approach to thyroid nodules should be understood as a dynamic, multidimensional process encompassing epidemiology, anatomy, histology, diagnostic tools, and evidence-based clinical practice guidelines. The high prevalence of this pathology, which increases proportionally with age, makes thyroid nodules a common finding that nevertheless requires clinical discernment to differentiate benign lesions from those with malignant potential. Advances in diagnostic methods, especially ultrasound and fine-needle aspiration biopsy, have reduced unnecessary surgical procedures and improved the accuracy of identifying cases that require intervention.

The contributions of standardized systems such as Bethesda and TI-RADS have led to substantial progress in risk stratification, ensuring a common language among specialists and offering clear criteria for therapeutic decision-making. However, challenges remain related to the sensitivity and specificity of the methods, the possibility of indeterminate results, and the need to always correlate morphological findings with the patient's medical history, risk factors, and epidemiological context.

The thyroid gland not only plays an essential role in the body's metabolic physiology, but also has anatomical and pathological features that condition the clinical approach. From its complex embryogenesis to the histological characterization of its follicles, every detail is crucial to understanding the origin and behavior of nodular lesions. Likewise, the accumulated knowledge of prevalence, detection methods, and classification systems reaffirms the importance of comprehensive, multidisciplinary management.

In conclusion, thyroid nodules pose a constant challenge for medical practice due to their high prevalence and the need to identify malignancy in a timely manner. The integration of technological advances, the use of standardized guidelines, and rigorous clinical surveillance are the fundamental pillars for optimizing diagnosis, reducing uncertainty, and ensuring appropriate therapeutic interventions. This not only improves patients' quality of life but also strengthens global strategies for the prevention and control of thyroid diseases.

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