Introduction

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma. Thyroid nodules are prevalent in up to 68 % of randomly selected individuals in whom high resolution ultrasound is performed. The majority of nodules are benign. Thyroid nodules are the clinical manifestation of a myriad of pathologic processes. The use of ultrasound has dramatically reduced the number of patients who undergo surgery for nodules. Several risk scoring systems have been developed which aim to reduce interobserver variability and allow clinicians to make decisions regarding further workup and follow-up. The most useful of these is the Thyroid Imaging Reporting and Data System (TIRADS) classification. The six tier Bethesda scoring system has reduced variability and increased the ability to clinicians to guide patients with thyroid nodules. There is good correlation between cytology and histopathologic outcomes. A significant proportion of patients will however fall into an indeterminate category. The American Thyroid Association uses a different system based on an estimated risk of malignancy from centers that deal with a high volume of patients with thyroid nodules and malignancy. The availability of molecular markers enhanced with next generation sequencing technology and the expression classifier are added diagnostic aids that can help in management. However, these are not available in many countries and in resource limited settings. A pragmatic approach to the diagnosis of indeterminate nodules includes utilizing pre- and posttest probability, clinical acumen, correlation of ultrasound findings and expert opinion in some settings. Using this approach high risk patients can be appropriately chosen for surgery while relegating patients with lower risk to watchful follow-up.

Keywords: thyroid; ultrasound; Bethesda scoring; follicular neoplasm; indeterminate nodule; Thyroid Imaging Reporting and Data System; review
by thyroid cells to divide. Most nodules are detected incidentally. Symptoms of growth and invasion such as dysphagia, dystonia, and stridor are rare. Bleeding into the nodule occurs rarely and presents with increase in size pain and tenderness or even transient thyrotoxicosis. The incidence of thyroid cancer is increasing rapidly and currently appears to be the most rapidly increasing malignancy among men and women in the general population [8]. This appears to be a worldwide phenomenon [9]. The clinician’s approach to the thyroid nodule over the years is to primarily distinguish the small number of nodules that harbor a malignancy from the majority that do not. At autopsy, up to 30 % of thyroid glands will harbor malignant nodules which are under 1 cm (microcarcinomas); many but not all of these will have an indolent course [10]. The approach to the thyroid nodule has been muddled by the lack of standardization of both imaging and cytologic techniques. The availability of high-frequency USG and the development of risk scores that can quantify the risk of thyroid malignancy is a significant advance that has demystified decision-making in thyroid nodules. Several USG features have been identified in multivariate analysis as associated with malignancy, specifically papillary cancer of the thyroid. These include the presence of microcalcifications and nodule hypoehochogenicity when compared with strap muscles, irregular margins, shape taller than wide on transverse view, central vascularity [11]. Follicular thyroid cancer has somewhat different features. They are more often iso- or hyperechoic, noncalcified, and regular smooth margins [12]. Some features on USG are associated with a low risk of differentiated thyroid cancer. A spongiform appearance defined as the aggregation of multiple microcystic components in more than 50 % of the nodule is strongly suggestive of a benign nodule [13]. Other USG features include hypoechogenicity, large coarse calcification, peripheral calcifications, puff pastry appearance, and comet tail shadowing.

**Thyroid Imaging Reporting and Data System (TIRADS) classification**

Several risk scoring systems have been developed which aim to reduce interobserver variability and allow clinicians to make decisions regarding further workup and follow-up. The most useful of these is the Thyroid Imaging Reporting and Data System (TIRADS) classification. Similar to the Breast Imaging-Reporting and Data System for breast lesion, the TIRADS system allows the user understand and explain to the patient the risk of malignancy in a nodule and the need for further workup including aspiration [14]. The TIRADS system correlates exceptionally well with the Bethesda system for cytology [15]. The American Thyroid Association uses a different system based on an estimated risk of malignancy from centers that deal with a high volume of patients with thyroid nodules and malignancy [1]. There is a significant correlation between both systems. However, some nodules that do not meet the criteria for malignancy in the American Thyroid Association guidelines appeared have increased risk of malignancy (18.2 %) [16].

USG-guided cytology and the standardization of interpretation of thyroid cytology has reduced ambiguity. The diagnostic groups reported under the six-tiered Bethesda system for reporting thyroid cytopathology have gained widespread acceptance [17]. Several factors contribute to nondiagnostic specimens including nodule component and the fine-needle aspiration cytology (FNAC) technique. Adequate specimens are categorized as benign, malignant, or indeterminate with the latter being divided into three specific categories each correlating with a different malignancy risk. These include atypia of undetermined significance, follicular or Hurthle cell neoplasms, and suspicious for malignancy [18]. 2–3 % of benign nodules as determined by FNAC will subsequently prove to be malignant [19]. Conversely, the same number of malignant nodules on FNAC will prove to be benign [20]. Large studies showed a high degree of concordance between the system and pathology, especially in the definitively benign and the definitively malignant categories with variability in the intermediate categories.

The indeterminate thyroid nodule will be defined as those nodules that have after an initial evaluation (history, physical examination, ultrasound, and FNAC) have received Bethesda classification of either III, IV, or V (BIII, BIV, and BV). This indeterminate category falls into a malignancy risk between 5 % and 75 % and represents up to 40 % of all FNACs. Cytologically indeterminate thyroid nodules are associated with a broad range (5–75 %) of malignant risk and accurately informing definitive management poses a challenge. Advancements in molecular testing of fine-needle aspiration biopsies have improved preoperative diagnostic accuracy and prognostication. For indeterminate nodules, such testing ideally will reduce the need for surgery for benign nodules and potentially guide appropriate extent of initial surgery for malignancy [21].

The association of gene mutations and translocation fusions with thyroid cancer has been described extensively [22]. Over the years, several markers of malignancy have been evaluated. Many of the early markers were suboptimal for clinical use. Panels of markers have been developed to improve efficiency and accuracy and commercialized. The Afirma Gene Expression Classifier (GEC) (Veracyte, Inc., South San Francisco, California, USA) uses microarray technology to analyze mRNA expression of 167 different genes, 142 of which are commonly, and 25 which are uncommonly seen with thyroid cancer. Only BIII and BIV are accepted for analysis and generate two possible results, benign and suspicious. In the BIII and BIV setting, the GEC has negative predictive value (NPV) of 95 and 94 %, respectively. In the BV category, the NPV was only 85 % [23]. The PPV in BIV and BV are low at 38 and 37 %, respectively, reaffirming the role of this test as a rule out (benign) than a rule in test. The usefulness of this test is largely determined by the institutional prevalence of malignancy in nodules [24] and appears to be most useful in a practice setting with the prevalence of malignancy in indeterminate lesions of 15–21 %.
The BII describes a group of FNAC specimens that contain cells with architectural or nuclear atypia that would not qualify it for BII but does not contain enough suspicious features that would warrant a higher-class assignment. This category was intended for limited use and expected to have a frequency of about 7%. Usage of this category by cytopathologists has been variable with studies reporting usage up to 27%. When patients in this category underwent surgery, malignancy was seen up to 14.5% [25]. Using USG features to estimate malignancy, risk in BII lesions has been examined. The reported cancer risk in BII lesions and high suspicion sonographic features was between 90 and 100%. The prevalence of at least one suspicious feature on USG in BII lesions ranged from 18 to 50% and increased the risk of malignancy to 60–90% [26]. The overall malignancy rate in these studies was 40–45%.

Fludeoxyglucose-positron emission tomography (FDG-PET) has been reported to have a high NPV when applied to the diagnosis of cytologically indeterminate thyroid nodules. In a systematic review and meta-analysis of six studies, FDG-PET had a low positive predictive value (PPV) (39%) and a high NPV (96%), when performed in thyroid nodules with BIII or BIV cytology [27]. Since there is significant interobserver variability in this category [28], one recommended approach is to obtain a second opinion from a high volume cytopathologist. Central cytopathologists from institutions with high volume make fewer indeterminate diagnosis (55 vs. 42%) than community-based cytopathologists [28]. In one study, a second opinion for a nodule originally read as indeterminate and subsequently reclassified as benign had an NPV 95%. The second opinion improves diagnostic accuracy from 60 to 74% and avoids diagnostic surgery in 25% of patients.

A repeat FNA may reclassify the lesion into a more definitive diagnosis. Malignancy rates are similar with single BII and two successive BII diagnoses. This approach has been recently questioned. Recent retrospective studies confirm this high NPV though this may be lower in community-based hospital settings [29]. A composite of clinical ultrasound and cytology and patient preference may be used to decide if surgery is required when molecular testing is not available [30].

Secondary Neoplasm/Suspicious for Follicular Neoplasm (Bethesda IV) consists of either arrangement of follicular cells with cell crowding and microfollicle formation and lacking nuclear features of papillary thyroid carcinoma or almost exclusively of Hürthle (oncocytic cells) [31]. The majority of tumors are benign follicular adenomas driven by the oncogenic RAS mutation with uncertain malignant potential. The risk for malignancy is intermediate (15–30%). The application of this category has provided a mean prevalence of 10% (1–25%) and mean cancer risk of 26% (14–33%). Traditionally, diagnostic excision has been used in this category. Molecular markers have added considerably to the diagnostic assessment in this category [32]. Patients with BIV cytology may be followed without surgery. Exceptions include populations with unusual prevalence of malignancy or high pretest probability of disease including family history high-risk sonographic features or prior irradiation. In the presence of these features, the pretest probability will often exceed 50% reducing the NPV to < 90%; this would be considered too low to avoid diagnostic thyroidectomy [32].

Aspirates with cytologic features that raise a strong suspicion of malignancy but insufficient for conclusive diagnosis are assigned BV. Approximately 1–6% of patients are assigned to this category and at an average 75% of patients have malignancy diagnosed at surgery. The pretest probability of disease is high necessitating surgery in patients with this category. Mutation testing has high specificity with low sensitivity. The seven-panel gene of mutations is associated with a PPV of 80–95% and an NPV of 72–75% [33]. Conceivably, a positive test may help plan the extent of surgery; a negative test does not obviate the need for one.

**Conclusions**

Decision-making in thyroid nodules has significantly improved because of processes available [34], including collaborative work between the endocrinologist, sonologist, cytopathologist, and surgeon, high-resolution ultrasound, USG-guided FNAC, and on the spot testing for adequacy. The consistent use of ultrasound- and cytology-based scoring systems has greatly reduced uncertainty. The use of clinical data that assesses the risk of malignancy coupled with adequate knowledge of the prevalence malignancy in the population, use of sonographic features in conjunction with the Bethesda scoring system allows for informed decision-making in thyroid nodule.

**References**


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Діагностика, клінічне значення та лікування вузлів щитоподібної залози

Резюме. Огляд літератури присвячений питанням діагностики та лікування вузлів щитоподібної залози (ЩЗ). Вузли ЩЗ виявили у 68 % випадково відібраних осіб, яким проводилось ультразвукове дослідження (УЗД) високої роздільної здатності. При цьому більшість вузлів мала доброякісний характер. Вузли ЩЗ є клінічним проявом багатьох патологічних процесів. Застосування УЗД дозволило різко зменшити число оперативних втручань на ЩЗ з приводу вузлового зоба. Розроблено декілька систем оцінки ризику, спрямовані на поліпшення діагностики вузлового зоба, з по- дальнішою можливістю клініцистів приймати рішення щодо подальшого спостереження за хворими на вузловий зоб. Найкориснішою з них є класифікація система TIRADS. Шестирівнева система бальних оцінок Bethesda також надає цінну інформацію клініцистам щодо менеджменту вузлів ЩЗ. При цьому встановлена кореляція між цитологічними та гістопатологічними результатами. Однак частка пацієнтів потрапляє до так званої невизначеної категорії. Американська тиреоїдна асоціація використовує систему, що ґрунтується на оціночному ризику малігнізації вузлів ЩЗ. Наявність молекулярних маркерів вдосконаленої технології найновішого покоління з класифікацією експресії належить до сучасних додаткових діагностичних методів, що можуть сприяти ефективному менеджменту тиреоїдних вузлів. Водночас ці методи є недоступними в багатьох країнах. Прагматичний підхід до діагностики таких вузлів містить використання комплексного підходу клініцистів, фахівців з УЗД, цитологів. При використанні цього підходу пацієнтів з високим ризиком можна належним чином відібрати для подальшого хірургічного лікування, а за пацієнтами з меншим ризиком здійснювати динамічне спостереження.

Ключові слова: щитоподібна залоза; ультразвукове дослідження; Bethesda scoring; вузлові утворення; Thyroid Imaging Reporting and Data System; огляд