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Review Article

Overview of Thyroid Nodules and Cysts Management

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Abstract

Introduction: Thyroid nodules or growth are quite common among people, and they are mostly benign lesions. Despite their non-malignant nature in general, some of them pose a serious threat of being cancerous. The cancerous nodules must be surgically removed, whereas the non-cancerous ones must avoid unnecessary surgical removal. The roadmap to differentiating between the malignant and benign thyroid growths lies in detailed history taking and clinical examination followed by appropriate imaging. Based on these findings, a decision to perform a fine needle biopsy is made, which may be complemented by molecular tests. Finally, the decision for surgical excision of the partial or complete thyroid gland is made.

Aim of Work: The aim of this study is to discuss the overview of thyroid nodules.

Materials and Methods: This review is a comprehensive search of PUBMED from the year 1997 to 2018.

Conclusion: Thyroid nodules are usually benign and do not require any treatment other than follow-up tests. Nevertheless, the small percentage of nodules that do turn out to be malignant is of concern. Clinical examination, history taking, and diagnostic imaging do help clinicians decide on the possible need for biopsy. Fine needle aspiration biopsy, along with molecular tests, further help clinicians decide on the possibility of surgically removing the thyroid gland. It's a battle between removing the gland that is malignant vs. not removing the gland that is benign.

Keywords: *Thyroid Nodule; Serum thyrotropin; Calcitonin; FNAC; Papillary Thyroid Carcinoma; Medullary Thyroid Carcinoma; Thyroidectomy*

Introduction

A thyroid nodule is a swelled lesion of the thyroid gland, and if the nodule becomes fluid-filled, it becomes a thyroid cyst. They are a very common occurrence among the human population; some reports suggest up to 60% of people have thyroid nodules if detected by

high-definition ultrasonography. Although the majority of thyroid nodules are considered benign, some 5 - 5% are considered malignant [1].

Epidemiologically speaking, thyroid nodules are commonly associated with endocrine diseases with approximately 5% palpable lesions. The prevalence is much higher if detected on high-definition ultrasonography and autopsy reports. 10% of presented nodules can be malignant with slight variations when detected on ultrasound, CT, or MRIs. Irradiation during childhood, exposure to radiation fallout, and family history of thyroid cancer (e.g. multiple endocrine neoplasia syndrome type 2, familial adenomatous polyposis) are possible risk factors for malignant thyroid nodules [2].

The initial evaluation must include history and clinical examination for possible malignancy. Thyroid-stimulating hormone (TSH) levels and various imaging techniques help evaluate further its diagnosis. Fine needle aspiration biopsy remains the gold standard for diagnosing malignant lesions and the decision to undergo surgical management. Recent advancement in molecular diagnosis has shown to be a promising tool in preoperative diagnosis and avoiding unnecessary surgeries [3].

History and physical exam

A clinical exam with thorough history taking tailored to identifying clues suggestive of thyroid malignancy. A thorough clinical exam must include location, size, consistency of the thyroid nodule, associated symptoms such as dysphagia, dysphonia, dyspnoea, and symptoms of hypothyroidism or hyperthyroidism. Careful palpation followed by a throat examination with an endoscope might reveal several details. History taking should include information concerning prior radiation therapy of the head and neck area. Family history of thyroid disorders includes familial medullary thyroid cancer (MTC), which originated from calcitonin-producing C-cell tumors. Another one originates from follicular cells known as familial nonmedullary thyroid cancer and papillary thyroid cancer (PTC). Follicular cell-derived familial thyroid cancer has been associated with several syndromes, such as Cowden disease, Carney complex, Werner syndrome, and familial polyposis [2].

Cowden disease is an autosomal dominant disease caused due to a mutation in the PTEN gene and presents itself with hamartomatous neoplasms of the skin, oral mucosa, gastrointestinal tract, central nervous and genitourinary systems, with breast and thyroid cancers being the commonest. Carney complex is also an autosomal dominant condition, which presents itself with cardiac and cutaneous myxomas, spotty skin pigmentation, various endocrinopathies, and malignancies of endocrine and nonendocrine origin. Less commonly, thyroid cancer can be encountered in patients with Werner syndrome, of which the main feature is premature aging and familial polyposis, which is primarily associated with colon cancer [4].

Patient History or Characteristics	Findings of Physical Examination	Findings Seen on Imaging
Family history of MEN, MTC, and PTC	Firm nodule	Suspicious ultrasound features
History of head and neck irradiation	Nodule fixed to adjacent structures	Lymphadenopathy
History of Hodgkin and non-Hodgkin lymphoma	Growth of nodules, especially during therapy to suppress serum TSH	
Age <20	Abnormal cervical lymphadenopathy	
Age >70	Paralysis of the vocal cords	
Male sex		
Symptoms of compression: hoarseness, dysphagia, dysphonia, dyspnea, cough		

Table 1: *Features suggestive of the increased potential for thyroid carcinoma in a patient with thyroid nodule [5].*

Laboratory testing

Serum thyrotropin or TSH

Initial Lab examination of all thyroid nodules must include serum thyrotropin or TSH (thyroid-stimulating hormone). As the name suggests, thyrotropin is a pituitary hormone that stimulates both T4 (thyroxine) and T3 (triiodothyronine) hormones. Malignancy risk increases in a thyroid nodule with increased TSH within the normal range. On the other hand, a low TSH usually signifies benign nodules. Iodine-123, a radioisotope, is injected and taken up by a hot nodule (high functioning). A hot nodule on an iodine scan with low TSH is usually a hyperfunctioning thyroid nodule or autonomously functioning thyroid nodule. Conversely, a low-functioning cold nodule with subnormal TSH is indicative of malignancy [6].

Thyroglobulin

Thyroglobulin is a protein made by follicular cells of thyroid tissue and they subsequently combine with iodine to make thyroid hormones. Elevated levels of thyroglobulin in serum may suggest the return of thyroid cancers such as papillary and follicular types, but their presence could also be due to many benign conditions, and therefore their routine examination is not recommended [7].

Calcitonin

Calcitonin is a calcium-regulating hormone secreted by parafollicular C cells of the thyroid gland. It is considered a marker of medullary thyroid cancer and C cell hyperplasia. To increase the sensitivity of the test, pentagastrin (calcitonin stimulant) is intravenously administered and calcitonin is measured. Such elevated basal or pentagastrin-stimulated calcitonin levels indicate medullary thyroid cancer [8].

Ultrasonography

Ultrasonography is a procedure that uses high energy sound waves to examine tissues inside the body. It is a safe, non-invasive and cheap method that provides detailed information regarding the size and structure of thyroid nodules. Several studies have attempted to define malignant features as seen in ultrasonography, such as irregular margins of nodules, microcalcifications, hypoechogenicity and increased intranodal vascularity. These features are more often associated with malignant lesions than benign ones [9].

Ultrasound Feature	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Microcalcifications	26.1-59.1	85.8-95.0	24.3-70.7	41.8-94.2
Hypoechogenicity	26.5-87.1	43.4-94.3	11.4-68.4	73.5-93.8
Irregular margins or no halo	17.4-77.5	38.9-85.0	9.3-60.0	38.9-97.8
Solid	69.0-75.0	52.5-55.9	15.6-27.0	88.0-92.1
Intranodule vascularity	54.3-74.2	78.6-80.8	24.0-41.9	85.7-97.4
More tall than wide	32.7	92.5	66.7	74.8

Table 2: *Ultrasound characteristics of thyroid nodules predictive of malignancy [9].*

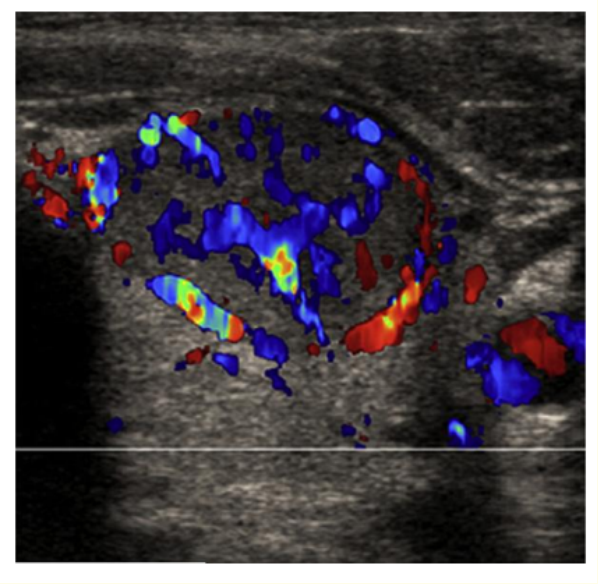

Figure 1: *Color Doppler US of a thyroid nodule showing marked internal vascularity, indicating increased lielihood of malignancy. Histology demonstrated PTC [9].*

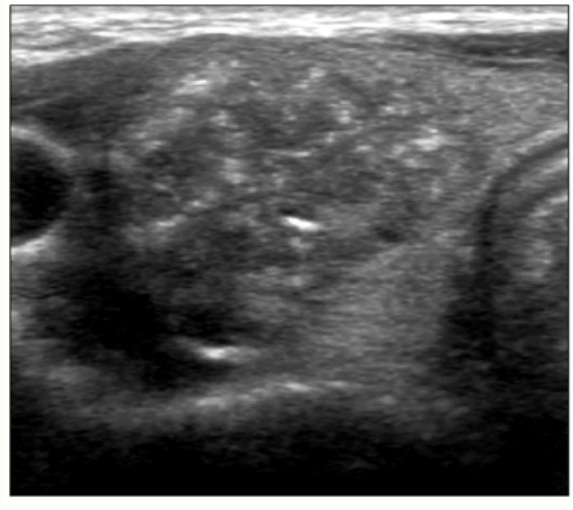

Figure 2: *Microcalcification in thyroid mass. US shows numerous microcalcifications within the thyroid mass [10].*

Identification of lymph nodes with hypervascularity, cystic changes and microcalcifications on ultrasound is also important, especially with thyroid nodules on the same side. Also noted should be the extra-capsular growth of nodules from the thyroid capsule to neighboring muscles and nerves. All these features show a great tendency toward malignancy [11].

Ultrasound elastography

Elastography is a newer technique that gives us the opportunity to virtually palpate the thyroid nodule. Most malignant tumors have very stiff stroma due to the presence of collagen fibers and this stiffness can be virtually palpated. However, certain benign lesions can be stiff as well. This technique has a very high sensitivity (82% - 97%) and specificity (96%-100%) [12].

FNA biopsy

Fine needle aspiration biopsy is a reliable, safe, and cost-effective diagnostic tool in the diagnosis of thyroid nodules. It is usually preferred to do ultrasound-guided FNA rather than hand palpated because it reduces the rate of false negatives. Several factors influence the decision to perform FNA, such as history, size, extra-capsular growth, abnormal cervical lymph nodes, and Ultrasonic indicators for malignancy. The following table categorizes thyroid nodule features and possible FNA recommendations [5].

Nodule Sonographic or Clinical Features	Nodule Threshold Size for FNA	Recommendation
High-risk history		
• Nodule with suspicious sonographic features	> 5 mm	A
• Nodule without suspicious sonographic features	> 5 mm	I
Abnormal cervical lymph nodes	All	A
Microcalcifications present in nodule	≥ 1 cm	B
Solid nodule		
• And hypoechoic	≥ 1 cm	B
• And iso- or hyperechoic	≥ 1 - 1.5 cm	C
Mixed cystic-solid nodule		
• With any suspicious ultrasound features	≥ 1.5 - 2.0 cm	B
• Without suspicious ultrasound features	≥ 2.0 cm	C
Spongiform nodule	≥ 2.0 cm	C
Purely cystic nodule	FNA not indicated	E

Table 3: *Sonographic and clinical features of thyroid nodules and recommendations for FNA [5]. Recommendations A: strongly recommends based on good evidence. Recommendation B: recommends based on fair evidence. Recommendation C: recommends based on expert opinion. Recommendation E: recommends against based on fair evidence. Recommendation I: recommends neither for nor against as evidence is insufficient.*

Cytology

A sizeable amount of cytological results are non-diagnostic and are advised for repeat FNAC. Yet, a section of repeated FNAC yields unsatisfactory results. Generally speaking, results from fine needle aspiration cytology can be grouped into six categories using the 2017 updated Bethesda classification system. 4 Category 1 is defined as non-diagnostic or insufficient; category 2 benign, and Category 3 is Atypia of Undetermined significance or Follicular Lesion of Undetermined Significance. Category 4 is Follicular Neoplasm or Suspicious for a Follicular Neoplasm, and categories 5 and 6, suspicious for malignancy and malignant, respectively. Further management may include thyroidectomy, a repeat of FNAB, or molecular testing for further evaluation of undiagnosed cases [13].

Diagnostic Category	Risk of Malignancy, %	Usual Management
Category 1: Non-diagnostic or Unsatisfactory	0 - 5	Repeat FNAB with ultra-sound guidance
• Cyst fluid only		
• Virtually acellular specimen		
• Obscuring blood, artifacts		
Category 2: Benign	0 - 3	Clinical and sonographic follow-up
• Benign follicular nodule (eg, adenomatoid nodule)		
• Chronic lymphocytic (Hashimoto) thyroiditis		
• Granulomatous (subacute) thyroiditis		
Category 3: Atypia of Undetermined significance or Follicular Lesion of Undetermined Significance	10 - 30	Repeat FNAB, molecular testing, or lobectomy
• Focal nuclear atypia		
• Predominance of Hurthle cells		
• Microfollicular pattern in a hypocellular specimen		
Category 4: Follicular Neoplasm or Suspicious for a Follicular Neoplasm	25 - 40	Molecular testing, lobectomy
• Crowded and overlapping follicular cells some or most of which are arranged as microfollicles		
Category 5: Suspicious for Malignancy	50 - 75	Near total thyroidectomy or lobectomy
• Suspicious for papillary thyroid carcinoma		
• Suspicious for medullary thyroid carcinoma		
• Suspicious for metastatic carcinoma		
• Suspicious for lymphoma		
Category 6: Malignant	97 - 99	Near total thyroidectomy
• Papillary thyroid carcinoma		
• Papillary differentiated carcinoma		
• Medullary thyroid carcinoma		
• Undifferentiated anaplastic carcinoma		
• Squamous cell carcinoma		
• Carcinoma with mixed features		

Table 4: *The Bethesda system for reporting thyroid cytopathology: implied risk of malignancy and recommended clinical management [13].*

Molecular testing

The indeterminate category of results from FNAC can be further evaluated with molecular testing. Molecular testing uses the DNA from the same sample acquired by FNAC and sequences the gene. After sequencing, it looks for specific mutations in BRAF, RAS, TERT, TP53,

and relevant genes, which, when present, are almost always malignant. A study of 239 patients on whom mutational testing was done along with FNAC showed a negative predictive value of 96% and a positive predictive value of 80% [14].

Treatment

In cases of benign thyroid nodules, which account for more than 90% of all thyroid nodules, they need to be just followed up over time with ultrasound. FNAC should only be indicated if they display features of malignancy on ultrasound follow-ups. According to guidelines, sonographic follow-ups are made at 6 - 12 months for high-risk nodules, 12 to 24 months for low- to intermediate-risk nodules, and at least 24 months (if ever) for very low-risk nodules larger than 1 cm [15]. Clinically relevant benign thyroid nodules may also be managed by percutaneous ethanol ablation, radiofrequency, laser, microwave ablation, and high-intensity focused ultrasound [16].

For thyroid nodules that come as malignant or suspiciously malignant on FNAC, surgery is the treatment of choice. Lobectomy or total thyroidectomy can both be performed on smaller (< 4 cm) Bethesda Class 5 or 6 tumors. Total thyroidectomy is indicated in larger nodules (> 4 cm) Bethesda Class 5 or 6, with evidence of extrathyroidal extension, lymph node involvement or distant metastases, or both. Indeterminate nodules (Bethesda Class 3 or 4) may be managed by lobectomy. Possible complications from surgery are hemorrhage, hypocalcemia, and injury to the recurrent laryngeal nerve [17].

Conclusion

Although thyroid nodules are very common, most are usually benign and do not require any treatment other than follow-up tests. Nevertheless, the small percentage of nodules that do turn out to be malignant is of concern. Thorough history taking with detailed clinical examination, laboratory serum tests for TSH, and diagnostic imaging like ultrasound guide clinicians towards the possible need for biopsy. Fine needle aspiration biopsy (considered the gold standard), along with molecular tests, further help clinicians decide on the possibility of surgically removing the thyroid gland. Malignant thyroid glands are surgically excised, whereas non-malignant ones are followed up over months and years. Doctors do their best to avoid surgery on non-malignant nodules as surgery carries its own risk of complications. At the same time, doctors also try not to miss out on possible malignant lesions as they can be fatal. It's a battle between removing the gland that is malignant vs. not removing the gland that is benign.

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