Solitary Thyroid Nodule: A Clinical Approach

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ABSTRACT

Thyroid nodule is a commonly encountered clinical problem. The detection rate of solitary thyroid nodule has increased with better imaging techniques. The causes are multiple and malignancy is an usual concern, although uncommon. The evaluation begins with taking a history, performing the physical examination, and then choosing appropriate investigations to arrive at a diagnosis. This article discusses important issues related to evaluation of a solitary thyroid nodule.

Keywords: Solitary thyroid nodule, Thyroid malignancy, Fine needle aspiration cytology.


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INTRODUCTION

Thyroid nodule is a lesion within the thyroid gland which is distinct from its surrounding parenchyma. It may be clinically palpable or incidentally detected on imaging. Nodules are more common as age increases and they occur more frequently in women. The prevalence is 4% by palpation, 19 to 67% by ultrasound examination, and 50% in autopsy series. Clinically nonpalpable nodules are detected by ultrasonography, which increases nodule prevalence from 30% in patients younger than 50 years of age to 50% in patients greater than 60 years of age. Although around 95% of thyroid nodules are benign in nature, the major concern is whether it is a malignant nodule. However, there are certain historical, laboratory and radiological features which raise the suspicion for malignancy.

By and large there are five categories of thyroid nodules—hyperplastic, colloid, cystic, inflammatory and neoplastic. The basic step in evaluation begins with differentiating medical from surgical disease. Surgery is indicated when there is suspicion of malignancy, compressive symptoms, airway obstruction, hyperthyroidism and for cosmetic reasons.

HISTORY

The thyroid nodule is often discovered incidentally during a clinical examination performed for another purpose. So patients may not be aware of its presence. The history will guide further investigations to decide about the nature of the nodule.

1. Size: The incidence of malignancy may be higher in nodules more than 4 cm in diameter. All nodules larger than 1 cm and nonpalpable nodules with clinical or suspicious imaging need further evaluation.

2. Rate of growth: Non-neoplastic goiters are indolent and slow growing over years. Very rapidly growing nodule over hours with pain suggests hemorrhage into an existing nodule. Almost 90% of hemorrhagic nodules are benign, the remaining 10% are malignant and this rate is even higher than the average nonhemorrhagic nodule.

Rapid growth over weeks is more strongly associated with malignancy, and rapid growth during levothyroxine therapy is especially suggestive of cancer. Similarly, a sudden change in the size of a pre-existing nodule may indicate malignancy. Lymphoma, anaplastic thyroid carcinoma, and metastasis to the thyroid are the most frequent causes of thyroid nodules greater than 3 cm developing within 2 months.

Some forms of thyroiditis may present with rapid growth but it is usually associated with pain, e.g. subacute/viral (de Quervain’s) thyroiditis. Pyogenic thyroiditis is very rare and it evolves over days to weeks and associated with other signs of inflammation. This may help in differentiating it from a neoplasm.

Riedel’s thyroiditis, when it develops rapidly, is painless in nature and firm to palpation, may mimic anaplastic carcinoma thyroid. If the fibrosis extends to adjacent structures, it can again simulate a malignancy. However, presence of lymph nodes would favor a malignancy above thyroiditis.
**Associated Symptoms**

If there are significant compressive and obstructive symptoms such as hoarseness, and dysphagia, evaluation for malignancy is urgently needed.

By and large, malignancies are nonfunctional so symptoms of hypo or hyperthyroidism are unusual with malignancies.

**Age and Gender**

Thyroid nodule in a patient at the extremes of age are alarming for a malignancy. Around 20 to 50% of solitary nodules in patients younger than 20 years of age are malignant.\(^\text{12,13}\) Pediatric thyroid carcinoma (diagnosed at age 18 years or younger) presents most commonly in the teenage years (with a mean age of 16 years) and in girls 5.6 times more often than in boys.\(^\text{14}\) In patients greater than 70 years old, malignant disease is not as common, but when present it has a considerably worse prognosis.\(^\text{15}\)

When a thyroid nodule is present, the risk of malignancy in men is twice that of women.\(^\text{16}\)

**Diet**

Dietary Iodine content significantly affects the natural prevalence of thyroid pathology.

Patients from iodine-sufficient areas have a higher rate of malignancy than those from iodine-deficient areas (5.3% vs 2.7%). However, follicular and anaplastic carcinomas are relatively more common in iodine-deficient areas.\(^\text{16}\)

**Radiation Exposure**

Patients with history of radiation exposure to the neck are at high-risk for the development of both benign and malignant thyroid masses. Around 70 to 95% of thyroid cancers occurring after radiation exposure are papillary thyroid carcinoma.\(^\text{17}\) Young age at exposure and longer duration of exposure and female gender significantly raises the risk of papillary carcinoma.\(^\text{17}\)

**Other Tumors**

A history of tumors in other regions may indicate a tumor syndrome and raise the possibility of thyroid neoplasm. Gardner’s syndrome (multiple soft tissue and bone tumors and intestinal polyposis) and Cowden’s syndromes (multiple hamartomas, fibrocystic breast disease, and breast cancer due to PTEN gene mutation) are both autosomal dominant inherited syndromes associated with well-differentiated thyroid cancer. MTC is associated with Men types IIa and IIb which have an autosomal dominant inheritance. Associated mucosal neuromas and Marfanoid habitus will be suggestive of Men IIb. Thus, a detailed family history may provide a clue to these tumoral syndromes. If there is a high degree of clinical suspicion, the index case may be subjected to RET proto-oncogene testing and then further screening of family members is needed.

**Physical Examination**

Physical examination consists of local examination of thyroid and systemic examination for features of hypo/hyperthyroidism and other stigmata of malignancy or other etiology. The thyroid gland and nodules within it move with swallowing, whereas other masses external to the thyroid do not. The size, site, shape consistency and presence of any other palpable nodules should be noted. Nodule with firm consistency is usually due to autoimmune thyroid disease whereas a stony hard consistency favors malignancy. Firm nodule along with fixity suggests invasion and may be a pointer toward malignancy.

**Pemberton’s Sign**

For large thyroid lesions, this sign helps to identify the degree of substernal extension. Patient is asked to raise his arms over the head, which leads to enlargement of the mass or airway compression by venous congestion if the mass has a large substernal component.

Finally, the neck should be carefully palpated to evaluate for palpable lymphadenopathy. Multiple, firm to hard, large, fixed lymph nodes are indicative of metastatic carcinoma which may be arising from the thyroid or elsewhere. After the history and physical examination, risk stratification should be done and appropriate test should be selected for further definite diagnosis.

**Serology and Biochemical Tests**

Initial screening test for all patients with a thyroid nodule is serum TSH level to know if the patient is euthyroid, hypo- or hyperthyroid. Most of the patients with a thyroid nodule are euthyroid and if they are not euthyroid, then the underlying pathology is likely to be benign and functional.

When hypothyroidism is confirmed, anti thyroid peroxidase antibodies should be assayed to evaluate for Hashimoto’s thyroiditis. A baseline preoperative ionized calcium estimation is helpful, since a parathyroid adenoma may mimic a thyroid nodule. This also gives a clue to MEN I or II and helps decide further plan of management.

Routine evaluation of thyroglobulin and calcitonin levels is not recommended since this approach is not cost effective.\(^\text{18}\) However, if the patient has a positive family history of MTC, a serum calcitonin should be included in the initial test as it is sensitive in detecting even small MTCs. In these patients with personal or family history of MTC mutational
screening of the RET protooncogene should be employed. Thyroglobulin levels are useful as a surveillance test in well-differentiated thyroid carcinoma after a total thyroidectomy but it has no role in initial evaluation of a thyroid nodule.

**Fine-Needle Aspiration Cytology**

Fine-Needle Aspiration Cytology (FNAC) is the most important diagnostic evaluation for a thyroid nodule. It is the safest, most cost-effective, and most reliable technique to differentiate between benign and malignant diseases of the thyroid. It is estimated that its use reduces the number of thyroidectomies by half and the overall cost of thyroid nodule medical care by one quarter while doubling the surgical confirmation of carcinoma. However, the success of this modality depends on a good aspiration technique and an experienced cytopathologist. FNAC can be done with or without USG guidance. USG guided FNAC is more reliable, rapid, accurate and safe. The specimen should be evaluated immediately on-site to judge the adequacy of FNA specimen. For proper reporting, smear should be adequate. For a thyroid FNA specimen to be satisfactory for evaluation at least 6 groups of benign follicular cells are required and each group should be composed of at least 10 cells.

Current sensitivity and specificity generally exceed 90 and 70%, respectively. However, if there is a strong clinical suspicion of malignancy and FNAC result is negative, patient should be periodically reassessed. Since, the size of needle used is very small (21 to 24 gauge), needle-track seeding is unlikely. The false negative rate varies from 1 to 5% and is associated with cysts or nodules smaller than 1 cm or masses greater than 3 cm. Prior use of FNAC reduces the need for frozen section study for diagnosis, and reduces the operative time.

FNACs are reported as clearly malignant, benign, suspicious, or nondiagnostic. Another scheme of reporting is the Bethesda system (Table 1). Bethesda 1 and 2 are clearly benign, 5 and 6 are clearly malignant whereas 3 and 4 are the suspicious lesions. It is important to note that a nondiagnostic result should not be interpreted as benign. On the other hand, it indicates that the cells are insufficient for evaluation. Atypia of undetermined significance or follicular lesion of undetermined significance includes cases which cannot be classified as benign or follicular neoplasm. Rather than a surgical recommendation for all patients based on this result, repeat FNAC of such nodules should be performed. The repeat cytology result is benign in 50 to 60% of cases, negating the need for surgery.

FNAC cannot reliably distinguish follicular adenoma or carcinoma because diagnosis of carcinoma requires tumor invading the thyroid capsule or blood vessel lumens. However, if there is a densely cellular smear with lacks colloid, and microfollicular pattern, follicular carcinoma is more likely. Benign lesions have an abundance of colloid with small numbers of follicular cells which are arranged in a macrofollicular pattern. Also there are numerous macrophages.

The newly developed molecular methods when applied to FNA specimens offers improved diagnostic accuracy. Reverse transcription PCR to detect thyroglobulin mRNA and thyrotropin-receptor mRNA from a lymph node is accurate for diagnosing metastatic thyroid cancer. BRAF gene mutations, if detected in the aspirate sample, are specific for papillary thyroid carcinoma and can yield the correct diagnosis of papillary thyroid carcinoma in approximately 10% of otherwise indeterminate FNAs.

Cystic lesions are difficult to diagnose because the fluid rarely contains adequate cellularity for cytologic diagnosis. If cyst is FNAed, all fluid should be evacuated, and then reexamine thyroid for any residual palpable mass. If such a mass is noted it should undergo FNAC. Most thyroid carcinomas (85%) are solid, with 3% being cystic and 12% being mixed solid and cystic. When the cytopathology is indeterminate, FNAC should be repeated.

The cystic lesions can be treated with sclerosing agents such as ethanol, and it can be ablated.

A thyroid nodule in a patient with a family history of medullary carcinoma or papillary carcinoma should also prompt FNAC and consideration of surgery (Figs 1A to D).

**Imaging Studies**

Imaging modalities like ultrasound are far more superior to detect thyroid nodule as compared to clinical palpation. Ultrasound is noninvasive, easily available and can help in differentiating malignancy from benign disease. It is also helpful in serial follow-up of a nodule especially if it is less than 1 cm. Alternatively, if the lesion is greater than 1 cm but not palpable, USG-guided FNAC is the investigation of choice. It is also useful to evaluate the thyroid bed for local recurrence after treatment and in identifying metastatic lymph nodes.

**Table 1:** The Bethesda system for reporting thyroid cytology: recommended diagnostic categories

<table>
<thead>
<tr>
<th>Bethesda 1</th>
<th>Nondiagnostic or unsatisfactory</th>
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<tbody>
<tr>
<td>Bethesda 2</td>
<td>Benign</td>
</tr>
<tr>
<td>Bethesda 3</td>
<td>Atypia of undetermined significance or follicular lesion of undetermined significance</td>
</tr>
<tr>
<td>Bethesda 4</td>
<td>Follicular neoplasm or suspicious for a follicular neoplasm</td>
</tr>
<tr>
<td>Bethesda 5</td>
<td>Suspicious for malignancy</td>
</tr>
<tr>
<td>Bethesda 6</td>
<td>Malignant</td>
</tr>
</tbody>
</table>

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Table 2: Ultrasonographic features of benign and malignant nodule

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margins</td>
<td>Clear</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Shape</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Micronodules</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Hyper/normal</td>
<td>Hypoechoic</td>
</tr>
<tr>
<td>Structure</td>
<td>Cystic/spongiform</td>
<td>Solid</td>
</tr>
<tr>
<td>Color Doppler flow</td>
<td>Peripheral</td>
<td>Central</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

The terminology ‘Thyroid Imaging Reporting and Data System’ (TIRADS) was first used by Horvath et al to standardize the reporting of results of thyroid USG. This is supposed to be helpful in the stratification of nodules in benign and malignant (Table 3). Horvath et al described 10 ultrasound patterns of thyroid nodules. He related the rate of malignancy according to the pattern.

Russ et al proposed a TIRADS classification which is a further modification. Based on the ultrasound features, the lesions are divided in six categories, ranging from a normal thyroid gland to a malignant nodule (Table 4).

Table 3: TIRADS system of classification

<table>
<thead>
<tr>
<th>TIRADS</th>
<th>Description</th>
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<tbody>
<tr>
<td>TIRADS 1</td>
<td>Normal thyroid gland</td>
</tr>
<tr>
<td>TIRADS 2</td>
<td>Benign lesion</td>
</tr>
<tr>
<td>TIRADS 3</td>
<td>Probably benign nodule</td>
</tr>
<tr>
<td>TIRADS 4</td>
<td>4A indeterminate</td>
</tr>
<tr>
<td>TIRADS 5</td>
<td>Nodule suspicious for malignancy</td>
</tr>
<tr>
<td>TIRADS 6</td>
<td>Malignant nodule</td>
</tr>
</tbody>
</table>
Table 4: The TIRADS classification algorithm

<table>
<thead>
<tr>
<th>High suspicious aspects</th>
<th>≥3 signs and/or adenopathy—TIRADS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Taller than wide shape</td>
<td></td>
</tr>
<tr>
<td>• Irregular or microlobulated margins</td>
<td></td>
</tr>
<tr>
<td>• Microcalcifications marked hypoechoic</td>
<td></td>
</tr>
<tr>
<td>Low suspicious aspects</td>
<td></td>
</tr>
<tr>
<td>• None of the high suspicious aspect</td>
<td></td>
</tr>
<tr>
<td>• Moderately hypoechoic</td>
<td></td>
</tr>
<tr>
<td>Probably benign aspects</td>
<td></td>
</tr>
<tr>
<td>• None of the high suspicious aspect</td>
<td></td>
</tr>
<tr>
<td>• Isoechogetic</td>
<td></td>
</tr>
<tr>
<td>• Hyperechogetic</td>
<td></td>
</tr>
<tr>
<td>Benign aspects</td>
<td></td>
</tr>
<tr>
<td>• Simple cyst</td>
<td>TIRADS 2</td>
</tr>
<tr>
<td>• Spongiform nodule</td>
<td></td>
</tr>
<tr>
<td>• White knoty aspect</td>
<td></td>
</tr>
<tr>
<td>• Isolated macrocalcification</td>
<td></td>
</tr>
<tr>
<td>• Typical subacute thyroiditis</td>
<td>TIRADS 1</td>
</tr>
<tr>
<td>Normal thyroid US</td>
<td></td>
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</tbody>
</table>

Routine use of CT or MRI is not indicated in the evaluation of a thyroid nodule, but each is useful in specific circumstances. Both can accurately determine substernal extension and invasion of surrounding structures, such as esophagus, larynx, or trachea, and should be used only if invasion or substernal extension is suspected. Although CT scan is now readily available at most centers, the use of contrast dye delivers an iodine load that can delay postoperative thyroid scanning for 4 to 8 weeks and can also cause a subclinically hyperthyroid patient to enter thyroid storm; so, it should be avoided.

Elastography

Quantitative elastography is a noninvasive ultrasound procedure which gives information about tissue stiffness. The stiffness depends upon the composition and structural organization of the lesion. When pressure is exerted on thyroid tissue with ultrasound probe, strain values of the thyroid nodule and the parenchyma can be obtained. This pressure can be applied by using a probe from outside or using the in vivo compression caused by carotid artery pulsation.

Quantitative elastography provides a time elasticity graph, plotted on the region of interest, in compression and relaxation cycle. Thus, two images of thyroid are acquired, before and after compression with the probe. The tissue displacement is noted by analyzing the imaging beam. A dedicated software is used for accurate measurement of tissue distortion.

By elastography, two types of elasticity assessments are obtained. First, visual scoring of colors within and around the nodules. It is assessed, using 4 to 5-scale scoring systems. Second, two regions of interest are identified over a target region and the adjacent reference region. Then, a strain ratio is automatically calculated through the software. The likelihood of malignancy increases with an increase in the strain ratio.

Thus, elastography is a feasible and noninvasive screening tool for reducing the FNACs. However, further studies are needed to validate its utility.

Isotope Scanning

There are few indications of radioactive iodine or technetium 99m(Tc) scanning. Patients with suppressed TSH should undergo isotope scanning (Flow Chart 1). Ninety-five percent of nodules are cold on radioactive iodine scanning. The frequency of malignancy in cold nodules is 10 to 15% vs 4% in hot nodules. Thus, both hot and cold nodules are likely to be benign. Chances of malignancy are only slightly more in cold than hot nodules. So this test is not always helpful in discriminating benign from malignant nodules. Radioactive iodine scanning is used in the hyperthyroid patient to differentiate between a toxic nodule > 1 cm in diameter and the diffuse pattern in Grave’s disease. The ability of isotope scanning to detect metastatic disease is its most important diagnostic utility.

Genetic Tests

Genetic tests are indicated in selected cases. Germline mutations in the RET protooncogene cause MEN 2a, MEN 2b, and familial MTC. Mutational screening of the RET protooncogene serologically is the currently used method for screening individuals at risk for MTC. If the FNAC is suggestive of MTC or there is a family history of MEN or MTC, RET screening is indicated. The identification of these syndromes also helps to look for concomitant pheochromocytoma or parathyroid adenoma. This genetic information is extremely useful in evaluating non-index cases so that prophylactic surgery can be performed earlier and the potential for cervical lymph node dissection can be avoided.

For patients with indeterminate FNA cytology, molecular characterization of FNA aspirates for identification of particular molecular markers of malignancy is now a recent approach. The mRNA classifier system can identify BRAF, RAS, RET/PTC, and PAX8/PPAR gamma mutations. Thus, the risk of malignant transformation can be known beforehand.

CONCLUSION

Thyroid nodules are very common in the general population, although thyroid cancer is relatively uncommon. The goal of the evaluation of the solitary thyroid nodule is to identify whether the patient will require surgical treatment and to identify a malignancy. The evaluation of the solitary thyroid
nodule begins with patient history, risk factor assessment, and clinical examination, which will guide the further choice of investigations (Flow Chart 1). All patients with a thyroid nodule should have serum TSH measured and undergo ultrasonography. Ultrasound is often useful in guiding the FNA for small or deep nodules or when multiple nodules are present. Further evaluation is done by FNAC depending on patient risk factors, physical examination findings, nodule size and appearance on ultrasound and serum TSH.

Benign asymptomatic thyroid nodules smaller than 4 cm can be observed in low-risk patients. Thyroid nodule greater than 4 cm in size, or FNAC suggesting it to be ‘malignant,’ ‘suspicious for malignancy,’ or ‘indeterminate’ should prompt surgical excision. Asymptomatic and small nodules classified under ‘follicular lesions of undetermined significance’ require at least a repeat FNAC. Thyroid nodules that cause compressive symptoms should be treated surgically. Autonomously functioning (hot) thyroid nodules may be treated with radioactive iodine ablation or surgery depending on the clinical scenario. Genetic testing is useful in selected cases with family history of MEN 2 and, familial MTC.

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