Solitary Thyroid Nodule – An Insight

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Introduction

Thyroid nodules present a challenge in their diagnosis, evaluation, and management. Often these abnormal growths/lumps are large in size and develop at the edge of the thyroid gland, so that they are felt or seen as a lump in front of the neck. The prevalence of these nodules in a given population depends on a number of factors like age, sex, diet, iodine deficiency, and even therapeutic and environmental radiation exposure. Prevalence increases with age, with spontaneous nodules occurring at a rate of 0 - 0.8% per year, beginning early in life and extending into the eighth decade1,2. True solitary thyroid nodules (STN) occur in 4 - 7% of the adult population. They are present in 5% of persons at an average of 60 years. They are more common in females (6.4%) as compared to males (1.5%) and this predisposition exists throughout all age groups. Many palpable thyroid nodules, thought to be solitary, are actually part of a multinodular thyroid gland. In general, a nodule must reach a size of 1 cm in diameter to be detectable by palpation. Thyroid nodules could be adenomas or neoplasms. Most thyroid nodules are benign hyperplastic lesions, but 5 - 20% of these nodules are true neoplasms in nature. Solitary thyroid nodule first seen can be due to asymmetrical enlargement of one lobe as in chronic lymphocytic thyroiditis (i.e., Hashimoto’s thyroiditis), simple goitre, or unilateral agenesis, or rarely due to developmental errors such as ectopic tissue1-4. Childhood thyroid nodules need special attention due to higher incidence of malignancy, i.e., 15 - 25% as compared to adults. Further, thyroid cancer runs a more aggressive course in children and is associated with early metastasis locally to regional lymph nodes and distant sites including lungs and bones5,6. The ultimate aim in the evaluation of solitary thyroid nodule (STN) is to differentiate benign hyperplasia from true neoplasms. Thus, to evaluate STN in terms of comprehensive and appropriate management, the medical team must include a primary care physician, an endocrinologist, a pathologist, a radiologist, and a head and neck surgeon.

Currently, many investigations including diagnostic imaging studies, serologic and cytogenetic tests as well as histopathological techniques are available to evaluate STN. Out of all these investigations, fine needle aspiration cytology (FNAC) has become the diagnostic tool of choice for the initial evaluation of STN3-12.

Aetiology and classification3,6

STN can be classified into benign and malignant nodule. Generally, most (90%) thyroid nodules are benign and can be classified as adenomas, colloid nodules, cysts, infectious nodules, lymphocytic or granulomatous nodules, hyperplastic nodules, thyroiditis, and congenital abnormalities.

Thyroid adenomas

True adenomas are encapsulated and histologically classified as papillary, follicular, and Hurthle cell types. The follicular adenomas can be subdivided according to the size of follicles into colloid, foetal and embryonal varieties. Follicular adenomas are the most common and are most likely to mimic the function of normal thyroid tissue, and usually present as a single nodule. Clinically, the patient presents with slow growth of the nodule over many years, and with time the nodule grows larger and its function increases until it is sufficient to suppress TSH secretion, but all the adenomas do not become autonomous. Ultimately, the remaining part of the gland undergoes atrophy and loss of function, and the scintiscan shows radio-iodine accumulation only in the region of the nodule (a hot nodule). At this time TSH is suppressed (chemical thyrotoxicosis) but the patient may or may not be overtly thyrotoxic. Ultimately, the patient develops frank thyrotoxicosis (toxic adenoma) which may be precipitated by iodine exposure such as from radiographic contrast dyes. Hyperfunctioning adenomas are a frequent cause of T3 toxicosis and are amenable to ablation by surgery or 131I treatment.

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Malignant

Thyroid nodules can be classified as:

I. Differentiated:
   1. Papillary adenocarcinoma: a) Pure papillary; b) Mixed papillary and follicular carcinoma (variant including tall cell, follicular, oxyphil, solid). Papillary carcinoma is the most common of thyroid malignancies, accounting for 80 - 90% of all thyroid cancers.
   2. Follicular adenocarcinomas (variants including malignant adenoma, Hurthle cell carcinoma, oxyphil carcinoma, clear cell carcinoma, insular carcinoma).

II. Medullary carcinoma (not a tumour of follicular cells)

III. Undifferentiated:
   1. Small cell (to be differentiated from lymphoma).
   2. Giant cell.
   3. Carcinosarcoma.

IV. Miscellaneous:
   1. Lymphoma, sarcoma.
   2. Squamous cell epidermoid carcinoma.
   3. Fibrosarcoma.
   4. Mucoepithelial carcinoma.
   5. Metastatic tumour.

Since the thyroid gland has a rich vascular supply, it is a common site of metastatic tumours from primary tumours elsewhere, e.g., malignant melanoma and carcinoma of lung, breast, and oesophagus. Amongst thyroid neoplasms, lymphoma is the most common tumour occurring in women between the age of 55 - 75 years, who have chronic lymphocytic thyroiditis with positive serum antithyroglobulin antibodies.

Evaluation of solitary thyroid nodule (STN)

The evaluation of STN is done by taking a detailed medical history, general physical examination, metabolic profile (thyroid function tests), imaging and invasive procedures including FNAC. So, for evaluation, three questions must be taken care of:

1. Is the nodule benign or malignant;
2. Is the nodule causing pressure symptoms on the adjoining structures of the neck;
3. Is the nodule secreting excess of thyroid hormone.

History and examination

Evaluation of STN includes history of the thyroid mass, past medical history, family and social history, a thorough review of all systems including a careful, complete head and neck examination. Past history of radiation exposure to neck is very important. Symptoms such as neck pain, dyspnoea, hoarseness of voice, stridor and dysphagia usually suggest thyroid malignancy, but are not diagnostic. Past medical history or family history of phaeochromocytoma, hypertension, chronic diarrhoea and constipation, hyperparathyroidism, and episodes of irritability or nervousness suggest the possibility of familial MEN-2 or 2b syndrome.

Points in favour of benign pathology are:

a. Family history of Hashimoto’s thyroiditis;
b. Symptoms of hypo-or hyperthyroidism;
c. Pain or tenderness associated with the nodule;
d. Surface of nodule being soft, smooth, and mobile;
e. Multinodular goitre without a dominant nodule;
f. Female sex.

Points in favour of malignancy are:

a. Young patients (< 20 years age) or old (> 70 years age);
b. Male sex;
c. H/O external neck radiation during childhood or adolescence;
d. Recent change in voice (hoarseness or dysphonia), difficulty in swallowing (dysphagia);
e. Past or family history of thyroid carcinoma;
f. On physical examination, firm consistency of nodule, its irregular shape, its fixation to underlying or overlying tissues, and suspicious regional lymphadenopathy.

If a nodule is of long standing and not enlarging, it is likely to be benign. Benign nodular lesions are more common in females than males. The reverse is true for malignant lesions. Hence, nodular lesions raise more suspicion of carcinoma in men than in women.
Metabolic profile and other markers

1. **Thyroid function tests:**

These are not useful in the assessment of patients with thyroid nodules because most patients with thyroid cancer are euthyroid. Benign disorders like autonomously functioning adenoma or Hashimoto’s thyroiditis are more often associated with hypothyroidism except for Hashitoxicosis. There is a strong association between Hashimoto’s thyroiditis and primary thyroid lymphoma.

2. **Serum thyroglobulin level:**

It cannot differentiate a benign from a malignant thyroid nodule unless the level is markedly increased, in which case metastatic thyroid cancer should be suspected. It is indicated for monitoring patients with nodules being followed non-operatively and in those patients who have undergone total thyroidectomy for thyroid cancer, excluding medullary thyroid cancer. Serum thyroglobulin is more increased in follicular carcinoma but may sometimes be increased in benign thyroid disorders. Therefore, it is not routinely recommended in the evaluation of STN.

3. **Serum calcitonin level:**

It is increased in patients with medullary thyroid cancer (MTC) or multiple endocrine neoplasia type II (MEN-II).

4. **DNA analysis (molecular analysis):**

Recently, DNA testing has become an effective method for the diagnosis of MEN 2a and 2b syndromes. RET proto-oncogene located in the para-centromeric region of the short arm of chromosome 10 is the site of mutation in 90% patients with familial medullary thyroid cancer (MTC) and MTC associated with MEN2a and 2b. DNA testing should be carried out in all patients with MTC in order to identify possible germline mutations in the RET proto-oncogene. Further, genetic counselling should be advised to all family members with RET mutation and these members should be informed about prophylactic thyroidectomy. Patients who are RET oncogene positive should always have a 24-hour urine collection with measurement of levels of VMA, metanephrine, and catecholamine to rule-out co-existing phaeochromocytoma.

5. **Serum carcinoembryonic antigen (CEA) level:**

It is increased in MTC.

6. **Serum anti-TPO antibody and anti-Tg antibody levels:**

These are helpful in chronic autoimmune thyroiditis especially if serum TSH is elevated.

**Imaging**

1. **Ultrasonography of thyroid**

It is a safe, non-invasive, inexpensive, and effective method to know whether a nodule is solid, cystic, or a mixture of the two. Even a 1 mm size non-palpable nodule within the thyroid tissue can be detected with high resolution ultrasonography. Solid or mixed lesions are consistent with tumour, but may be either benign or malignant. Positive predictive criteria of malignancy include solid hypoechoic nodules, presence of calcification, irregular shape, absence of halo and cystic elements. The main limitation of this technique is its failure to differentiate malignant thyroid nodules from benign ones. But its main indication is accurate measurement of the size of a nodule, and also acts as a guide for FNAC. Ultrasonographic imaging has no role in screening for thyroid nodules in asymptomatic patients.

2. **Radio-isotope scanning**

This technique is based on the fact that malignant thyroid tissue takes up less radioactive iodine than normal thyroid tissue. Scanning with I131 has been replaced by I123 or Tc99m scans to lower the dose of radiation delivered to the thyroid gland during the investigation. Depending upon the ability of the thyroid to take-up radioactive isotope, thyroid nodules are further classified into cold, warm, and hot. Cold nodules are hypofunctional while warm nodules are normal, and hot nodules are occasionally hyperfunctional. Scanning the thyroid with I123 or Tc99m can indicate the functional activity of a nodule and of the thyroid, and correlate the location of palpable nodules with nodules seen with scanning. About 85% of nodules on scanning are cold, and these lesions have a 10 - 25% chances of malignancy. Of the 5% nodules shown to be “hot” on scanning, about 1% are malignant. Thyroid scanning is indicated in the
assessment of thyroid nodules only in those patients who have follicular thyroid nodules on FNAC. The major drawback of this imaging is its failure to differentiate between benign and malignant thyroid nodules with great accuracy, while other drawbacks include an inability to delineate thyroid gland as well as misinterpretation of the functional status of the thyroid nodule if normal functioning thyroid tissue overlies the cold solitary thyroid nodule, or if the thyroid gland is asymmetric.

The role of an iodine scan is established in cases of toxic adenoma to exclude it from malignancy. The uptake is markedly high within the nodule, and markedly low or absent uptake is seen in the rest of the gland.

3. CT scanning and MRI

These have a limited role in the initial evaluation of STN. But their main indications include suspected tracheal involvement either by invasion or compression, extension into the mediastinum (retrosternal lesions), or recurrent disease. MRI is more accurate than CT in distinguishing recurrent or persistent thyroid tumour from post-operative fibrosis.

4. Fine needle aspiration cytology (FNAC)

It has become the investigation of choice because of its safety, cost effectiveness, and accuracy. But it needs expertise and experience. It is the most specific investigation to differentiate between benign and malignant nodules. The technique is very simple to perform, having no complications except a little discomfort. In FNA, cellular material is aspirated by a syringe and a fine needle under negative pressure. But the drawback is missing of the malignant area, especially follicular neopasm. This can be overcome by multiple site aspirations, i.e., 3 - 6 aspirations. A satisfactory specimen contains at least five or six groups of 10 to 15 well-preserved cells. The cells are classified by their cytological appearance into benign, indeterminate, or suspicious and malignant. FNAC specimens of follicular neoplasms and Hurthle cells are usually interpreted as indeterminate or suspicious. This has resulted in low FNAC accuracy rates of about 40% for follicular carcinoma. The diagnosis of follicular carcinoma also requires the identification of capsular or vascular invasion which is not possible with FNAC technique. Therefore, the use of a large needle biopsy and intra-operative frozen section analysis in addition to standard FNAC has improved diagnostic accuracy in difficult FNAC cases for follicular carcinomas, but is associated with increased morbidity and increased complication rates in the form of haematoma, tracheal injury and laryngeal nerve injury, injury to other neck structures and cutaneous implantation of malignant cells. In cases of cystic thyroid nodules, the accuracy is increased if aspiration is done from the margin of the nodule rather than from the cystic fluid and debris in the centre.

The overall sensitivity, specificity, and accuracy of FNAC technique is 83%, 92% and 95% respectively. In FNAC, both false positive and negative results occur.

According to guidelines of Papanicolaou Society of Cytopathology for the examination of fine needle aspiration specimens from thyroid nodules, false negative diagnosis is defined as a diagnosis of non-neoplastic lesion, which does not normally require surgical intervention, rendered on a malignant lesion; and its rate is computed as the number of false negative diagnoses divided by the total number of FNACs in the series multiplied by 100. While a false positive result is defined as a diagnosis of neoplasm, which needs surgical excision, rendered on a non-neoplastic lesion; and its rate is computed as the number of false positive diagnoses divided by the total number of FNACs in the series multiplied by 100.

Accuracy of FNAC is closely related to the histologic type of thyroid carcinoma which is being evaluated. Diagnosis is correct for papillary thyroid carcinoma in about 90 - 100% of FNAC specimens when correlated with the histology of the final surgical specimen. Undifferentiated (anaplastic) carcinoma, MTC and primary thyroid lymphoma also have characteristic cytologic features which help in arriving at a correct diagnosis in about 90% of FNAC specimens.

Thyroid peroxide (TPO) immunocytochemistry with a monoclonal antibody termed MoAb47 has been reported to significantly increase the accuracy of FNAC in patients with follicular carcinoma. Many persistently non-diagnostic FNAC specimens may be neoplastic,
possibly 50%. So the best option probably is either close monitoring or surgical removal of the nodule. Some endocrinologists prescribe a trial of TSH suppression which can sometimes cause shrinkage of benign nodules. But higher percentage of benign nodules do not shrink. So the diagnostic value of TSH suppression is doubtful. In such cases even the role of ultrasound guided FNAC is unclear.

5. Surgery:

It should be considered for large tumours (> 2 or 4 cm) especially in young persons in order to avoid repeated evaluation. In such cases, results of FNAC are less reliable.

Management

When a diagnosis of colloid nodule (see Fig. 1) is made cytologically, thyroidectomy is not required except for cosmetic or symptomatic reasons, and these patients should be observed safely. A second FNAC is recommended 6 to 8 months after the initial FNAC if the nodule becomes larger in size. Patients with a benign nodule should undergo ultrasound evaluation of the size of the lesion and a baseline thyroglobulin level should be obtained. Patients may be prescribed thyroxine in doses sufficient to maintain a serum TSH level between 0.1 - 1.0 ulU/ml. About 50% of these nodules significantly decrease in size in response to the TSH suppression. Thyroidectomy should be done if a nodule enlarges or develops in a patient whose serum thyroglobulin rises inspite of TSH suppression therapy with thyroxine. But the contraindication is previous irradiation of the thyroid gland. In such cases, total or near-total thyroidectomy is recommended with FNAC because of higher incidence of thyroid cancer (40%). Some patients with a hyperfunctioning nodule, i.e., an adenoma, become euthyroid after treatment with I\textsuperscript{131} only to become

![Algorithm showing diagnostic and management approach to a patient with thyroid nodule](image-url)
hypothyroid in later years. These hyperfunctioning nodules are rarely carcinogenic and need surgery. When a cyst is encountered on FNAC, it should be drained completely; this is curative in about 75% of simple cysts, although some require a second or third aspiration. If the cyst persists after three attempts at aspiration, or the size of the cyst is more than 4 cm in diameter, or if the cyst is found to be a complex (both solid and cystic) cyst on ultrasound examination, unilateral thyroid lobectomy is recommended because these cysts have a tendency to undergo malignancy in 15% of cases. Other indications of thyroid lobectomy include recent rapid increase in the size of thyroid nodule and the presence of pressure symptoms. Patients with a thyroid nodule and family history of papillary or Hurthle cell cancer probably need thyroidectomy.

**Conclusion**

A majority of the thyroid nodules present with a lump in front of the neck, seen or felt on self examination. These are more common in females. 90% of them are benign in nature, adenoma being the commonest amongst benign causes. FNAC is a very reliable and powerful screening method in the pre-operative diagnosis of STN with high specificity and sensitivity, and can differentiate those thyroid nodules which require surgery or not. Combined use of FNAC, thyroid scan, and ultrasonography can detect them with 90% accuracy. Thyroid scan caries great diagnostic, therapeutic and prognostic significance in toxic nodular goitre.

**References**