

Thyroid Nodule Evaluation and Management — A Physician's Perspective

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SUMMARY

Thyroid nodule has always caused a lot of apprehension in the minds of both physician and patient. Many times patients are afraid of it thinking it to be a 'CANCER'. Thyroid nodule has a high prevalence of 3 to 7% in the normal population. A nodule in the thyroid gland has always placed the physicians in a situation of dilemma as far as its approach is concerned. While majority of thyroid nodules are benign – Adenoma, cyst, multinodular goiter, Hashimotos' thyroiditis, subacute thyroiditis constituting a significant percentage, about 5% may harbor malignancy.

Clinical features like increase in size, pain, undue firmness or fixation, and the presence of local adenopathy may suggest malignancy. Malignant conditions include papillary follicular, medullary and undifferentiated thyroid carcinomas.

After excluding a toxic adenoma by simple TSH test and radio nuclide scan FNAC has always been the simplest and first line investigation in diagnosing a solitary thyroid nodule with accuracy of 90-95%. Ultrasonography has a limited role, helping at times while doing FNAC under ultrasound guidance.

Benign adenoma may be treated conservatively by administration of thyroid hormone replacement therapy to suppress TSH and prevent further growth. Those lesions which have suspicion of malignancy clinically and FNAC does not completely exclude malignancy should be resected. Hyperfunctioning solitary thyroid nodules can be destroyed by administration of RAI or resected. The basic therapy for thyroid carcinoma is surgical resection- total or near total thyroidectomy. Residual/ metastatic thyroid disease, that can be shown to accumulate isotope, is treated by administration of

large doses of I¹³¹ on one or more occasions. These patients after surgery are followed by serum thyroglobulin estimation and radioactive iodine scan of whole body periodically.

Thyroid nodule is a discrete swelling with no palpable abnormality elsewhere¹. It could be a cyst, adenoma or carcinoma. A thyroid nodule is clinically palpable when size is >1 cm. Thyroid nodules are present in 3 to 7% of adult population². They are 3-4 times more frequent in females than male. The true incidence of isolated swelling is somewhat more than clinically estimated. Clinically impalpable nodules are often detected on ultrasound or during surgery. Approximately 5% of isolated swelling are malignant³. The prevalence of malignancy in isolated swelling was thought to be more than in multinodular swelling. However, contrary to previous belief, it is now known that the incidence of malignancy is almost the same in multiple as it is in solitary nodule⁴.

Thyroid nodule raises strong suspicion of malignancy in the minds of all patients. Therefore, every physician should seek the help of cytopathologist to rule out malignancy and then the patient should be advised accordingly.

The following neck swellings may mimic the thyroid swelling and may move with deglutition.

1. Cervical lymphadenopathy
2. Cystic hygroma
3. Thyroglossal cyst
4. Bronchocele
5. Aneurysm
6. Laryngocele
7. Parathyroid cyst and adenoma.

These should be ruled out before making the clinical diagnosis of thyroid nodule.

Differential Diagnosis of Thyroid Nodule

1. Solitary toxic nodule
2. Cyst
3. Neoplasm
4. Multi nodular goiter
5. Hashimoto's thyroiditis-about 10% of patients present as a solitary nodule.
6. Sub acute thyroiditis
7. Thyroid hemiagenesis
8. Metastasis
9. Tuberculosis

I. Toxic Adenoma—"Autonomously Functioning Thyroid Nodule"

Nodule is usually large enough to be palpable and thyrotoxicosis is mild. Definitive diagnosis is made by thyroid scan—there is increased uptake in the nodule (HOT NODULE) and diminished uptake in the remainder of the thyroid gland. Treatment of choice is radionuclide ablation. Relatively large dose of radioiodine is required, therefore regular follow up for later development of hypothyroidism is needed. Surgery is limited to enucleation of adenomas or lobectomy. Repeated injection of ethanol under ultrasound guidance can also be done. But on account of pain it is not very popular⁵.

II. Thyroid Cyst

Cysts are commonly seen in age group of 20-40 yr and more in females. It constitutes about 30% of all clinically diagnosed solitary nodule which is in fact an isolated cyst or mixed solid cystic swelling⁶. Cysts are usually formed as a result of colloid degeneration or as a result of involution of follicular adenoma. Initial basic investigation is FNAC. But at times it fails to provide result because cells lining the margins of the cyst may not come on FNAC and it might be inconclusive to make a diagnosis. Many a times FNAC done for diagnostic purposes also resolves the cyst. However, reaccumulation is frequent and needs further evaluation and management.

Papillary carcinoma is often associated with cyst formation and 10-15% cystic swelling are histologically malignant, 30% in cases of females and 20% in cases of males. Therefore all cysts should not be considered as

nonmalignant. Bleeding in the cyst may present as sudden painful swelling but it resolves over a period of few weeks.

III. Neoplasm

- i. These may be benign or malignant (5% nodules are malignant)³
 - A. *Benign* (Follicular epithelial cell adenoma) commonly referred to as thyroid adenoma.
 - B. *Malignant* nodules are of following types.
- ii. Follicular epithelial
 - A. Well differentiated
 1. Papillary—80-90%
 2. Follicular—5-10%
 - B. Undifferentiated—Anaplastic
- iii. C-cell medullary thyroid cancer—10%
- iv. Others
 - Lymphomas, sarcomas—1-2%.

Management of Benign Nodule (Follicular Epithelial Cell Adenoma)

89% of benign thyroid nodule increase in their volume by $\geq 15\%$ over 5 years². Generally they involute and chances of malignancy are rare. TSH suppression with Levothyroxine decreases the size of 30% nodules and may prevent growth. If nodule size does not decrease after 6-12 months of suppressive therapy than treatment is discontinued and nodule is followed by clinical examination and ultrasound. If there is increase in size or symptoms than plan for repeat FNAC and if FNAC is inconclusive than proceed for surgical excision and biopsy.

Papillary Thyroid Carcinoma

This is the commonest malignancy of thyroid. It is multifocal and invades locally. It usually presents as a single nodule. Exposure to external neck radiation increases the risk with peak occurrence 20-25 yr later. Its lymph node involvement is common which increases the risk of recurrence and mortality. In India coexistent tubercular lymph node may be there which would not take up radioiodine on scan and FNAC of lymph node is needed to exclude associated tubercular lymphadenitis.

Follicular Carcinoma

This is more common in iodine deficient regions. It is difficult to differentiate from follicular adenoma by

FNAC. Therefore most of the times FNAC report mentions follicular neoplasm, not malignancy. All these suspicious cases should undergo excisional biopsy. The patients of follicular carcinoma present at a late stage, hence mortality rate is high.

Medullary

These tumors are cold nodules. Serum calcitonin is the marker of residual or recurrent disease. Treatment is primary surgical, as these tumors do not take up radioiodine. External radiation and chemotherapy is needed in advanced diseases.

Anaplastic

As it is undifferentiated, uptake of radioiodine is negligible. It has got a very poor prognosis and most of the patients die within 6 months of diagnosis. Radioiodine uptake is negligible. Chemotherapy with anthracycline and paclitaxel may be of some help.

Thyroid Lymphoma (Rare)

Often arises in the background of Hashimoto's thyroiditis and it presents as a rapidly expanding thyroid mass. Diffuse large cell lymphoma is most common. These tumors are highly sensitive to external radiation. Surgical resection should be avoided as initial therapy for fear of spread.

Multinodular Goiter (MNG)⁸

Clinically at times it presents as a solitary nodule and multinodularity is diagnosed on ultrasound hence brief discussion is given below. These can be divided into

- Nontoxic and
- Toxic

Nontoxic

Seen in 12% of adults and more common in females, iodine deficient region and generally asymptomatic. If symptoms occur they are generally compressive symptoms. Laryngeal nerve involvement suggested by hoarseness while sudden onset pain suggests hemorrhage in the nodule. Multiple nodules of varying size are felt on palpation. TSH is usually within normal range and thyroid biopsy is required if there is dominant or enlarging nodule. MNG usually does not predispose to malignancy, but malignant transformation is seen occasionally. Radioiodine is used for the treatment as it achieves 40-50% decrease in goiter size and may ablate selectively region of autonomy. When there is acute compression, steroid treatment or surgery is required. T4 suppression is rarely effective as it increases the risk of thyrotoxicosis.

Toxic MNG

It presents with features of goiter and/or sub-clinical hyperthyroidism. It is more common in elderly and generally presents with atrial fibrillation, palpitation, nervousness, tremor and weight loss. Thyroid scan shows heterogeneous uptake. Surgery is the definitive treatment. Nevertheless a trial of radioiodine should be considered before subjecting patient to surgery as many of them are elderly. After iodine treatment the new autonomous area emerge as soon as older autonomous areas are ablated.

Hashimoto's Thyroiditis

10% of all cases of Hashimoto's thyroiditis may present as a solitary nodule. It needs mention as this nodule may be the only functioning part of the gland and surgical excision should not be hurriedly done. It is

Table 1: Characteristics of thyroid cancers⁷

	<i>Papillary</i>	<i>Follicular</i>	<i>Medullary</i>	<i>Anaplastic</i>
Incidence	70-80%	5-10%	10%	1-2%
Average life (yrs)	42	50	50	57
Female (%)	70	72	56	56
Death due to thyroid cancer	6%	24%	33%	98%
Invasion				
Juxta nodal	+5	+1	+6	+3
Blood vessel	+1	+3	+3	+5
Distant site	+1	+3	+2	+4
Resemblance to normal thyroid	+1	+3	+1	±1
I ¹²³ uptake	+1	+4	0	0
Degree of malignancy	+1	+2 to +3	+1 to +4	+8

the most common cause of hypothyroidism. It is autoimmune in origin. Hypothyroidism is reflected by increase in TSH level with decrease FT4. FNAC and TPO antibody also help in diagnosis. Life long thyroxine replacement, regularly monitored by TSH level is required. Goal is to keep TSH level in lower half of reference range.

Subacute Thyroiditis

It sometimes presents as solitary thyroid nodule. It is characterized by painful thyroid swelling, fever and raised ESR. In such cases follow up shows resolution of lesion which at times is referred as “**Vanishing nodule**”. Clinical course consists of initial thyrotoxic phase followed by hypothyroid phase and the patient becomes euthyroid within a span of 1-2 yr. It may be misdiagnosed as Graves’ disease during thyrotoxic phase or as Hashimoto’s disease during hypothyroid phase.

Thyrotoxic phase of thyroiditis can be differentiated from Graves’ by RAIU (Thyroiditis shows decrease uptake, Graves’ shows increase uptake), similarly hypothyroid phase of thyroiditis can be differentiated from Hashimoto’s by FNAC and TPO antibody. NSAID, Steroids and β -blockers are the mainstay of the treatment in thyroiditis.

Clinical Evaluation

While examining a thyroid nodule following things are worth remembering. High suspicion on clinical grounds should be done in rapidly growing, hard nodule, fixed to surrounding structure, vocal cord paralysis and regional lymphadenopathy. Age below 20 or above 70 yr, history of head and neck radiation, nodule > 4 cm, partially cystic swelling, male gender and clinical symptom of dysphagia, dysphonia and cough should raise moderate suspicion for carcinoma.

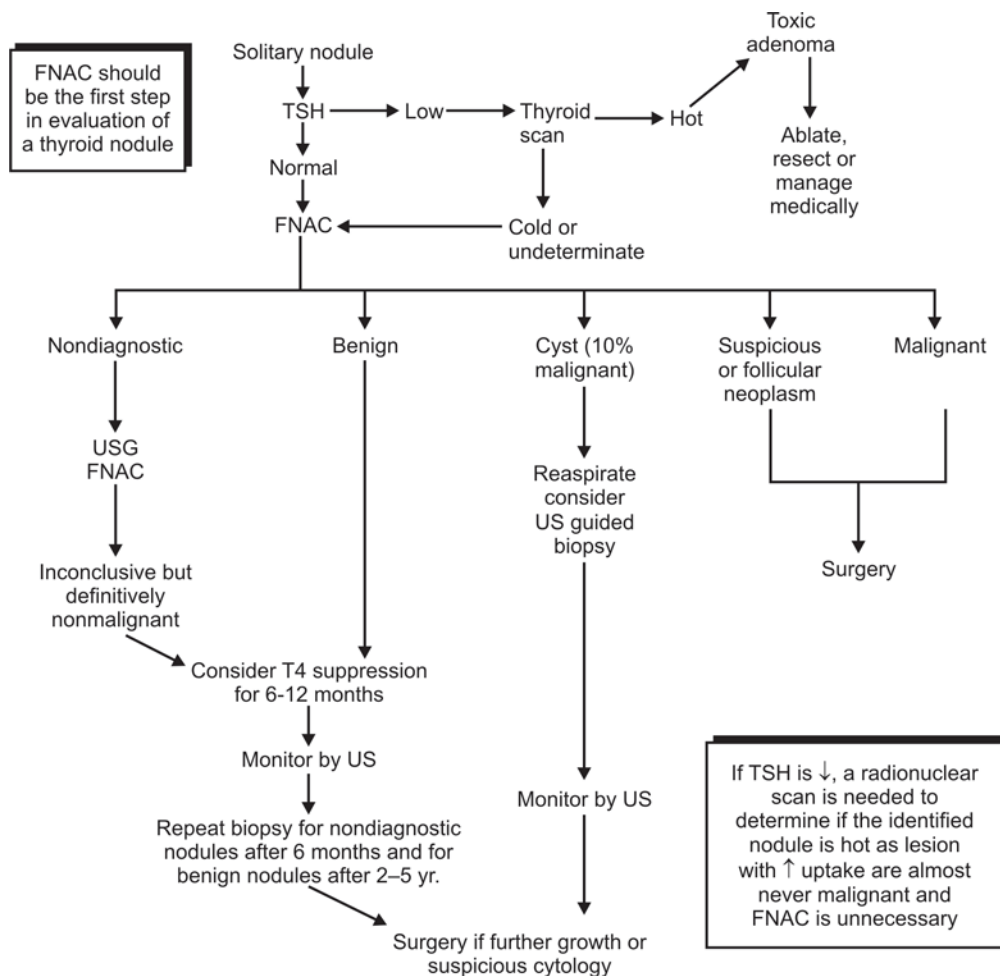


Fig. 1: Approach to a patient with thyroid nodule¹¹

Diagnostic Modalities in Evaluation of Thyroid Nodule (Fig. 1)

A. FNAC

This is the investigation of choice for evaluation of thyroid nodules. An aspirate is considered "adequate" if it contains a minimum of six grouping of well preserved thyroid epithelial cells consisting of at least 10 cells per group⁹. This diagnostic procedure appears to be 90-95% accurate in experienced hands. False positivity and false negativity of FNAC is 4%. Sometimes FNAC is inconclusive. The causes for inconclusive FNAC are:

- Cystic lesion – cells along the margin of cyst.
- Small nodule
- Fibrotic reaction
- Doubtful report
- Cannot assess malignant capsular invasion in neoplasm.

So in these cases we have to go for repeat FNAC from the largest nodule under ultrasound guidance. If still doubt persists than excisional biopsy should be done.

B. Ultrasound

Ultrasonography has got a limited role as it cannot differentiate between benign and malignant nodule. It is a sensitive tool to ascertain and monitor size and number of thyroid nodules. Also clinically solitary nodule may turn out to be a case of Multinodular goiter on ultrasound. It aids in diagnosis by repeating FNAC under ultrasound guidance. It is helpful in the follow up of thyroid cancer after treatment by determining recurrence of nodules that can represent cancer. Moreover its value as a diagnostic tool is highly dependent on the skill of examiner.

C. Thyroid scan

The main role of thyroid scan is in differentiating a nodule between a hot and cold depending on the radio iodine uptake. Hot nodules almost always rule out the possibility of a malignant nodule. Cold nodules have 10% chance of being malignant. If there is increased vascularity around cold nodule than there is an even higher probability of malignancy and this can be assessed by a perfusion scan. It has also got a role in detecting the residual or recurrent malignant tissue after thyroidectomy for thyroid cancer.

D. Others

- Calcitonin level are raised in medullary carcinoma.
- Galectin 3, telomerase and monoclonal TPO antibody are being used with varying success, but no specific

tumor marker is still available which can reliably distinguish between benign and malignant thyroid nodules¹⁰.

Management and Follow-up of Carcinoma Thyroid¹²

Though lobectomy is advocated for stage I malignancy and it is also associated with low incidence of hypoparathyroidism and injury to recurrent laryngeal nerve, but in follow up for malignancy, thyroglobulin (Tg) estimation and Thyroid scans are required, which would be of no use if thyroid tissue is left. Therefore, near total thyroidectomy is preferable in almost all patients. As most tumors are TSH responsive, after near total thyroidectomy TSH suppression is done by giving thyroxine and suppressing TSH. (In low risk patients TSH is suppressed to low but detectable range 0.1 to 0.5IU/L, in high risk patient TSH may be suppressed to undetectable level) and FT₄ is monitored to avoid thyrotoxicosis.

Thereafter a clinician can proceed as per the following plan (Fig. 2):

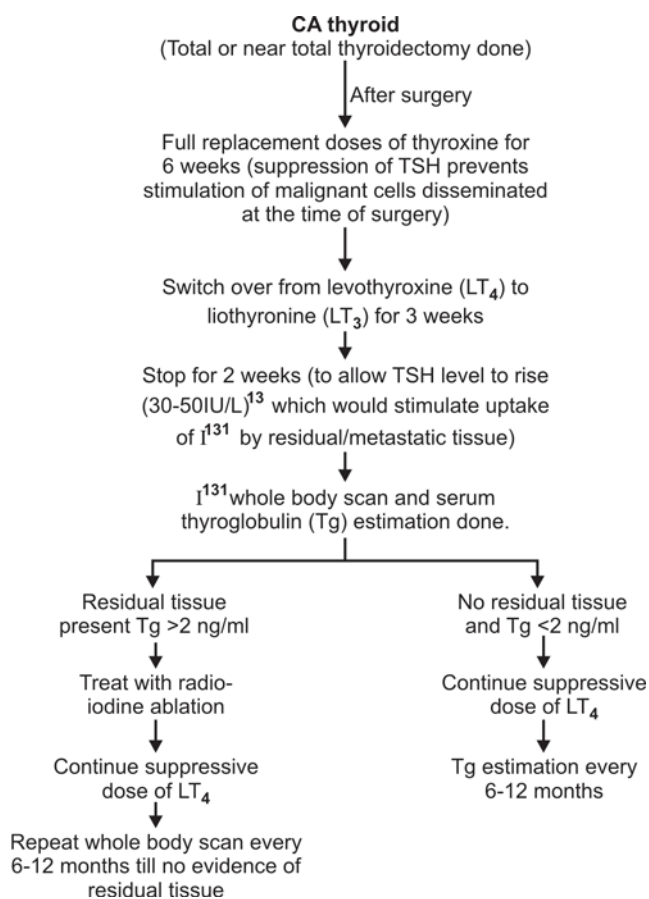


Fig. 2: Management plan for carcinoma thyroid

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