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# Thyroid nodules and their management

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No More dilemma

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## Introduction:

Thyroid nodule is a common occurrence. Majority of these nodules may be present without clinical evidence of thyroid disease. Statistics reveal that the incidence of palpable thyroid nodule is about 5%. Ultrasound neck is very sensitive in picking up thyroid nodules. Ultrasound can diagnose thyroid nodules even as small as ½ cm. Studies have shown that only 3-5% of thyroid nodules show malignant transformation.

Causes of thyroid nodules include:

## Benign causes:

1. Goiter
2. Hashimoto's thyroiditis
3. Simple / hemorrhagic cysts
4. Follicular adenoma
5. Subacute thyroiditis

## Malignant causes:

1. Papillary carcinoma
2. Follicular carcinoma
3. Hurthle cell carcinoma
4. Medullary carcinoma
5. Anaplastic carcinoma
6. Primary thyroid lymphoma
7. Metastatic malignant lesion

Tools of diagnosis as far as these thyroid nodules include:

1. Ultrasound neck
2. FNAC
3. Molecular / genetic marker analysis of fine needle aspiration biopsies

## Clinical features:

Majority of thyroid nodules are incidental in nature. These nodules are commonly

picked up during routine ultrasound of neck performed for some other problem. At this juncture it should be pointed out that carcinoma is common in single nodule than in multi nodular thyroid disease. A palpable neck node along with a firm thyroid nodule should always lead to suspicion of thyroid malignancy with nodal metastasis.

Palpation:

It is very difficult to pick out thyroid nodules less than 1.5 cm by palpation. The sensitivity of palpation varies from individual to individual. Moreover it is very difficult to palpate any nodule in a patient with thick and short neck. Nodules which are more than 4 cm are sinister. If these nodules are fixed to the skin and adjacent structures then extra glandular spread of malignancy will have to be suspected.

Features that point towards malignancy:

1. History of prior neck irradiation
2. Male gender
3. Extremes of age (20 & 70)
4. Family h/o medullary carcinoma thyroid / Multiple endocrine neoplasia
5. Growing nodule
6. Firm / hard nodule
7. Nodule with ill defined edges
8. Nodule that is fixed
9. Nodules associated with dysphonia / dysphagia / cough

Features in physical examination that could cause concerns of malignant transformation:

1. Thyroid nodules larger than 4 cms (20% risk of malignant transformation)
2. Firmness on palpation
3. Fixation of nodule to underlying structures
4. Cervical adenopathy
5. Vocal cord paralysis

Among the features listed above cervical adenopathy and vocal cord paralysis have the maximum predictive value for malignant transformation (up to 100%).

In patients with rapid enlargement of thyroid nodule a diagnosis of anaplastic carcinoma or primary lymphoma of thyroid should always be considered.

Growth of nodular goitre into the superior mediastinum can easily be identified by the presence of Pemberton's sign. This sign gets manifested because of partial occlusion of venous return from the thorax due to obstruction by the enlarging mass. This will be seen as enlargement of jugular vein and flushing of the face when the

patient is asked to lift both the hands above the head. This maneuver further narrows the mediastinal outlet which is already compromised by the presence of enlarging thyroid mass.

Hormone status in patients with thyroid nodule:

Patients with thyroid nodule are usually euthyroid. It is always worthwhile to perform TSH estimation in these patients as a routine. If TSH values are reduced then T3 and T4 estimation should be performed since hyper functioning nodules are 10% common in patients with single nodule thyroid.

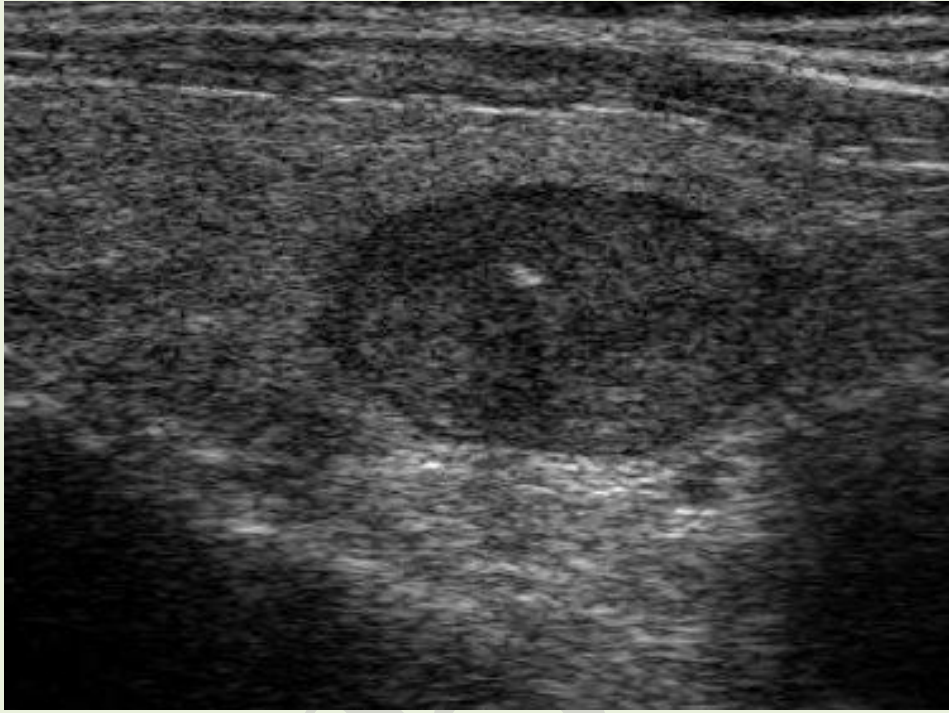
Estimation of serum calcitonin levels should be performed in all patients with solitary nodule thyroid with family history of medullary carcinoma thyroid / MEN types 2 a or b.

Role of ultrasound imaging in the diagnosis of thyroid nodule:

This is the most preferred imaging modality in evaluating a patient with thyroid nodule. It identifies even small nodules that cannot be palpated.

Advantages of ultrasound imaging:

1. It is very sensitive test which picks up even small nodules which cannot be palpated
2. Presence of multiple nodules can easily be identified.
3. Ultrasound can be used to assess the size of these nodules accurately and hence periodical scanning will pick up rapid increase in the size of these nodules
4. Certain features seen in ultrasound imaging points towards malignant transformation of the nodule. These features include solid mass (shown as hypo echoic areas), increased vascularity of nodules, presence of micro calcifications within the nodules, presence of irregular margins and absence of halo.
5. Ultrasound imaging is very useful in identifying suspicious nodules for performing FNAC



Picture showing ultrasound of benign nodule of thyroid

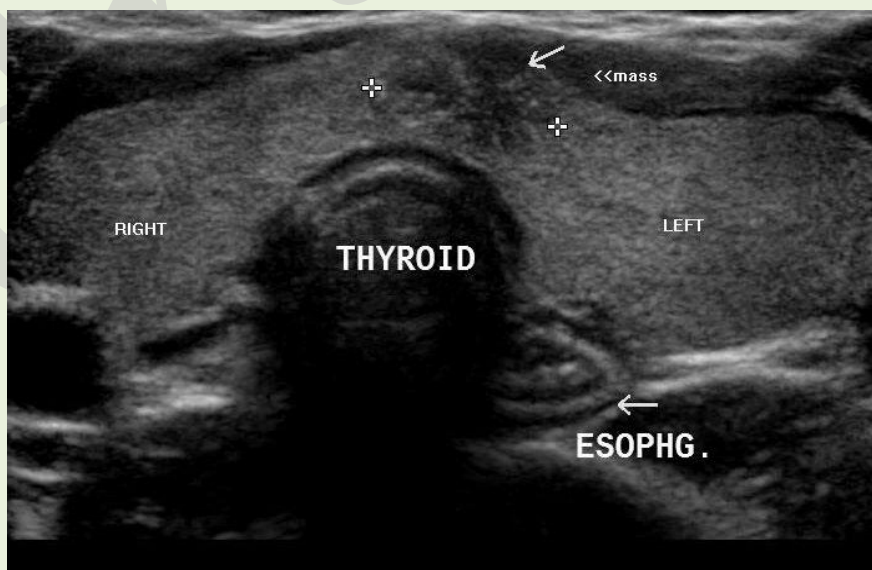
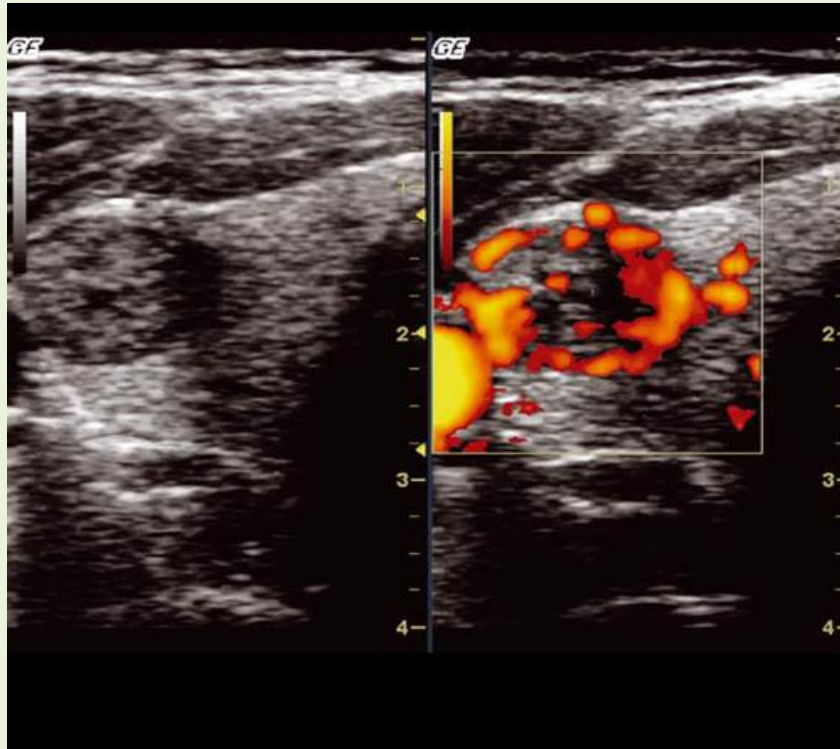


Figure showing hypo echoic nodule as seen in ultrasound



Picture showing increased vascularity of thyroid nodule suggestive of malignancy in ultrasound

Radioisotope imaging:

This helps to ascertain whether a nodule is a functioning one or not. It does not provide an accurate estimate of the size of the nodule. Commonly used radioisotopes for this purpose include Technetium 99, I 123 and I 131. It has been estimated that about 90% of thyroid nodules are cold and non functioning. About 10% of these non functioning nodules show malignant transformation. The only use for this procedure is that it warns that the nodule is hot and functioning so that FNAC need not be performed on a hot nodule. Performing FNAC in hot nodules causes abnormally

high increase of thyroxin in the blood causing thyrotoxicity which may have deleterious effects.

I 123 is more physiologic than technitium 99. Technitium 99 gets washed out of the gland and hence allows for shorter scanning time (20-30 minutes). Scanning can be immediately started after administering Technitium 99. If I123 is used then scanning can be started only after 24 hours after administration of the isotope. The scanning time lasts atleast 4 - 6 hours. Radiation exposure is more or less similar for both isotopes. Imaging resolution is better with Technitium 99 than radioiodine. Nodules below 1cm cannot be reliably detected by either of this scanning modality. Radioactive iodine scans can identify hot and cold nodules. The incidence of malignancy is more in cold nodule than hot nodule. Hot nodule is hyperfunctioning thyroid nodule, where as a cold nodule is a hypofunctioning nodule.

Indications for radioisotope imaging:

1. Identification of a functional solitary nodule when initial serum TSH is decreased.
2. If FNAC is reported as follicular neoplasm or suspicious lesion then the finding of Hot nodule in a scan may decrease the suspicion of malignancy
3. For detecting neck node metastasis.

Thallium 201 scan: is a very useful diagnostic tool to differential benign and malignant thyroid nodules. Three mCi of Thallium - 201 is used to image the thyroid gland. The uptake of the isotope is categorized into low uptake, intermediate uptake and high uptake. The risk of malignancy is more in high uptake lesions, and low in low uptake lesions.

Role of CT and MRI in thyroid nodule imaging:

CT scans are highly sensitive in detecting thyroid nodules. It is more useful to reveal mediastinal extension, retro tracheal extension and retroclavicular extension of the mass. Since the gland contains high iodine content, the brightness of the gland is increased on a CT even without contrast. MRI plays a minor role in the evaluation of thyroid nodule. Its major advantage over CT scan is that contrast agent (gadolinium) can be used without causing any interference to Radio nucleotide scanning.



## CT scan neck showing thyroid nodule

### PET scan:

This scanning modality has been extensively used in diagnosing head and neck malignant lesions. Malignant cells show increased uptake of FDG because of increased metabolic demands due to cell division. This is of no use as far as thyroid nodules are concerned because there is no significant increase in FDG uptake between normal thyroid cells and malignant cells of thyroid gland. Normal values of FDG intake have no relevance, but patients with avid uptake of FDG then they need to be more thoroughly evaluated for thyroid malignancy.

### FNAC:

Is the gold standard in evaluation of thyroid nodule. Since a majority of thyroid nodules are benign, this test is a must to identify the rarer malignant nodule.

### Indications for FNAC:

1. Every patient with a thyroid nodule is a candidate for FNAC.
2. Before embarking on FNAC examination serum TSH estimation & ultrasound is a must
3. As a rule of thumb functioning nodules need not undergo FNAC because risk of malignancy is very low in them.
4. All cold / hypo functioning nodules as identified by radio nucleotide scan should undergo FNAC examination.
5. Nodules of any size which show positive features in ultrasound should undergo FNAC examination.

### Procedure:

FNAC can be performed either by palpation / ultrasound guidance. If the nodule is palpable then it can be used as a guide as it would reduce the cost of investigation. The commonly available 22 / 27 gauge needles can be used to perform FNAC. Pathologists suggest using 25 / 27 gauge needles because samples harvested using them tend to be less bloody.

Various syringe holders have been advocated in order to enhance the suction effect produced. They include:



1. Cameco syringe pistol
2. Tao instrument
3. Inrad aspiration biopsy syringe / gun

It should also be borne in mind that the intrinsic suction effect provided by surface tension which these smaller diameter needles produce makes these fancy equipments redundant.

If FNAC is performed under ultrasound guidance then sampling should be done in different areas of the nodule including its wall, solid elements within and even calcified areas should not be ignored. Sampling should avoid cystic areas as yield from them invariably contains less cellular elements.

On insertion of the needle into the thyroid nodule a dwelling time of 2 – 5 seconds should be allowed. The needle should stay within the nodule during this dwelling interval. Then 3 forward and backward oscillations are performed in order to enhance the quality and quantity of yield. This maneuver also reduces blood contamination of the specimen.

Local anesthesia should be administered for all deep seated thyroid nodules. This will greatly reduce patient's discomfort and also enhance their active co operation.

For a thyroid FNAC to be reported as benign at least 6 groups of benign looking follicular cells should be present in a smear. Each of these groups should contain not less than 10 cells. It should also be stressed that any specimen containing abundant colloid should be considered benign even if the mandatory 6 groups of cells are not present in the smear. A sparsely cellular specimen with abundant colloid should always indicate a macro follicular node and hence certainly benign.

Two types of smears are prepared. Air dried and wet smears.

**Dry smear:** Two methods can be used. Diff - Quick method and May Grunwald - Giemsa methods. In quick dry method, the aspirate is expelled on to a glass slide, and is air dried. This method is best for immediate reading by the pathologist. The dried smear highlights the background colloid, cell architecture and cytoplasmic details. This technique is useful in the diagnosis of medullary and lymphoid tumors.

The wet smear (papanicolaou) is a wet smear that requires immediate fixation with 95% alcohol. This method is best suited for detecting papillary cancer.

FNAC will be reported as:

1. Unsatisfactory
2. Intermediate
3. Malignant

Intermediate group can be further subclassified into:

1. Follicular lesion of undetermined significance (FLUS)
2. Follicular neoplasm
3. Suspicious for malignancy as per Bethesda thyroid cytology classification

Ancillary procedures can be used to improve the accuracy of FNAC. These include:

1. Immunohistochemistry
2. Ploidy studies
3. Molecular markers
4. Reverse polymerase chain reaction

FNAC is the most important method in the diagnosis of malignant nodule. Other procedures that increase the accuracy of FNAC include studies of mutation involving BRAF, RAS, RET / PTC genes. Majority of papillary carcinomas will have mutations of the above mentioned genes. Mutations involving Ras proto oncogenes have been implicated in the pathogenesis of follicular carcinoma of thyroid gland.

It has been shown that sampling errors in FNAC increase as the size of the thyroid nodule increases. When the size of the nodule increases to 4 cms the false negative results also increase by 30%.

Ultrasound guided FNAC can be performed if the nodules are small (1cm / less in size). It increases the accuracy of the procedure.

Frozen section analysis:

Thyroid tissue suspicious of malignancy can be subjected for frozen section analysis while the patient is still on the operation table. This will reduce the rate of patients who need to come back to the operation theater for completion thyroidectomy. The hemithyroidectomy specimen is sent for frozen section evaluation while the surgeon waits in the operation room. The report usually is expected within 15 mins. If it turns out to be mitotic lesion then total thyroidectomy is resorted to. If the report comes as benign lesion then the wound is closed and the patient is extubated.

American thyroid association guidelines regarding management of thyroid nodule:

American thyroid association has come out with detailed guidelines for managing patients with thyroid nodule. The salient feature of these guidelines is the incorporation of mutational analysis. These guidelines include:

1. All patients with asymptomatic thyroid nodule under 1 cm size should undergo

repeated ultrasound examination every year. FNAC is indicated in these patients only when there is a change in the growth pattern as evidenced by a rapid increase in the size of the nodule. Biopsy of nodules under 1 cm is indicated only when there is a history of radiation exposure or family history of thyroid malignancy.

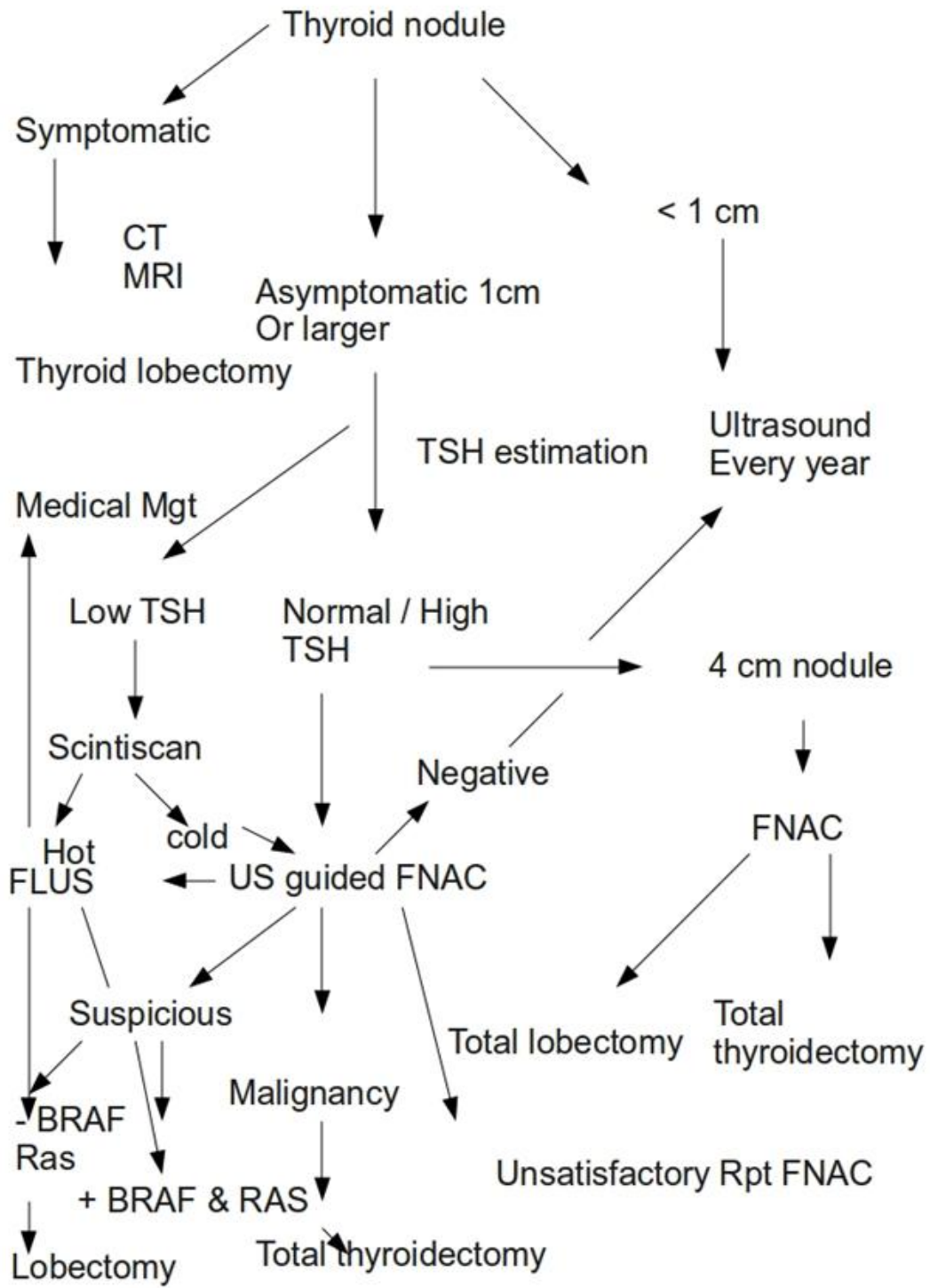
2. Patients with asymptomatic thyroid nodule over 1 cm in size should undergo TSH estimation. Reduced TSH values in these patients should arouse suspicion of hot nodule (hyper functioning nodule). These patients should undergo thyroid uptake scan. Since patients with hot nodules have less than 1% risk of malignant transformation they are better managed medically by a medical endocrinologist.

3. If the nodule is asymptomatic and is 4 cm or more in size, FNAC should be done. This is because that these patients require surgery and a pre operative diagnosis of malignancy or otherwise will help in deciding whether the patient is going to undergo total thyroidectomy or hemithyroidectomy. If FNAC report turns out to be unsatisfactory then it should be repeated again. If FNAC is reported as follicular lesion of undetermined significance then it should be submitted for mutational studies. If FLUS (follicular lesion of undetermined significance) turns out to be positive for BRAF and RAS mutations then the patient should be submitted for total thyroidectomy. If mutational studies are not available then these patients should be offered diagnostic lobectomy. If FNAC reports the lesion as benign then these patients should be followed periodically by performing ultrasound examinations for any abnormal increase in size of the nodule. Attempts at suppressing the lesion by suppressing TSH levels are not effective. If FNAC report turns out to be malignancy then total thyroidectomy should be resorted to. Before embarking on total thyroidectomy ultrasound examination of neck should be performed to pick up any suspicious nodes which are too small to be palpated.

4. Patients with symptomatic thyroid nodules (symptoms caused due to obstruction) should be surgically managed. Symptoms could be airway obstruction or difficult in swallowing or change in voice. Change in voice occurs commonly in malignancy.



Image showing a patient with thyroid nodule



Management algorithm of thyroid nodule

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