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 glands so that they are felt or seen as a lump in front of the neck.

SOLITARY THYROID NODULE
Definition & classification
An isolated nodule in the thyroid gland

1. Benign (90%)
   A. Cysts
   B. Adenomas
      - Papillary
      - Follicular (Common)
      - Hurthle Cell type
      - Embryonic
      - Fetal
   C. Toxic adenoma: solitary hyper-functioning thyroid nodule
   D. Non toxic adenoma: solitary nonfunctioning thyroid nodule.

2. Malignant
Primary thyroid carcinomas are the commonest. Far less common are: lymphomas or metastatic tumor disease. Papillary carcinomas is the most common of thyroid malignancy, accounting for 80-90% of all thyroid cancers, but only represent 1% of all malignancies. Thyroid cancer has a favorable prognosis and accounts for less than 0.5% of cancer deaths.

Many palpable thyroid nodules, thought to be solitary, are actually part of multi-nodular thyroid gland. The main aim in the evaluation of STN is to differentiate benign from malignant lesions at a reasonable cost & trauma to the patient.

EPIDEMIOLOGY
A palpable thyroid nodule is usually > 1 cm. Prevalence varies considerably worldwide, depending on regional iodine sufficiency. Iodine deficient areas: up to 50% of adults. Iodine sufficient areas: ~5% of adults (U.S.A). It is more common in women (6.4%) than men (1.5%). 10% women & 2% men in another study. Prevalence increases linearly with age.

Prevalence by ultrasonography is 30-40% to 50%. Prevalence at autopsy is up to 50%. Childhood STN has a higher incidence of Thyroid Cancer i.e. 15-20% as compared to adults.

MECHANISM / ETIOLOGY
Thyroid nodules develop as monoclonal neoplasms that arise from a single mutated cell. Molecular basis of nontoxic solitary adenomas is poorly understood. They probably arise from somatic mutations of genes that stimulate signaling cascades involved in cell proliferation. Most toxic adenomas arise from mutations that stimulate the Thyroid-Stimulating Hormone (TSH) receptor signaling pathway. Most have acquired somatic activating mutations in TSH receptor. These mutations stimulate cyclic adenosine monophosphate cascade, leading to enhanced thyroid follicular cell proliferation and function.

SYMPTOMS
A. Nontoxic adenomas: Large adenomas present as a neck mass. Smaller adenomas are typically asymptomatic.
B. Toxic adenoma: Mild symptoms of thyrotoxicosis.
C. MEN - 2 (multiple endocrine neoplasia). Multifold symptoms
D. Multiple symptoms of other endocrine diseases

**SIGNS**
Most palpable nodules are > 1 cm in diameter. Ability to detect a palpable thyroid nodule on physical examination depends on location within the gland, superficial versus deeply embedded, anatomy of patient’s neck, including degree of adiposity and experience of examiner.

**HISTORY AND PHYSICALS**
In both prospective and retrospective studies, the sensitivity and specificity rates for detecting thyroid malignancy by history and physical examination were around 60% and 80% respectively.

Only about 20% of patients with later confirmed malignancy had, when initially seen, neither suspicious historical features nor evidence of any potential malignancy on neck examination.

**DIFFERENTIAL DIAGNOSIS**
- Primary thyroid cancer
- Functioning adenoma
- Nonfunctioning adenoma
- Cyst
- Thyroid lymphoma
- Cancer metastatising to the thyroid
- Hashimotos Thyroiditis.
- Simple Goitre
- Development defects e.g. - ectopic tissue.

**DIAGNOSTIC APPROACH**
Evaluation consists of 2 components. Determine if nodule is autonomously functioning and possibly causing hyperthyroidism or has high risk of malignancy. Nodules with high risk of malignancy require surgery whereas benign can be followed up.

**HISTORICAL IMPORTANCE**
a) Age and sex
Thyroid nodules are more common in women and increase in incidence with age. Male sex and youth (<15-20 years) should therefore raise greater suspicion. Old age (>70 years) is also a risk factor for malignancy.
b) Exposure to radiation (age, type, and location)
Increased risk of both benign and malignant thyroid lesions persists for at least 3 decades beyond time of exposure.
c) Family history of medullary thyroid cancer or multiple endocrine neoplasia (MEN - 2 or 2b syndrome) consisting of Phaeochromocytoma. HTN, Chronic diarrhea/constipation, hyper parathyroidism.
d) Rapid enlargement, pain or tenderness over the nodule.
dysphasia, dysphonia, or hoarseness.
e) Fixture of nodule to underlying structures, very hard or firm nodule, movement with swallowing & regional lymphadenopathy.
f) Laboratory assessment: Serum TSH measurement should precede imaging studies and FNA biopsy.

**BENIGN LESIONS**
Family history of Hashimoto’s thyroiditis, symptoms of hypo or hyperthyroidism, pain or tenderness associated with the nodule, surface of nodule being soft, smooth, and mobile, multinodular goitre without a dominant nodule and female sex.

**MALIGNANCY CHARACTERS**
- Young patients (< 20 years age) or old (> 70 years age), male sex, H/O external neck radiation during childhood or adolescence, recent change in voice, past family history of thyroid carcinoma.
- Firm consistency of nodule, irregular shape, fixation to underlying or overlying tissues, and suspicious regional lymphadenopathy.
- Long standing and not enlarging nodules are likely to be benign. Benign nodular lesions are more common in females than males. Nodular lesions raise more suspicion of carcinoma in men than in women.

**LABORATORY TESTS**
Measurement of TSH levels to direct diagnostic approach, with free T4, as a complementary test.
a) Low TSH level
- Repeat TSH measurement, with measurement of free $T_4$ and free $T_3$ to establish degree of hyperthyroidism.
- Perform thyroid scintigraphy (I$^{123}$iodine or $^{99m}$technetium) to exclude Hyperthyroidism
b) Normal TSH level
- Proceed to FNAB.
c) High TSH level
- Repeat TSH measurement, with measurement of free $T_4$.
- Suspect Hypothyroidism for further evaluation.
- Consider observation of nodule if levothyroxine therapy is instituted.
- Consider FNA biopsy if clinically warranted.
- Serum Thyroglobulin levels: more increased in follicular carcinoma than in benign lesion. (Less useful in diagnosis).
Serum calcitonin levels: Increased in medullary thyroid cancer and in MEN-II.

DNA analysis: Mutations seen in the Ret - Proto-oncogenes are used to survey medullary carcinoma of Thyroid (MTC) & MEN syndromes.

Serum carcinoembryonic antigen (CEA) levels are increased in MTC.

Serum anti-TPO antibody and anti-Tg (thyroglobulin) antibody levels: estimations are useful in chronic autoimmune thyroiditis especially if serum TSH is elevated.

**IMAGING - THYROID**

Thyroid scintigraphy (123iodine or 99mtechnetium)

Radionuclide scans in evaluation of solitary nodules should be limited to patients with a low TSH level to identify autonomously functioning nodules (~5%). Radionuclide scans are unnecessary in setting of a normal TSH level, and one may proceed directly to FNA biopsy. Nodules with increased uptake (hot) are toxic adenomas and almost never malignant. (~1-4% chances only). Nodules that accumulate radionuclide equal to surrounding tissue (warm), or nodules with low uptake (cold), are most often benign (~80%) but may be malignant in to 25% and therefore require FNA biopsy. Cold nodules are usually up to 25% hypo functional. This test does not differentiate a benign & malignant thyroid nodule, with greater accuracy, and also at times misinterprets functional status of thyroid.

**ULTRASONOGRAPHY**

Often reveals multi nodular goitre rather than solitary thyroid nodule. Dominant palpable nodules should be managed as solitary thyroid nodules even if ultrasonography reveals additional non-palpable nodular disease. Even a 1 mm size nodule could be detected with a high resolution USG. This test also doesn’t differentiate malignant from benign nodules. Hypo echogenicity in solid nodules, presence of micro calcifications, irregular shape, intra nodular vascular spots, absence of halo & cystic elements suggests high malignancy. Alternatively comet tail sign and coarse calcification suggests lower risk of malignancy.

**USG GUIDED FNA BIOPSY**

It provides visualization of needle tip during procedure to ensure accurate sampling & reduces false-negative rate (compared with palpation-guided FNA biopsy). It is especially useful in the following circumstances:

- Nodules that are difficult to palpate
- Repeat FNAC for a previous non diagnostic specimen

CT SCAN / MRI

CT Scanning & MRI role is limited, except to see the spread & compression of neighbouring structures.

PET-SCAN

With the advent of the increased use of PET scanning in the staging and surveillance of various malignancies, the phenomenon of the PET identified thyroid incidentalomas is becoming more prevalent. These PET detected nodules have been shown in some studies to harbor a higher malignancy risk.

**FNAB / FNAC**

It is a most accurate test for the evaluation of thyroid nodules. Tissue samples are obtained for cytologic analysis using 22- to 25-gauge needles, with or without local anesthesia. Specimen adequacy requires ≥ 2 slides showing ≥ 6-8 cell clusters. /or 5 or 6 groups of 10 - 15 well preserved cells.

- False-positive rate: ~1.1%
- False-negative rate: ~2.3% (Papanicoloan guidelines)
- Overall accuracy > 95%
- Sensitivity: 83%
- Specificity: 92%

**MAJOR LIMITATIONS**

- Inability to distinguish follicular adenomas from follicular carcinomas, as carcinomas require to reveal vascular or capsular invasion of the adenoma.
- Specimen inadequacy:, especially in cystic lesion.

Large needle biopsy: May be used to diagnose follicular carcinoma, though beset with increased complication rates. Core biopsy (with or without USG guidance) should be considered after two futile aspirations. Thyroid peroxide (TPO) immuno chemistry with a monoclonal antibody termed Moab 47 increase the accuracy of FNAC in patients with follicular carcinoma. Nodules of 2-4 cm should be studied by surgical removal than by FNAC.

FNAC DIAGNOSTIC categories and recommended actions. BRITISH THYROID ASSOCIATION GUIDELINES (Table I)

**TREATMENT APPROACH**

Treatment approach depends on outcome of the complete
### Table I

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Description</th>
<th>Action recommended</th>
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<tbody>
<tr>
<td>Thy-1</td>
<td>Non-diagnostic, insufficient sample. Cyst containing colloid or histiocytes only, in the absence epithelial cells</td>
<td>To repeat FNAC. Ultrasound- guidance May help. If cyst aspirated to dryness with no residual swelling. clinical/ ultrasound follow alone may be sufficient</td>
</tr>
<tr>
<td>Thy-2</td>
<td>Benign, non-neoplastic. Cyst containing benign epithelial cells.</td>
<td>Repeat FNAC in 3-6 month. Two non-neoplastic results 3-6 months apart should exclude neoplasia</td>
</tr>
<tr>
<td>Thy-3</td>
<td>Follicular or Hurthle cell lesion/ suspected follicular or Hurthle neoplasm. (Figure1)</td>
<td>MDT discussion-diagnostic lobectomy</td>
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<tr>
<td>Thy-4</td>
<td>Suspicious of malignancy. (figure-2)</td>
<td>MDT discussion-surgical intervention. e.g. Total thyroidectomy</td>
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<tr>
<td>Thy-5</td>
<td>Diagnostic of malignancy</td>
<td>MDT discussion - surgical intervention, e.g. Total thyroidectomy.</td>
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**Fig. 1**

**Fig. 2:** Thyroid follicular cells in a microfollicular pattern

**Fig. 3:** Cytology of a Papillary Thyroid carcinoma. Showing the fibrovascular core and an intranuclear inclusion (arrowed)
functional and cytological evaluation. (Fig.1)

MANAGEMENT

1. Malignant Nodule
   Surgical resection, followed by possible ablative therapy with radioactive 131iodine. (Fig.2&3)

2. Follicular Neoplasm
   Surgical resection. (Fig.4)

3. Suspicious Cytology
   Surgical resection

4. Benign Nodule
   Monitor nodule size over time by periodic palpation and ultrasonography. Use of TSH suppression with levothyroxine, in the hope of shrinking the nodule, is now generally not recommended. Most studies show no effect on nodule size. Thyroidectomy should be done if a nodule enlarges or develops in a patient whose serum thyroglobulin rises in spite of TSH suppression with thyroxin. Risk of thyrotoxicosis must be considered if Levothyroxin is used. If instituted, use 0.05-0.1 mg/d, and monitor nodule size by ultrasonography. Serum TSH should be monitored with the goal of attaining a subnormal, but not immeasurable, TSH level (0.3-1 mU/L). Levothyroxin-suppressive therapy should be discontinued if there is no evidence of reduction in nodule size. Its contraindicated in patients > 60 years of age, postmenopausal women, and persons with a low TSH level Repeat FNA analysis of benign nodules that have not grown substantially is not warranted.

5. Non diagnostic specimen
   Ultrasonographic guided FNAB.

6. Toxic Adenoma
   Radioactive 131iodine ablation (most common)
   Surgical resection
   Ant thyroid drugs (less preferred)
   Percutaneous ethanol sclerotherapy.

7. Thyroid Cysts
   Aspiration will resolve 25-50% of cysts, but fluid reaccumulation is common. Aspiration could be repeated thrice. Surgery is indicated for growing or painful cysts, recurring after three aspirations, size > 4cm, or complex (both solid and cystic). Percutaneous ethanol sclerotherapy has been tried.

MANAGEMENT SURVEY

A survey evaluated current trends in the management of the non toxic solitary thyroid nodule by expert endocrinologists in North America v/s similar European thyroid association survey. Clinical factors suggesting thyroid malignancy (e.g. rapid nodule growth and a large nodule of 5cm) lead a significant number of clinicians (40-50% p<0.00001) to disregard FNAB RESULTS and to choose a surgical strategy.

Nevertheless North American endocrinologists rely heavily on FNAB results as against the Europeans who are more lab oriented. Compared to the European thyroid association survey, North American endocrinologists differ and use less frequently the following,

a) Imaging scintigraphy; 23% v/s 66 %;(p<0.0001)
b) Ultrasonography; 34% v/s 80 %;(p<0.0001)
c) Serum calcitonin; 5% v/s 43% (p0.0001)
A non surgical strategy prevails in North America, and despite controversies on the effect of L-T4, is used by more than 40% in both Europe and North America.

INCIDENTALOMAS

Clinically non-palpable incidental thyroid swelling < 1 cm are called “incidentalomas”. These are not uncommonly noted during surgery or imaging performed for another purpose. In patients with low risk characteristics these nodules are less cancerous. Also, there is no evidence to show that treatment of such sub centimeter micro carcinomas improves outcome. The exception to the above is an incidentaloma identified by FDG-PET scan, which carries a 50% chance of malignancy.
and therefore should be operated.

**MONITORING**
Monitor nodules physically, by TSH levels, FNAC, and ultrasonographically annually. Repeat FNAB for enlarging nodules.

**COMPLICATIONS**
1. FNAB: Local discomfort, Hematomas, Infection.
2. THYROIDECTOMY / LOBECTOMY. Recurrent laryngeal nerve injury, Post-surgical hypothyroidism, hypoparathyroidism.

**PROGNOSIS**
Benign nodules; usually persist or grow slowly & Malignant transformation is rare. Malignant nodules; Prognosis depends on histology.

**PREVENTION**
Avoid exposure to external radiation. Adequate iodine intake may reduce the incidence of thyroid nodular disease.

**CONCLUSION**
A majority of the thyroid nodules present with a lump in front of the neck, common in females, 90% of them are benign, adenoma being the commonest amongst benign lesion. FNAC is a very reliable and powerful screening method in the pre-operative diagnoses of Simple Thyroid Nodule. Jointly, FNAC, thyroid imaging, and ultrasonography can detect them with 90% accuracy. Thyroid scan is indispensable for toxic nodular goitre.

**REFERENCES**
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