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Review Article

A Clinical Review for Management 0f Thyroid Nodules

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Abstract

Thyroid nodules are common clinical findings due to advances in radiological assessment by ultrasound and CT scans. Most of these nodules are incidental findings. It's important to differentiate benign nodules from premalignant or malignant lesions. We often don't find answers about the nature of the nodules by one modality, and it needs a combination of diagnostic modalities. A significant number of these cases also need follow-up for ongoing monitoring. These also have a significant psychological and financial impact on patients.

This review focuses on the various clinical, radiological, and histological clues based on international guidelines. The purpose is to provide a clear understanding and approach to managing such cases.

Keywords: Thyroid nodules, thyroid cancers.

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Introduction

Thyroid nodules are common clinical findings due to advances in radiological assessment by ultrasound and CT scans. Most of these nodules are incidental findings. It's important to differentiate benign nodules from premalignant or malignant lesions. We often don't find answers about the nature of the nodules by one modality, and it needs a combination of diagnostic modalities.

Clinical detection of thyroid nodules is 5%, so a normal thyroid examination doesn't exclude nodules. But it's ten times more with imaging such as ultrasound (USS). Nodules can be cancerous, adenoma, cysts, colloid cysts, inflammatory, etc.[1]

Risk factors for thyroid nodules

Risk factors for thyroid nodules are increasing age, female sex, iodine deficiency, neck radiations, etc. Approximately 5% of the nodules are malignant. Hyper-functioning nodules are very rare to be malignant. The risk factors for a nodule to be malignant are the following:

- The size of the nodule is directly proportional to the risk.
- Ultrasound features, as discussed below,
- FNAC grading, as discussed below,
- Lymph node involvement or
- Extra thyroidal disease, etc.
- Neck radiations,
- Positive personal or family history of thyroid cancer in first-degree relatives,
- Family or personal history of syndromes associated with thyroid cancer (MEN-II & III, Cowden syndrome, Werner syndrome, familial adenomatous polyposis, Carney complex, etc.)

90% of thyroid cancers are derived from thyroid follicles (papillary, follicular). The remaining are medullary thyroid CA, anaplastic thyroid cancers, lymphoma, or metastatic lesions.[2]

The first thing is to assess TSH

- TSH in the setting of a nodule needs an Iodine uptake scan to assess the functional status of the nodule (s). Hyper-functioning nodules have increased uptake with the low/absent uptake by the remaining thyroid gland. Usually, hyper-functioning nodules don't need FNAC as the risk of malignancy is very low.[2,3]
- Nodules with normal or high TSH don't need an uptake scan and should be assessed by USS with or without FNAC.

- Nodules with increased uptake on PET-Scan have a 30-40% risk of malignancy and need FNAC.[2,3]

Ultrasound (USS) findings

It's an operator-dependent assessment and needs expertise. It assesses nodules and the remaining thyroid for its echogenicity in thyroiditis, hypervascularity in Grave's, etc. It also helps for FNAC. USS thyroid should also routinely evaluate for cervical lymph nodes. Lymphadenopathy increases the risk of the nodule becoming malignancy, and the management plan is often different if lymph nodes are involved.

- Solid vs. cystic component: The solid component has a higher chance of malignancy, whereas purely cystic nodules are benign. Cystic nodules don't need diagnostic FNAC, but therapeutic fluid aspiration and alcohol-induced sclerosis can help for large, purely cystic nodules. A spongiform nodule (isoechoic nodule with more than 50% cystic area) has a <3% risk of malignancy and doesn't need diagnostic FNAC. Mix solid and cystic nodules have shallow risks, but the risk can increase, especially when the solid component is eccentric and hypoechogenic.
- The echogenicity of the nodule: Hypo echoic is darker & hyper echoic is brighter than the surrounding thyroid. The cystic fluid doesn't have echogenicity (isoechoic). The reduced echogenicity of the nodule compared to the surrounding thyroid and muscles increases the risk for malignancy. Solid & hypoechogenicity increase the malignancy risk of the solid nodules from 5-10% (solid without hypoechogenicity) to 10-20% (solid with hypoechogenicity). Isoechogenic or hyperechogenic nodules are less at risk for malignancy.
- Taller than broad nodules indicate growth against thyroid tissue plains and increase the risk of malignancy.
- Irregular borders (infiltrating or lobulated margins) indicate invasion of the adjacent tissue. Border irregularities increase the risk of malignancy.
- Interruption in capsular calcification indicates malignancies invading the capsules and extending to adjacent tissue. This type of calcification is very suggestive of malignancy.
- Calcification indicates a dystrophic process, and any pattern of calcification increases the risk of malignancy. Calcification can be microcalcification, interrupted peripheral calcification, calcifications in layers, etc. Punctate echogenicity foci indicate calcification.

Solid nodules with hypoechogenicity and additional findings (irregular borders, calcification, taller more than wide, etc.) increase the risk (TR4, TR 5, high risk) to more than 50-55% or even more.

TI-RADS (Thyroid imaging-reporting and data system) & ATA (American Thyroid Association) are two major systems used. The main difference is the size of nodules used as a cut-off for FNAC. ATA uses a smaller size than TI-RADS, except for high-risk or TR-5 nodules, where both systems agree upon the size of 1 cm. A low cut-off point by ATA has higher sensitivity and a low risk of missing a malignancy at the cost of higher numbers of negative FNAC. TI-RADS is categorized from 1 to 5 based on the summation of the scores allocated to each of the five criteria. In contrast, ATA classifies nodules as benign, very low risk, low risk, intermediate, and high risk for malignancy.[4-7]

Points on USS for TI-RAD Scoring system:

- Mixed solid and cystic has 1 point,
- Solid has 2 points,
- Ecgogenecity: hypoechogenicity also has 2 points), very hypoechoic carries 3 points, hyper or isoechoic scores 1 point,
- Tall: taller than wider gets 3 points,
- Calcification: lobulated margins have 2 points, extrathyroidal extension has 3 points, calcification gets 3 points for punctate, 2 points for peripheral, and 1 point for macro calcification.[7,8]

TI-RAD Grading:

- TR1: Zero point is TR 1
- TR2: 2 points is Tr2
- TR3: 3 points is Tr3
- TR4: 4-6 points is Tr4
- TR5: 7 or more points is Tr5.

TR1 is benign & TR2 is not suspicious; no FNAC is recommended for both.

TR3 is mildly suspicious and needs FNAC if 2.5cm or more and follow-up if 1.5cm or more.

TR4 is moderately suspicious and needs FNAC if 1.5 cm or more and follow-up if 1 cm or more.

TR5 is highly suspicious and needs FNAC if 1cm or more, follow-up if 0.5cm or more.

Nodules less than 1 cm should be biopsied if there is a local invasion, metastasis, or high-risk factor for malignancy in history. Otherwise, nodules smaller than 1 cm are not recommended for FNAC by both systems, as the risk of malignancy is very low.[9-12]

Fine Needle Aspiration Cytology (FNAC)

Limitations of FNAC

- Cytological assessment for nuclear and cytoplas-

mic abnormalities detects changes in the papillary CA. These changes are nuclear elongation, grooves, inclusions, chromatin clearing, etc. Cell changes such as papilla formation are also detected. These changes are classic for papillary but not for follicular cells. In addition, the follicular adenoma can be differentiated from the follicular CA only by capsular &/or vascular invasion. FNAC does not detect this architectural invasion. Also, papillary CA with follicular variant is not detected by FNAC.

- USS-guided FNAC reduces the risk of false negative results and complications. High-volume centers have more expertise and, hence, more reliable reporting. FNAC needs expertise and is more reliable in high-volume centers.
- It can be done without stopping NOACs. Warfarin is not stopped as long as INR is <2.5. Pain is the most common issue.[13,14]

FNAC Grading of the nodules:

FNAC is classified in I-V grades (Bethesda classification).

Grade I is an inadequate sample that does not have an adequate number of cells. Six groups of benign cells, each with at least ten (10) cells, are needed for the sample to be adequate. Repeat FNAC is required as the risk of missing malignancy is 5-10%.

Grade II is benign nodule and thyroiditis. There is a 1.5-3.0% risk of missing malignancy. The patient needs follow-up surveillance with repeat USS &/or FNAC.

Grades III & IV are indeterminate and need further assessment based on the baseline USS findings of the nodule.

- Grade III is follicular lesions or atypia of undetermined significance. It needs further assessment by repeat FNAC, genetic testing, or surgery. The risk of missing a malignancy is 6-30%. Repeating FNAC for grade III may also help if it turns out to be grade II on repeat FNAC.
- Grade IV is follicular neoplasm or suspected follicular neoplasm. The risk of malignancy is 10-40%. Further molecular testing, if available, may be recommended for suspected cases. Otherwise, lobectomy is advised.

Table 1: *Plan as per TI-RAD Class*

TI-RAD Class	FNAC	Follow up USS
TR1 is benign & TR2 is not suspicious;	No FNAC	
TR3 is mildly suspicious	FNAC if 2.5cm or more	If 1.5cm or more.
TR4 is moderately suspicious	FNAC if 1.5 cm or more,	If 1 cm or more
TR5 is highly suspicious	FNAC if 1cm or more,	If 0.5cm or more.
Nodule less than 1 cm	FNAC only if there is local invasion, metastasis, or high-risk factors for malignancy in history	

Table 2: *Thyroid nodule: risk assessment for malignancies*

Risk factors for malignancy	USS findings indicate risk	FNAC Grades indicating risk.
The size of the nodule is directly proportional to the risk. Lymph node involvement Extra thyroidal disease, etc Neck radiations, Positive personal or family history of thyroid cancer in first-degree relatives, Family or personal history of syndromes associated with thyroid cancer (MEN-II & III, Cowden syndrome, Werner syndrome, familial adenomatous polyposis, Carney complex, etc.)	The solid component has a higher chance of malignancy, whereas purely cystic nodules are benign. Hypoechoic increases the risk for malignancy. Solid nodules with hypoechogenicity increase the malignancy risk from 5-10% (solid without hypoechogenicity) to 10-20% (solid with hypoechogenicity). Taller more than wide nodules Irregular borders Interruption in capsular calcification Calcification: microcalcification, interrupted peripheral calcification, calcifications in layers, etc.	**Grades III & IV** are indeterminate and need further assessment based on the baseline USS findings of the nodule. **Grade V** is suspicious of malignancy. The risk of malignancy is 44-75%. Therefore, surgery (lobectomy or subtotal/total thyroidectomy) is recommended. **Grade VI** is malignant cytology, and the risk of malignancy is more than 94%. Therefore, surgery is recommended.
Surgery recommended for: •	• TR5 & TR4 • Large nodule with cosmetic concerns or compression symptoms	• Grade V or VI, • Suspicious grade III suspicious grade IV nodules

- USS can assist with such indeterminate cases and help clarify further plans. Surgery can be avoided if USS shows TR1 or TR2 features of these indeterminate (III or IV) nodules. However, surgery should be recommended if the USS shows TR4 or TR5 for these indeterminate nodules (III or IV).[15-17]
- Molecular testing for such indeterminate nodules is costly and unavailable in many setups. Also, protocols for these tests need standardization. However, these tests can help assess the risk further. These techniques include gene testing (DNA sequencing, gene mutations, gene expressions by assessing mRNA, etc.). These techniques have 50-70% sensitivities. Indeterminate nodules with negative molecular testing need surveillance and can avoid surgery. Positive gene abnormalities in these indeterminate nodules need surgery. However, some benign nodules also have some genetic mutations.[18-21]

Grade V is suspicious of malignancy. The risk of malignancy is 44-75%. Therefore, surgery (lobectomy or subtotal/total thyroidectomy) is recommended.[15,16]

Grade VI is malignant cytology, and the risk of malignancy is more than 94%. Therefore, surgery is recommended.[16,17]

Management of the nodules:

Surgery for nodules22-25

Any suspicious nodule with a higher risk of malignancy, either clinically, radiologically, or on FNAC, needs resection. Clinical indications are large nodules with cosmetic concerns or compression symptoms. Radiological includes TR5 & TR4. Histologically, nodules with grade V and VI or suspicious grade III or IV nodules.

Surgical options can be lobectomy or near-total or total thyroidectomy. Complete removal of the thyroid eradicates any remaining malignancy but also needs life-long thyroxine replacement. Lobectomy can avoid lifelong thyroxine replacement, but the risk of recurrence in the remaining thyroid is there.

Total thyroidectomy is preferred over lobectomy for any of the following cases:

- Extra-thyroidal extension
- Lymph node metastasis
- Nodule 4cm or bigger
- Nodules in the other lobe as well
- High-risk histological/cytological findings
- Patients are already on levothyroxine therapy (as now saving the remaining thyroid is of no use).
- High-risk surgical candidates who can't afford repeat surgery if needed for the remaining thyroid.

Non-surgical ablation

The ablation is done with radiofrequency ablation, thermal ablation, microwave ablation, high-frequency ultrasound wave ablation, etc. These can't be used for suspicious or malignant nodules as tissue diagnosis is missed & also there is a risk of recurrence of the malignancy in the remaining glands. The nodule should be benign both on USS and FNAC. At least two FNACs should be benign before using these non-surgical options.[22-25]

Follow-up of thyroid nodules

Repeat FNAC for any of the following:

- Increase in size: more than 50% increase in volume of the nodule on follow-up USS.
- Nodules with high-risk USS features (TR5) with initial benign FNAC should also repeat FNAC in 12 months.
- If the nodule increases in size or develops concerning findings, a repeat FNAC is needed.

Repeat Ultrasound

- Cytologically benign nodules with low or medium risk on USS need to repeat USS in 12-24 months. The next USS can be repeated in 2-3 years if stable. Any nodule that hasn't changed over five years of follow-up needs no further follow-up. If the nodule increases in size or develops concerning findings, a repeat FNAC is needed.

No Ultrasound or FNAC needed

- USS showing TR1 or TR2 doesn't need any follow-up as the malignancy risk is very low.
- Any nodule that hasn't changed over five years of follow-up needs no further follow-up.22-25

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