

Thyroid Nodule

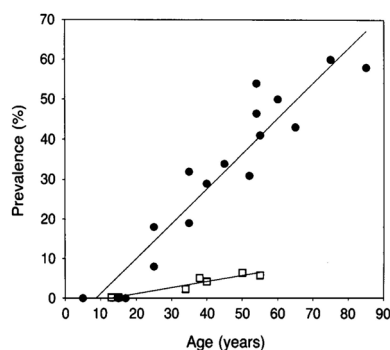
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손 태 서

Thyroid nodule

- Definition
 - a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma
- Nonpalpable nodules detected on US or other anatomic imaging studies are termed incidentally discovered nodules or 'incidentalomas'
- Guidelines
 - Revised ATA Management guidelines, *Thyroid* 19; 1167-1214, 2009
 - AACE/AME/ETA guidelines, *Endocrine Pract* 16(Suppl 1):1-43, 2010
 - Revised Korean Thyroid Association Guidelines, *Kor J Oto Head Neck Surg* 54;8-36, 2011

Prevalence of thyroid nodules



Mazzaferri EL, *N Engl J Med* 328:553-9, 1993

Causes of thyroid nodule

- | | |
|--|---|
| <ul style="list-style-type: none"> • Benign nodular goiter • Chronic lymphocytic thyroiditis • Simple or hemorrhagic cysts • Follicular adenomas • Subacute thyroiditis | <ul style="list-style-type: none"> • Papillary carcinoma • Follicular carcinoma • Hurthle cell carcinoma • Poorly differentiated carcinoma • Medullary carcinoma • Anaplastic carcinoma • Primary thyroid lymphoma • Sarcoma, teratoma, and miscellaneous tumors • Metastatic tumors |
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AACE/AME/ETA 2010

Initial evaluation of thyroid nodule

- | | |
|--|---|
| <ul style="list-style-type: none"> • History <ul style="list-style-type: none"> – Age – FHx of thyroid disease or cancer – Previous head or neck irradiation – Rate of growth of the neck mass – Dysphonia, dysphagia, or dyspnea – Sx of hyper- or hypothyroidism – Use of iodine-containing drugs or supplements – Thyroidal uptake on F-18 FDG-PET scan | <ul style="list-style-type: none"> • PEx <ul style="list-style-type: none"> – Location, consistency, and size of the nodules – fixation to surrounding tissue – Neck tenderness or pain – Cervical adenopathy • Lab <ul style="list-style-type: none"> – TSH <ul style="list-style-type: none"> • if subnormal, T-scan – Thyroglobulin <ul style="list-style-type: none"> • not necessary – Calcitonin <ul style="list-style-type: none"> • consider |
|--|---|

Factors suggesting risk of malignant potential

- Hx of head and neck irradiation
- FHx of medullary thyroid ca, MEN type 2, or papillary thyroid ca
- Age <14 or > 70 yrs
- Male sex
- Growing nodule
- Firm or hard consistency
- Cervical adenopathy
- Fixed nodule
- Persistent dysphonia, dysphasia, or dyspnea

AACE/AME/ETA 2010

When to perform thyroid US

- In all patients with known or suspected thyroid nodule, nodular goiter, or radiographic abnormality; e.g., a nodule found incidentally on CT or MRI or thyroid uptake on ¹⁸FDG-PET scan

Revised ATA Management guidelines, Thyroid 19; 1167-1214, 2009

- 1-2% of people ¹⁸FDG-PET scan imaging have thyroid nodules
 - the risk of malignancy is about 33%
 - the cancers may be more aggressive
 - prompt evaluation

- When a thyroid disorder is suspected on clinical grounds or if risk factors have been recognized

AACE/AME/ETA guidelines Endocrine Pract 16(Suppl 1);1-43, 2010

US characteristics of thyroid nodules

position, size, shape, content

	Risk of malignancy	Specificity
Echogenicity	marked hypo-echogenicity	41.4 – 92.2%
Calcifications	micro-calcification (small, intranodular, punctate, hyperechoic spots with scanty or no posterior acoustic shadowing)	44.2 – 95%
Margin/Halo	irregular or micro-lobulated margin absence of halo	48.3 – 91.8%
Vascularity	chaotic arrangement or intranodular vascular images	80%
	more tall(anteroposterior) than wide(transverse)	

- The value of these features for predicting cancer is partially blunted by the low sensitivity.
- No US sign independently is fully predictive of a malignant lesion.
- The coexistence of ≥ 2 suspicious US criteria greatly increases the risk of thyroid cancer.

US findings

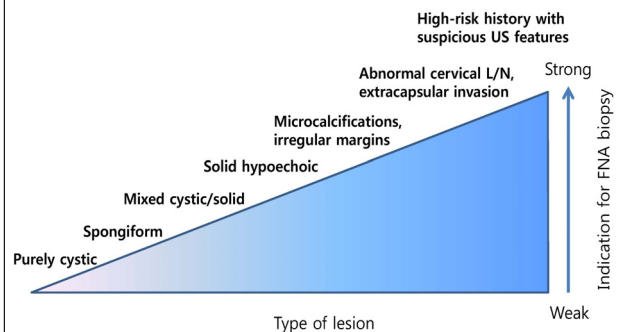
- Benign appearing nodules
 - Purely cystic
 - Iso/hyperechoic, halo, smooth margins, peripheral vascularity
 - Spongiform
- Suspicious appearing
 - Hypoechoic, irregular margins, punctate microcalcification, intranodular flow
- 66% of benign nodules have at least one positive US predictor of papillary thyroid cancer
- 66% of papillary cancers have at least one non-suspicious US feature

US for FNA decision making

Nodule		Recommendation
High-risk history		
Nodule with suspicious sonographic features	> 5 mm	A (good evidence)
Nodule without suspicious sonographic features	> 5 mm	I (neither for nor against)
Abnormal cervical lymph nodes	All	A
Microcalcifications present in nodule	≥ 1 cm	B (fair evidence)
Solid nodule and hypoechoic	≥ 1 cm	B
and iso- or hyperechoic	≥ 1-1.5 cm	C (expert opinion)
Mixed cystic-solid nodule		
with any suspicious ultrasound features	≥ 1.5 – 2.0 cm	B
without suspicious ultrasound features	≥ 2.0 cm	C
Spongiform nodule	≥ 2.0 cm	C
Purely cystic nodule	FNA not indicated	E (against)

ATA 2009

Indications for FNA biopsy



A spongiform appearance
: aggregation of multiple microcystic components in more than 50% of the nodule volume
: negative predictive value for malignancy of 98.5%

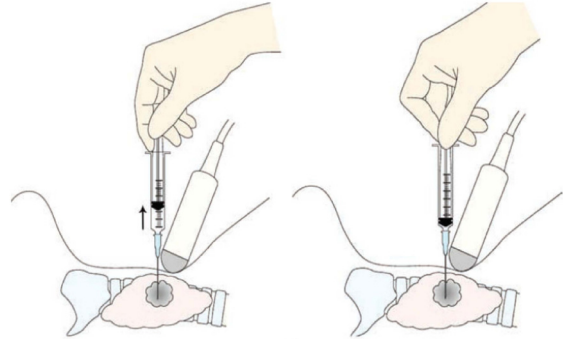
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Indications for FNA biopsy

- 일반적으로 ≥ 1 cm인 결절이 임상적으로 의미 있는 암의 위험이 있으므로 검사를 시행한다.
- purely cystic nodule, spongiform nodule : ≥ 2 cm
- 고위험군과 초음파검사상 악성을 시사하는 경우 0.5 cm 보다 큰 경우에만 FNAC를 시행하는 것을 우선적으로 고려한다.
- 다만, 악성이 의심되는 경부림프절 종대가 동반된 경우에는 크기에 관계없이 FNAC를 시행한다.
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Korea Thyroid Association 2011

FNA techniques; aspiration vs non-aspiration



Kim MJ et al, Radiographics 28: 1869-1886, 2008

Results of Thyroid Fine-Needle Aspiration

Feature, %	Mean	Range	Definition
Sensitivity	83%	65-98	Likelihood that patient with disease has positive test results
Specificity	92%	72-100	Likelihood that patient without disease has negative test results
Positive predictive value	75%	50-96	Fraction of patients with positive test results who have disease
False-negative rate	5%	1-11	Fine-needle aspiration negative: histology positive for cancer
False-positive rate	5%	0-7	Fine-needle aspiration positive: histology negative for cancer

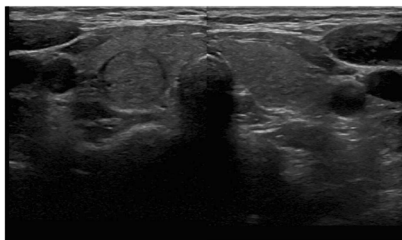
AACE/AME/ETA 2010

Ways to Minimize False-Negative Results

- Use ultrasound-guided fine-needle aspiration (UGFNA) biopsy
- Perform multiple punctures of the nodule so that several areas are sampled
- Consider repeated UGFNA biopsy for follow-up of benign nodules
- For multiple nodules, prioritize the nodule to biopsy according to ultrasonographic findings
- For cystic lesions, sample solid areas with UGFNA biopsy and submit cyst fluid for examination
- Obtain at least 6 properly prepared thin cell smears
- Use immediate wet fixation for Papanicolaou staining technique
- Review slides with an experienced cytopathologist

AACE/AME/ETA 2010

Anatomy



^{18}F FDG-PET

- Recently, ^{18}F FDG-PET scanning has been utilized in an effort to distinguish those indeterminate nodules that are benign from those that are malignant.
- ^{18}F FDG-PET scans appear to have relatively high sensitivity for malignancy but low specificity, but results vary among studies.
- The panel cannot recommend for or against routine clinical use of ^{18}F FDG-PET scan to improve diagnostic accuracy of indeterminate thyroid nodules.

• ATA 2009

Calcification

- Eggshell calcification
- Micro-calcification
 - multiple bright (< 2 mm) echoes without shadowing
 - vs Comet tail reverberation artifact
- Coarse-calcification
-

Spongiform

- A spongiform appearance
 - aggregation of multiple microcystic components in more than 50% of the nodule volume
 - 99.7% specific for identification of a benign nodule
 - 98.5% negative predictive value for malignancy

- 고위험인자를 동반하지 않으면서, 초음파검사 소견상 purely cystic 혹은 spongiform 소견을 보일 때에는 거의 대부분 양성이므로 크기가 2 cm 이상인 경우에 검사를 고려한다.

Korea Thyroid Association 2011

- Sonographic monitoring without biopsy may be an acceptable alternatives

ATA 2009

Family Hx

- Individuals with a close relative with thyroid cancer
 - increased risk (5-fold to 9-fold) for developing thyroid cancer themselves
- Familial nonmedullary thyroid cancer (FNMTc)
 - the diagnosis of two or more first-degree relatives affected by differentiated thyroid cancer of follicular cell origin
 - multifocality, early onset, more recurrence, higher degree of aggressiveness than nonfamilial thyroid cancers of follicular cell origin
 - up to 45% of cases with only two affected members may not be true FNMTc

Thyroid 15: 588-593, 2005

Toxic adenoma

- a solitary, autonomously functioning thyroid nodule
- acquired somatic, activation mutations in TSH-R
- Tx
 - Radioiodine ablation
 - Tx of choice
 - Surgical resection
 - Medical Tx (ATD)
 - not an optimal long-term Tx
 - PEI, RF ablation

Indications for Thyroid Scintigraphy

- A single thyroid nodule and suppressed TSH level
 - For MNGs, even without suppressed TSH, to identify cold or indeterminate areas for FNA
 - For large MNGs, especially with substernal extension
 - In the diagnosis of ectopic thyroid tissue
 - In subclinical hyperthyroidism to identify occult hyperfunctioning tissue
 - In follicular lesions to identify a functioning cellular adenoma that may be benign
 - To determine eligibility for radioiodine therapy
 - To distinguish low-uptake from high-uptake thyrotoxicosis
- The role of scintigraphy is limited in countries with iodine-rich diet

AACE/AME/ETA 2010

Thyroglossal cyst

- a fibrous cyst that forms from a persistent thyroglossal duct
- usually presents as a midline neck lump (in the region of the hyoid bone)
- painless, smooth and cystic, if infected, pain can occur
- A thyroglossal cyst will move upwards with protrusion of the tongue.
- are associated with an increased incidence of ectopic thyroid tissue.
- Thyroid scan and TFT preoperatively
- Tx : surgical resection

Thyroid ca in Graves' and Hashimoto's

- Thyroid cancer in pts with Graves' disease
 - incidence : 0.5 – 15%
 - Patients with Graves' and thyroid nodule are at higher risk to develop thyroid cancer compared to pts with diffuse goiter
 - Graves' disease seems to be associated with larger, multifocal, and potentially more aggressive thyroid cancer than MNG
Horm Metab Res 44:255-262, 2012
- Elevated risk of PTC in Korean pts with Hashimoto's thyroiditis
Head Neck 33:691-695, 2011
- PTC with Hashimoto's thyroiditis have less aggressive clinical presentation and better prognosis
Endocr Pathol 22:144-149, 2011

Calcitonin

- the level is greater than 100 pg/mL, medullary cancer is likely present
- 갑상선 결절의 초기 검사로 혈청 칼시토닌 측정을 고려할 수 있다 (권고수준 3: expert opinion). (*Korea Thyroid Association 2011*)
- The panel cannot recommend either for or against the routine measurement of serum calcitonin (*ATA 2009*)
- Measurement of basal serum calcitonin level may be a useful test in the initial evaluation of thyroid nodules (*AACE/AME/ETA 2010*)

Indeterminate cytology

- Atypia or follicular lesion of undetermined significance
 - 5-10% risk of malignancy
 - Repeat FNAC : 20-25% atypia
 - close follow up or surgery
- Molecular marker (BRAF, RAS, RET/PTC, galectin-3) may be considered (*ATA2009*)
- US-guided core needle biopsy (CNB) may offer additional information in selected cases with thyroid or neck masses and inadequate FNA biopsy cytologic results
(AACE/AME/ETA 2010)
- Follicular neoplasm or suspicious follicular neoplasm
 - 20-30% risk of malignancy
 - consider ^{123}I scan if TSH is in the low-normal range
 - unless concordant autonomously functioning nodule, surgery
- Suspicious for papillary carcinoma, Hurthle cell neoplasm
 - lobectomy or total thyroidectomy, depending on the lesion's size and other risk factors

Nondiagnostic/unsatisfactory

- US guidance should be used when repeating the FNA procedure
- Partially cystic nodules that repeatedly yield non-diagnostic aspirates need close observation or surgical excision
- If the cytological nondiagnostic nodule is solid, surgery should be more strongly considered
 - up to 7% of nodules continue to yield nondiagnostic cytology results despite repeated biopsies
 - maybe be malignant at the time of surgery (*ATA 2009*)
- Nodules with repeated inadequate cytology, core-needle biopsy (CNB) may be considered as a complementary tool (*AACE/AME/ETA 2010*)

Multinodular goiters

- Nodules with a suspicious sonographic appearance should be aspirated preferentially
- If none of the nodules has a suspicious sonographic appearance, aspirate the largest nodules only
- If TSH level is low or low-normal, $^{99\text{m}}\text{Tc}$ or ^{123}I scan should be performed to determine functionality of each nodule
 - FNA should be considered only for those iso-functioning or non-functioning nodules
- In the presence of cervical lymphadenopathy, FNA of the L/N

Long-term follow up (1)

- False negative rate of up to 5% of FNA
- Nodule growth is an indication for repeat biopsy
 - 20% increase in nodule diameter with a minimum increase in two or more dimension of at least 2 mm
- All benign thyroid nodules be followed with serial US examination 6-18 months after the initial FNA
 - If nodule size is stable, the next follow up may be longer, every 3-5 yrs
 - If nodule size increases, repeat FNA with US guidance
- Recurrent cystic nodules with benign cytology
 - surgical removal or percutaneous ethanol injection (PEI)

Long-term follow up (2)

- Routine suppression therapy of benign thyroid nodule is not recommended
- Growing nodules that are benign after repeat biopsy should be considered for continued monitoring or surgery based on symptoms and clinical concern

Cytologic diagnosis

AACE/AME/ETA 2010	ATA 2009	NCI 2009
1. Non-diagnostic	Non-diagnostic	Non-diagnostic
2. Benign	Benign	Benign
3. Follicular lesion/neoplasm (adenomatous hyperplasia, follicular neoplasms, Hurthle cell lesions, follicular variant of PTC)	Indeterminate (follicular or Hurthle cell neoplasm, follicular lesion of undetermined significance, atypia)	Atypia or follicular lesion of undetermined significance
		Follicular neoplasm Specify if Hurthle cell type
4. Suspicious	Suspicious	Suspicious
5. Malignant	Malignant	Malignant

AACE, American Association of Clinical Endocrinologist; AME, Associazione Medici Endocrinologi; ETA, European Thyroid Association; ATA, American Thyroid Association; NCI, National Cancer Institute

