



AUS, FN and SFM in Thyroid Cytology: When to Call It & When to Be Cautious

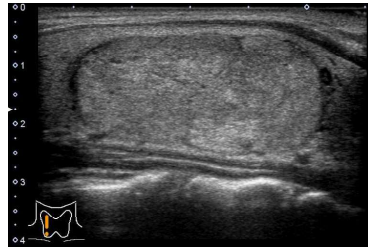
(Virtual slide review/ seminar slides & discussion)

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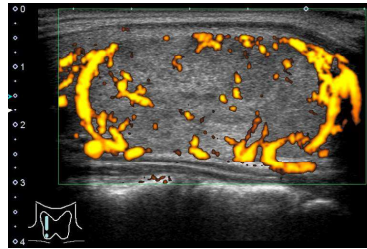


No potential COI to disclose

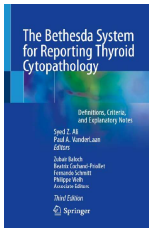
Case 1



Well-demarcated, oval, isoechoic, homogenous nodule



Increased vascular signal



Sample Reports (TBSRTC)

Example 1

FOLLICULAR NEOPLASM.

Example 2

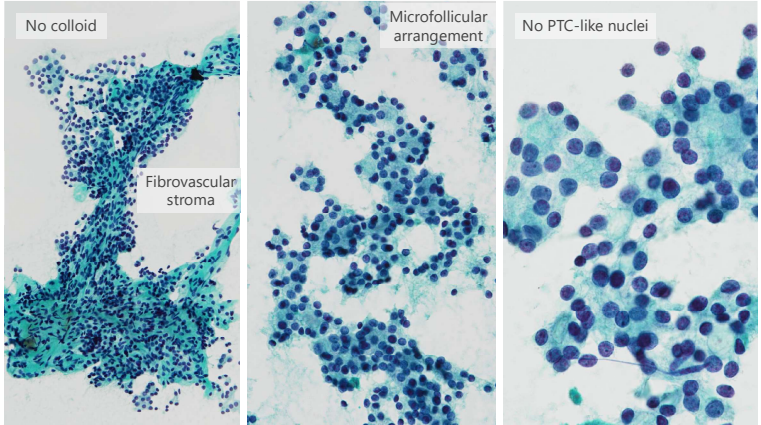
FOLLICULAR NEOPLASM.

Cellular aspirate of follicular cells with a predominantly microfollicular architecture, scattered isolated cells, and scant colloid. No nuclear features of papillary thyroid carcinoma are identified.

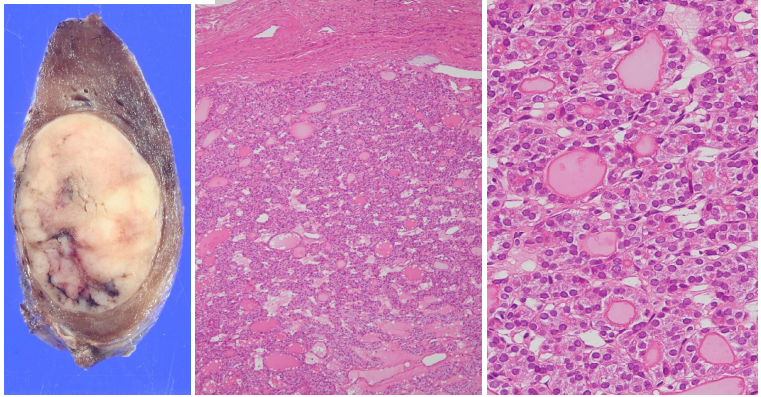
7th Case



Microfollicular
arrangement



Follicular adenoma



ROM & clinical managements for FN nodules

Category	Bethesda System		Japanese System	
	ROM	Clinical management	ROM	Clinical management
Follicular neoplasm	30% (23-34%)	Molecular testing Diagnostic lobectomy	12.6% (6.6-17.8%)	Resection Follow-up based on other clinical findings

Surgical indications for FN Nodules in Japan



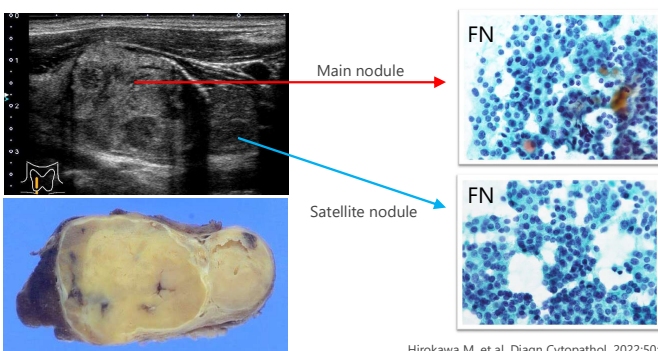
- Total thyroidectomy
 - Presence of metastatic lesion
- Lobectomy
 - High-grade cytological malignancy
 - Suspected malignancy on US
 - Large tumor diameter (>3-4 cm)
 - Rapid tumor growth

Hirokawa M, et al. Cytojournal. 2025 May 15;22:55.
Hirokawa M, Suzuki A. J Pathol Transl Med. 2025;59:214-224.

Sugitani I, et al. The 2024 revised clinical guidelines on the management of thyroid tumors by the Japan Association of Endocrine Surgery. Endocr J. 2025;72:545-635.

Follicular carcinoma diagnosed based on US and cytology

Both main & satellite nodules reveal FN with similar cytological findings



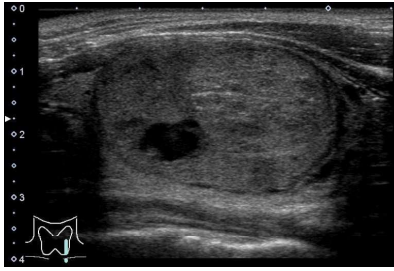
Hirokawa M, et al. Diagn Cytopathol. 2022;50:223-229.

2nd Case

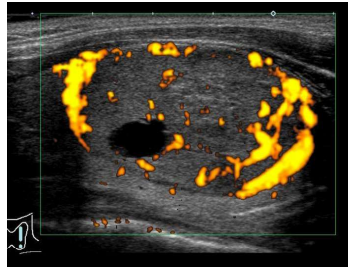


Oncocytic cells

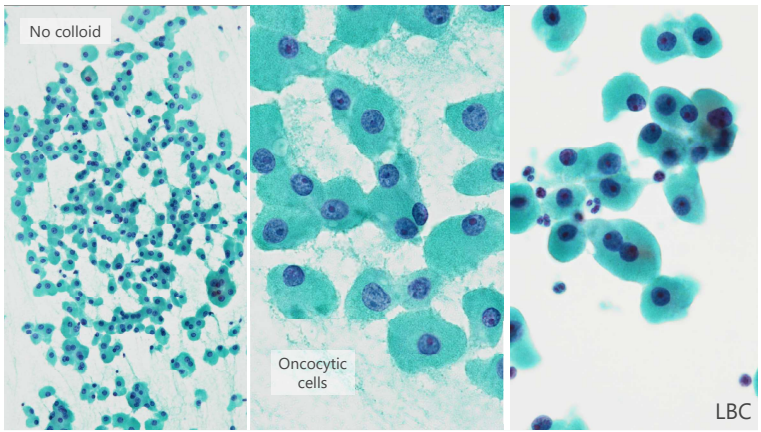
Case 2



Well-demarcated, oval, isoechoic, homogenous nodule
Focally cystic



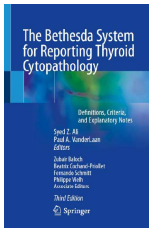
Increased vascular signal
(particularly at the periphery)



Cytological characteristics of Oncocytic Neoplasm

- Abundant finely granular cytoplasm, **intracytoplasmic lumina***
- Prominent nucleoli, **binucleation**
- Small (high N/C ratio) and Large (low N/C ratio) oncocytes
- Isolated cells, arranged in sheets, or crowded groups (uncommon microfollicles)
- Little or no colloid / lymphocytes / plasma cells,
- Foamy histiocytes, vascular network

*Suzuki A, et al. Cytopathology. 2016;27:495-498.



Sample Reports (TBSRTC)

Example 1

FOLLICULAR NEOPLASM (oncocytic follicular neoplasm).

Example 2

FOLLICULAR NEOPLASM (oncocytic follicular neoplasm).

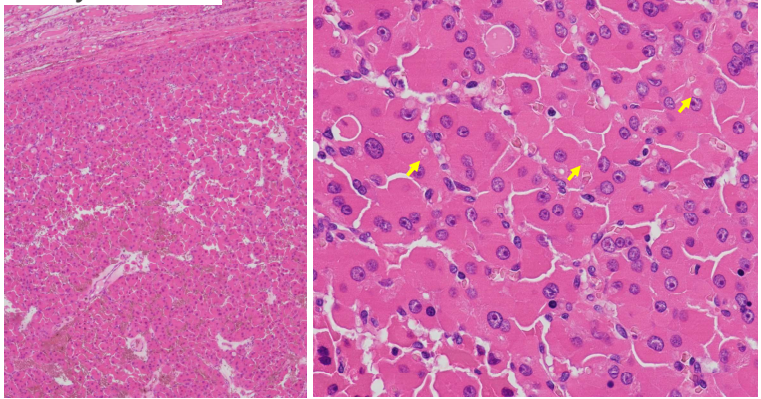
Cellular aspirate consisting predominantly of oncocytes in syncytial-like sheets and crowded clusters.

Example 3

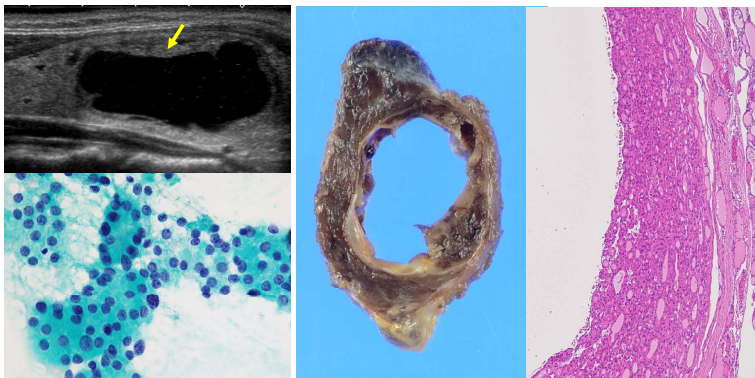
FOLLICULAR NEOPLASM (oncocytic follicular neoplasm).

Cellular aspirate consisting of abundant isolated oncocytes in the absence of colloid.

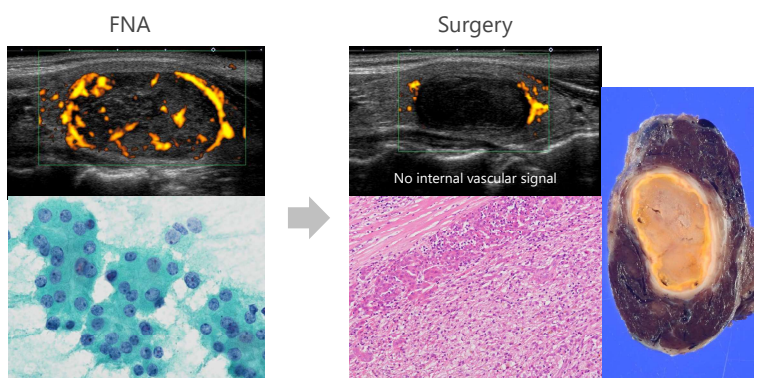
Oncocytic adenoma



Cystic change (oncocytic neoplasm)



Infarction due to FNA (oncocytic neoplasm)

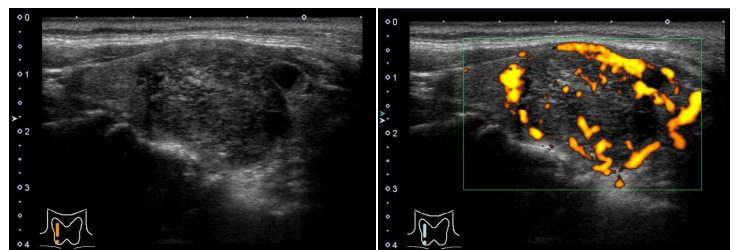


3rd Case



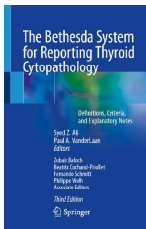
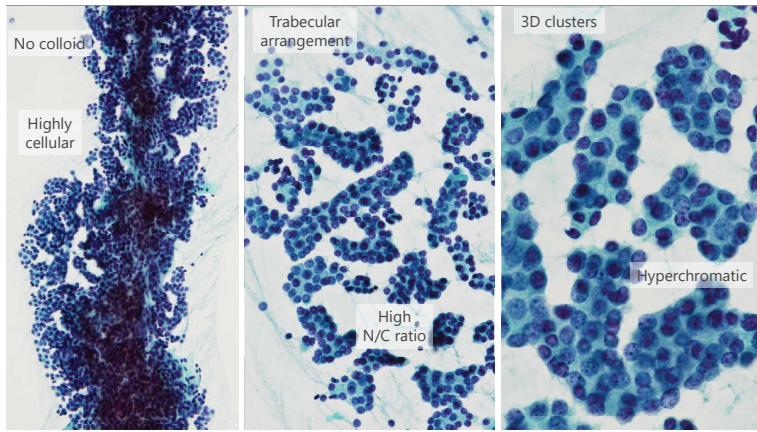
Trabecular
arrangement

Case 3



Well-demarcated, iso- to hypoechoic,
heterogenous nodule

Increased vascular signal



Sample Reports (TBSRTC)

Example 1

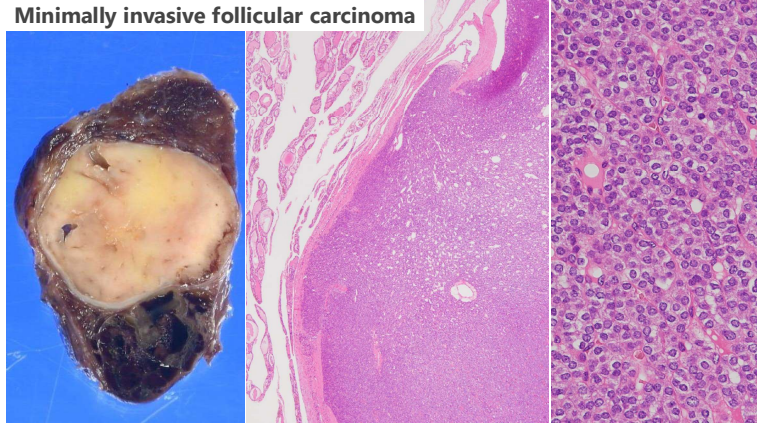
FOLLICULAR NEOPLASM.

Example 2

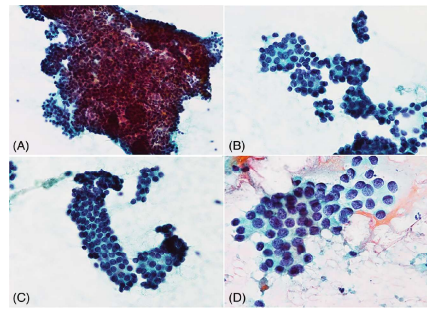
FOLLICULAR NEOPLASM.

Cellular aspirate of follicular cells with a predominantly microfollicular architecture, scattered isolated cells, and scant colloid. No nuclear features of papillary thyroid carcinoma are identified.

Minimally invasive follicular carcinoma



5 cytological findings suggestive of follicular carcinoma



- Dense follicles
- 3D microfollicles
- Trabecular arrangement
- Hyperchromasia
- Enlarged nuclei

Hirokawa M, et al. Gland Surg. 2020;9:1653-1662.
Hirokawa M, et al. Diagn Cytopathol. 2022;50:223-229.

Risk Stratification of FN based on 5 Cytological Findings

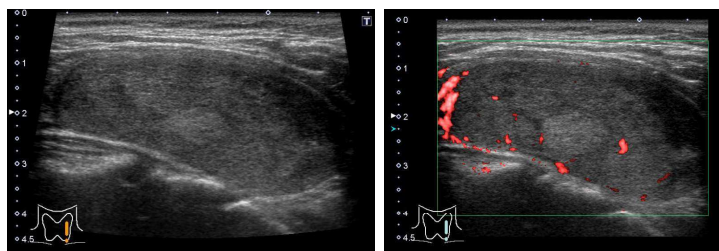
ROM of FN nodules with ≥ 2 findings was 60.0%

Findings	No. of Findings	Follicular carcinoma	Follicular adenoma	ROM	Reports
Dense follicles	0 (53)	8	45	15.1 %	Favor benign
Trabecular pattern	1 (25)	8	17	32.0 %	Intermediate
Three-dimensional microfollicles	2 (23)	14	9	60.0%	Favor malignant
Hyperchromasia	3 (7)	3	4		
Enlarged nuclei	4 (8)	5	3		
	5 (2)	2	0		

Higuchi M, et al. J Jpn Soc Clin Cytol. 2014;53:264-270 (JPN).

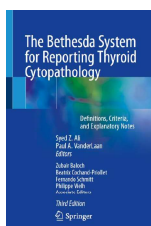


Case 4



Well-demarcated, oval, isoechoic, homogenous nodule

Non-increased vascular signal

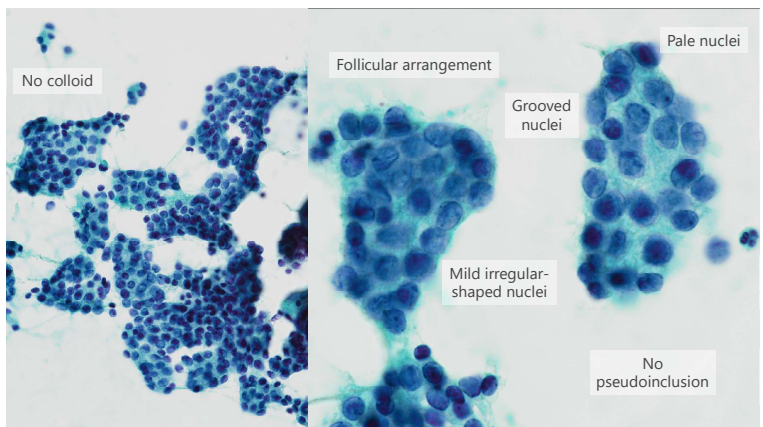


Sample Reports (TBSRTC)

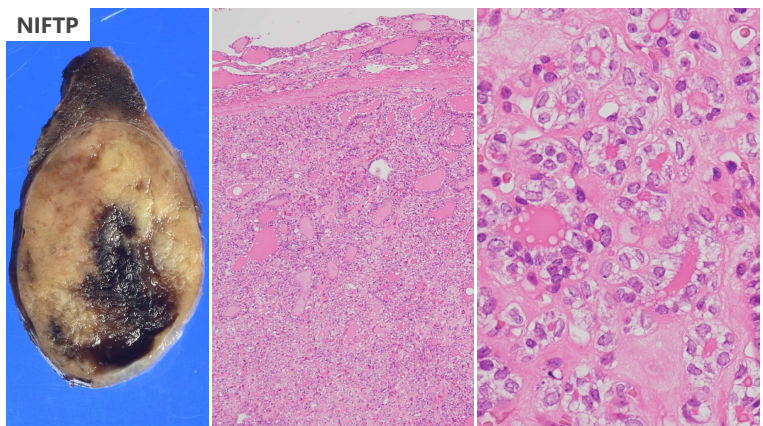
Example 4

FOLLICULAR NEOPLASM.

Note: Although the architectural features suggest a follicular neoplasm, some nuclear features raise the possibility of an invasive follicular variant of papillary carcinoma or its indolent counterpart, NIFTP; definitive distinction among these entities is not possible on cytologic material.



NIFTP



Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

- Essential
- 1. Encapsulation or clear demarcation.
 - 2. Follicular growth pattern with all of the following: <1% true papillae; No psammoma bodies; <30% solid/trabecular/insular growth pattern
 - 3. Nuclear features of papillary carcinoma (nuclear score of 2-3)
 - 4. No vascular or capsular invasion
 - 5. No tumour necrosis
 - 6. Low mitotic count (<3 mitosis / 2mm²)
 - 7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant (tall cell features, cribriform-morular variant, solid variant, etc)
- Desirable
- Immunohistochemistry or molecular testing for *BRAF* and *NRAS* mutation
- Diagnosis of NIFTP requires **surgical excision** to examine capsular invasion
 - Cytological diagnosis of NIFTP is **impossible**
 - NIFTP-suspected nodules should be put in the **FN** category

Prevalence of NIFTP among PTCs and FTAs in Japan

In Japan, NIFTP was more often diagnosed as **FTA** than PTC in the past.

Site	PTC → NIFTP	
	n	%
Japan, Kobe	50	0.5%
Japan, Fukuoka	12	3.1%
South Korea, Seoul	95	1.5%
South Korea, Seoul	5	0.2%
China, Shandong	16	0.3%
China, Wuxi	6	0.3%
Taiwan, Taipei	18	4.7%
Thailand, Bangkok	4	2.5%
Vietnam, Ho Chi Minh City	0	0%
	206	0.8%

Institution (in Japan)	FTA → NIFTP
A (29)	8 (27.6%)
B (21)	5 (23.8%)
C (17)	6 (35.3%)
D (26)	6 (23.1%)
E (11)	1 (9.1%)
F (46)	19 (41.3%)
Total (145)	45 (31.0%)

Hirokawa M, et al. Pathol Int. 2024;74:26-32.

Bychkov A, et al. Thyroid 2017;27:983-

Nuclear grade

	0	1	2	3
Western	FTA		PTC	
Japan	FTA			PTC
Mutation	RAS			BRAF

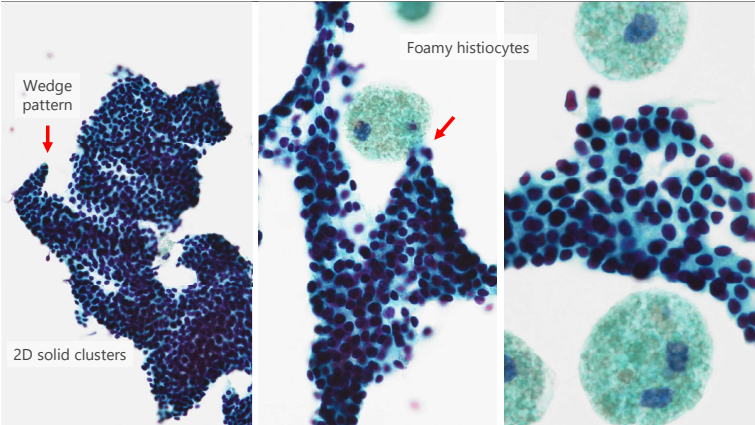
Changes in follicular neoplasm with NS2

	Western countries		Japan	
	Pre-NIFTP	Post-NIFTP	Pre-NIFTP	Post-NIFTP
Histological Diagnosis	Papillary carcinoma	NIFTP (downgrading)	Follicular adenoma	NIFTP (upgrading)
Cytology	AUS / FN / SFM	FN	FN	FN
Metastasis	None	None	None	None
Mutation	RAS	RAS	RAS	RAS
Management	Total thyroidectomy	Lobectomy	Lobectomy	Lobectomy

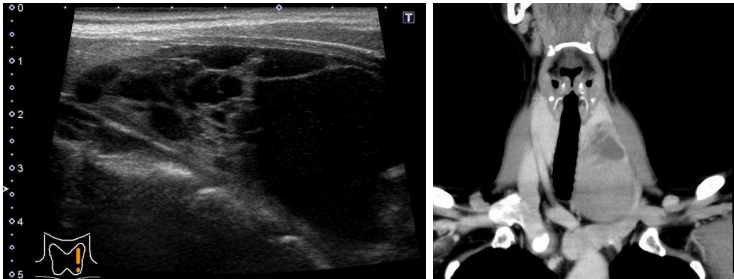
Hirokawa M, et al. Endocr J. 2017;64:1149-
Hirokawa M, et al. Endocr J. 2020;67:1071-
Hirokawa M, et al. Cancer Cytopathol. 2023:415-
Hirokawa M, et al. Pathol Int. 2024;74:26-

5th Case

Clusters with wedge pattern



Case 5



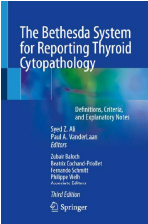
Solid and cystic nodule at the lower pole of left lobe

Cell arrangements of parathyroid adenoma, FN, and PDTC

Wedge pattern (sharp corner) indicates **parathyroid adenoma**

	PAs (15)	FNs (10)	PDTCs (10)
Arrangements			
Tissue fragments	60.0% (9)	50.0% (5)	60.0% (6)
Trabecular	93.3% (14)	80.0% (8)	70.0% (7)
Wedge	86.7% (13)	0% (0)**	30.0% (3)**
Insular	80.0% (12)	0% (0)**	50.0% (5)
Cribriform	53.3% (8)	0% (0)**	80.0% (8)
Microfollicular	26.7% (4)	100% (10)**	70.0% (7)
Isolated	53.3% (8)	30.0% (3)	70.0% (7)
Naked cells	73.3% (11)	40.0% (4)	30.0% (3)*

Suzuki A, Diagn Cytopathol. 2021;49:70-76.



Sample Reports (TBSRTC)

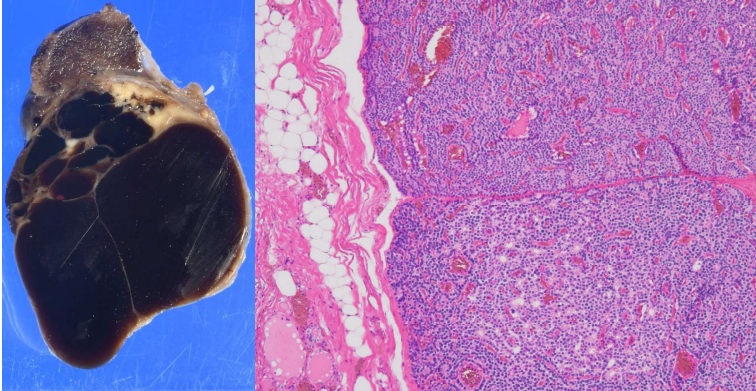
Example 5

FOLLICULAR NEOPLASM.

Cellular aspirate composed predominantly of crowded uniform cells without colloid.

Note: The features suggest a follicular neoplasm, but **the possibility of a parathyroid lesion cannot be excluded**. Correlation with clinical, serologic, radiologic, PTH level in the needle washout, and molecular test findings (if any) should be considered.

Parathyroid adenoma



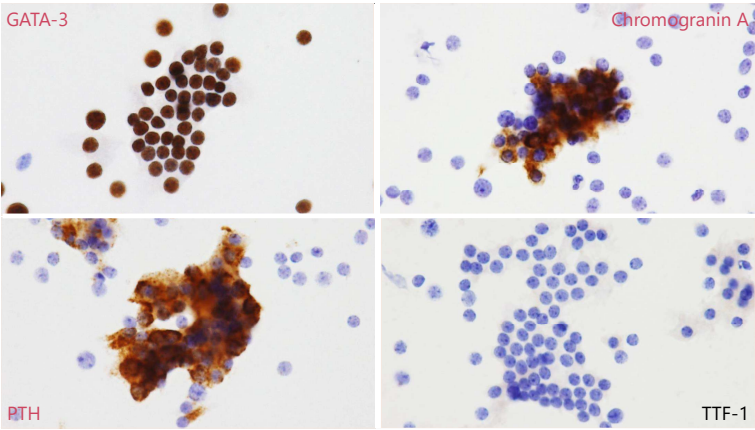
Immunocytochemical analysis of parathyroid and thyroid lesions

GATA-3 is most reliable antibody to distinguish them

Samples (number)	GATA-3	PTH	Chromogranin A	TTF-1
Parathyroid (82)	98.8% (81)	56.1% (46)	87.8% (72)	0% (0)
Normal – conventional (15)	100% (15)	33.3% (5)	80.0% (12)	0% (0)
Hyperplasia (12)	100% (12)	66.7% (8)	100% (12)	0% (0)
– conventional (5)	100% (5)	20% (1)	100% (5)	0% (0)
– LDC (7)	100% (7)	100% (7)	100% (7)	0% (0)
Adenoma (55)	98.2% (54)	60.0% (33)	87.3% (48)	0% (0)
– conventional (27)	100% (27)	22.2% (6)	74.1% (20)	0% (0)
– LBC (28)	96.4% (27)	96.4% (27)	100% (28)	0% (0)
Thyroid (5)	0% (0)	0% (0)	0% (0)	100% (5)
PTCs – LBC (3)	0% (0)	0% (0)	0% (0)	100% (3)
FTAs – LBC (2)	0% (0)	0% (0)	0% (0)	100% (2)

PTH, parathyroid hormone; TTF-1, thyroid transcription factor 1; LBC, liquid-based cytology; PTCs, papillary thyroid carcinomas; FTAs, follicular thyroid adenomas. * $p < 0.01$, ** $p < 0.001$.

Takada N, et al. Endocr J 2016;30:621-626.



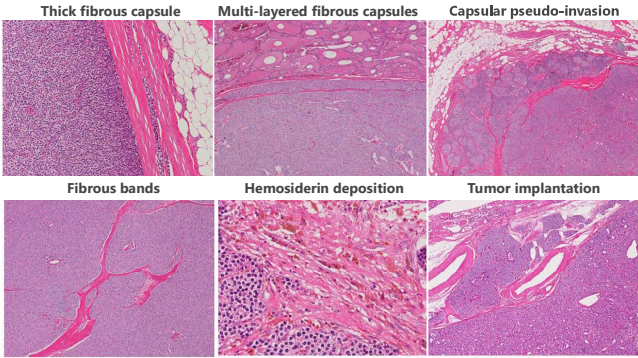
The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults

Kepal N. Patel, MD, Linwah Yip, MD, Carrie C. Lubitz, MD, MPH, Elizabeth G. Grubbs, MD, Barbara S. Miller, MD, Wen Shen, MD, Peter Angelos, MD, Herbert Chen, MD, Gerard M. Doherty, MD, Thomas J. Fahey III, MD, Election Kherfene, MD, Virginia A. Livolsi, MD, Nancy D. Perrier, MD, Jennifer A. Sipos, MD, Julie A. Sosa, MD, David Steward, MD, Ralph P. Tufano, MD, Christopher R. McHenry, MD, and Sally E. Carty, MD

Parathyroid Incidentaloma US. Fastidious neck US has led to the unexpected detection of enlarged parathyroid glands, sometimes termed parathyroid incidentalomas, ^{135,136} with a detection rate of about 1.5%. ¹³⁶ Normal parathyroids are too small to be seen on US, but enlarged glands often have characteristic US features that differentiate them from lymph nodes (LN), such as shape, location, hypoechogenicity, and a hilar or polar feeding vessel. ⁶ FNAB with PTH washout ¹³⁷ and/or molecular analysis can confirm their presence, but the diagnosis of hyperparathyroidism is rendered biochemically. Because parathyroid FNAB can cause hemorrhage producing surrounding fibrosis which results in alteration of surgical dissection planes and can cause histologic changes mimicking parathyroid carcinoma, FNAB of parathyroid glands is to be avoided when possible ⁶ (see “Concurrent Parathyroidectomy”).

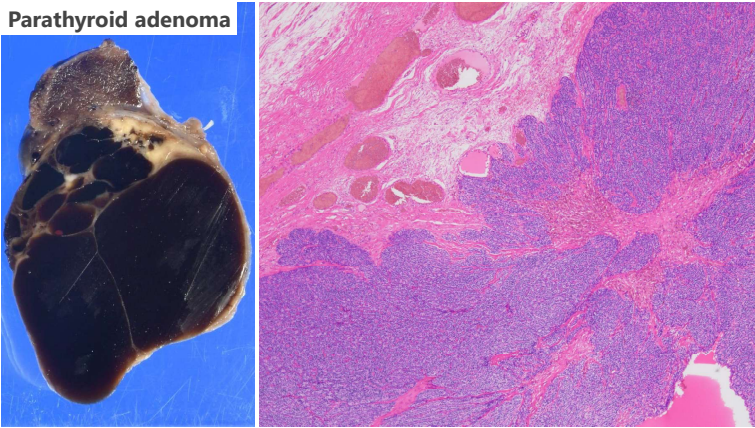
Patel KN, et al. Ann Surg. 2020 Mar;271(3):e21-e93.

Histological alterations following FNA for parathyroid adenoma



M Hirokawa et al. Pathol Int 2021; 71: 400-405

Parathyroid adenoma



6th Case

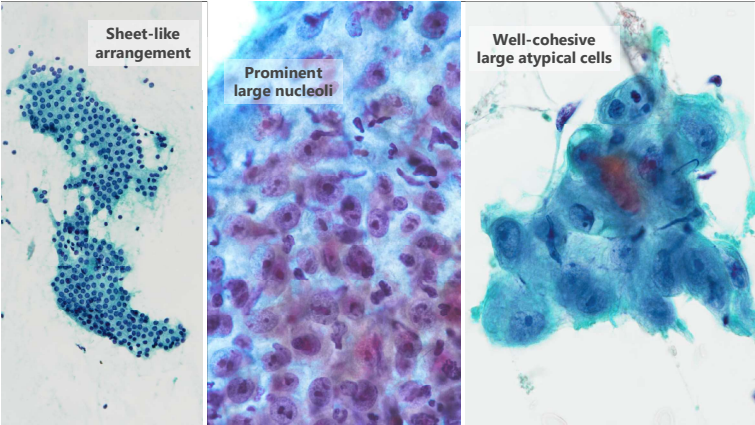


Large atypical cells

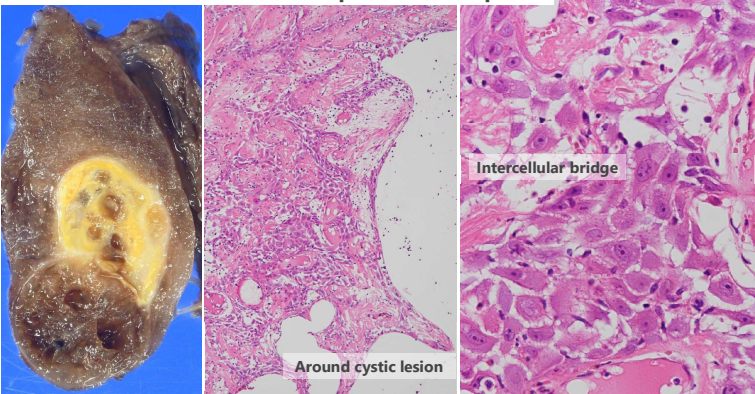
Case 6



Irregular-shaped, well-demarcated nodule with cystic change and calcification



Follicular nodule disease with squamous metaplasia

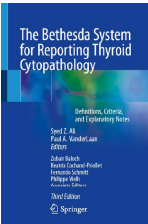


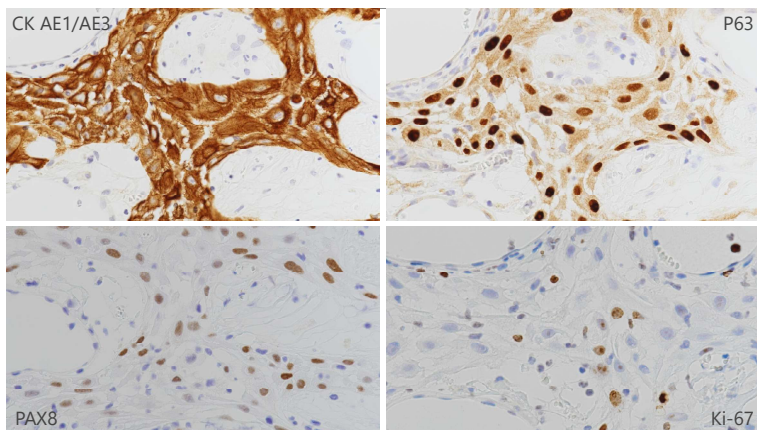
Sample Reports (TBSRTC)

Example 5

SUSPICIOUS FOR MALIGNANCY, NOT OTHERWISE SPECIFIED.

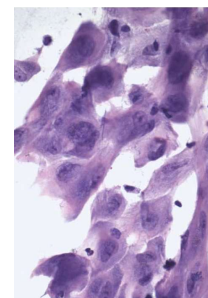
Note: Slides from the patient’s known primary tumor are not available for review (for patients with known malignancies). The overall cytomorphologic features likely represent a metastatic carcinoma. Re-aspiration for immunohistochemical studies might be helpful for definitive diagnosis, if clinically indicated.





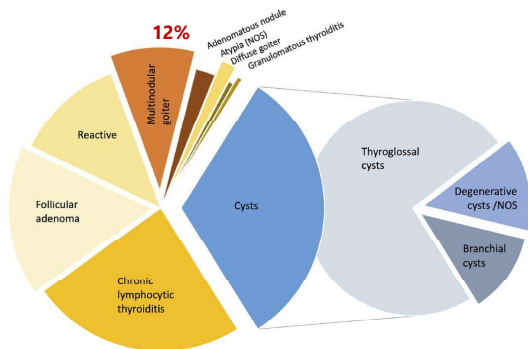
Atypical squamous metaplasia mimicking high-grade carcinoma

- Cohesive clusters
- Pleomorphic nuclei
- No mitosis
- No hyperchromasia
- No necrosis
- Association with cystic lesion
- Radiologic findings favor benign



Pellicer DL, et al. Diagn Cytopathol. 2013;41:706-9.

Non-malignant thyroid lesions with squamous differentiation



A Chambers M, et al. Int J Surg Pathol. 2022;30:385-392.

7th Case

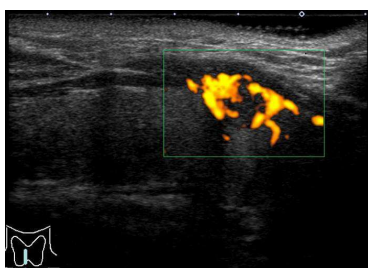


Pseudoinclusions

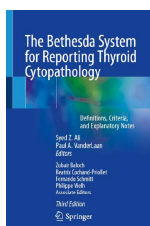
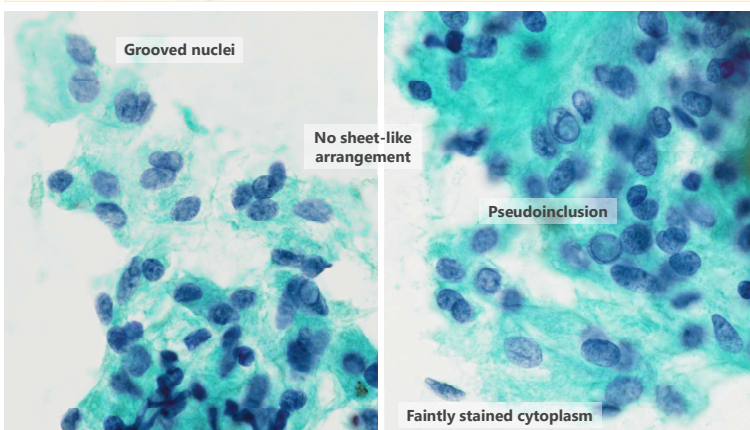
Case 7



Well-demarcated, round, hypoechoic, homogenous nodule



Increased vascular signal

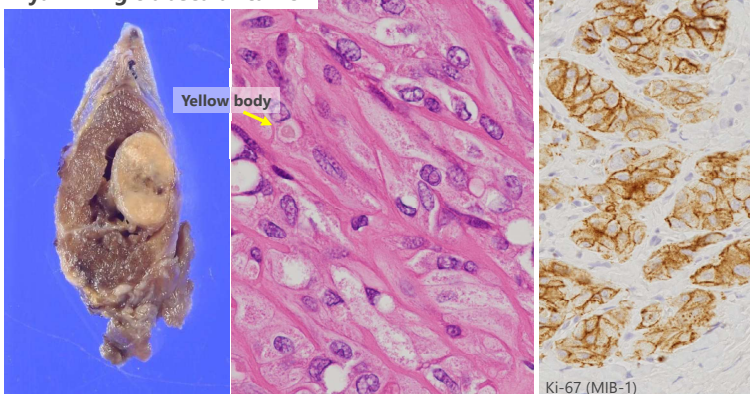


No Sample Reports (TBSRTC)

Hyalinizing trabecular tumor (HTT) shares many morphologic features with PTC, including nuclear grooves and abundant INPIs. Although it may be related to PTC, it is generally distinguished from PTC histologically based on its circumscription, trabecular growth pattern, and intratrabeular hyaline material.

These distinguishing features are difficult to appreciate by FNA, and **many HTTs are interpreted as Malignant or SFM**. Cytoplasmic staining for MIB-1 (as opposed to the nuclear staining pattern used in other contexts to establish a proliferative index) is a distinctive feature of HTT and can be helpful as an adjunct to cytomorphology.

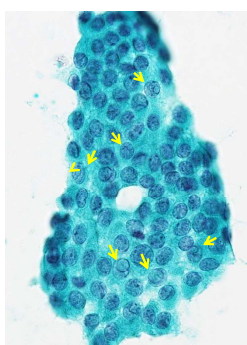
Hyalinizing trabecular tumor



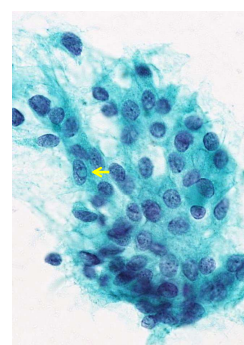
Thyroid lesions exhibiting pseudoinclusions

- Papillary thyroid carcinoma (>90%)
- Hyalinizing trabecular tumor (100%)
- Medullary thyroid carcinoma (19 to 58%)
- Anaplastic thyroid carcinoma (28%)
- Adipocyte (100%)
- Schwannoma (29%)

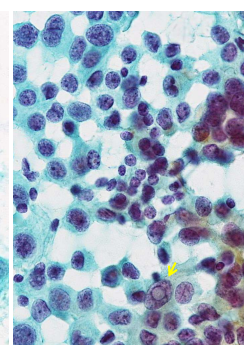
PTC



HTT



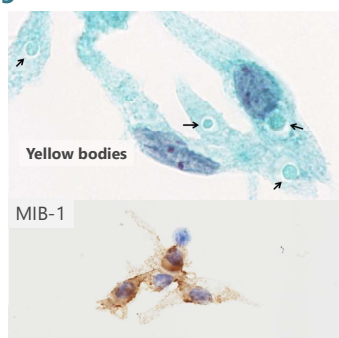
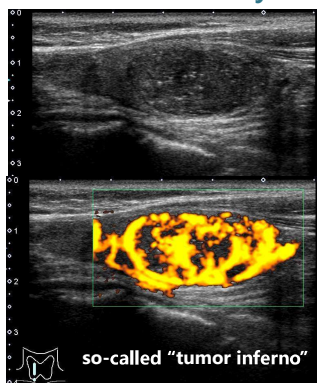
MTC



Differential diagnoses of HTT & PTC

	HTT	PTC
Arrangement	Radiating, No sheet	Sheet-like, Papillary, Follicular
Nuclear palisading	Vague, Curved (surrounding hyaline materials)	Distinct, Straight
Cell shape	Spindled, Elongated, Cytoplasmic process	Round, Oval
Cell border	Indistinct	Distinct
Cytoplasm	Faintly stained, Filamentous, Yellow body	Densely stained, Homogeneous, Metaplastic, Septate vacuoles
Nuclei	Pseudoinclusion (all cases), Groove	Pseudoinclusion (not always), Groove, Powdery chromatin
Background	Hyaline material (basement membrane), Psammoma body	Ropy colloid, Psammoma body, Foamy cells, Lymphocytes, Multinucleated giant cell
Immunostaining		
Cytokeratin 19	Negative	Positive
KI-67 (MIB-1)	Cell membranous positivity	Nuclear positivity
Molecular testing	<i>PAX8/GLIS3</i>	<i>BRAF, RET/PTC</i>

Clues of Hyalinizing trabecular tumor

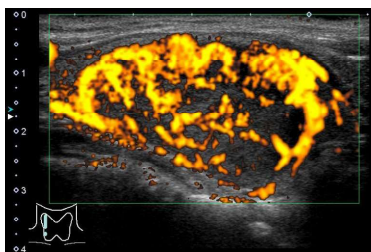


Hirokawa M, Suzuki A. Acta Cytol. 2025;69:7-15.
Kobayashi K et al. J Med Ultrason (2001). 2007;34:43-7.

Case 8

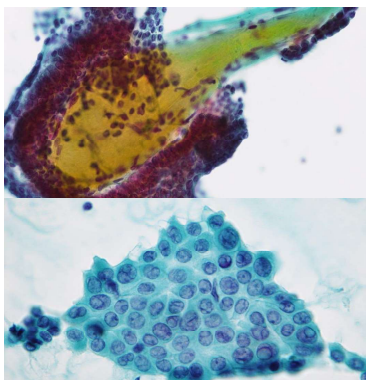


Well-demarcated, hypoechoic, homogenous nodule

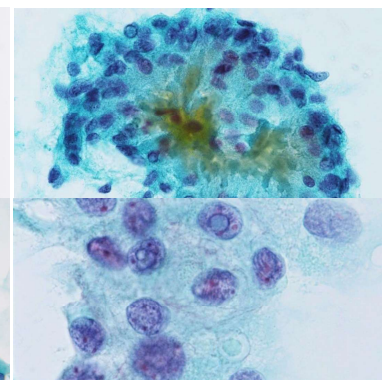


Increased vascular signal

Papillary thyroid carcinoma



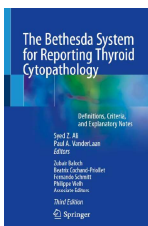
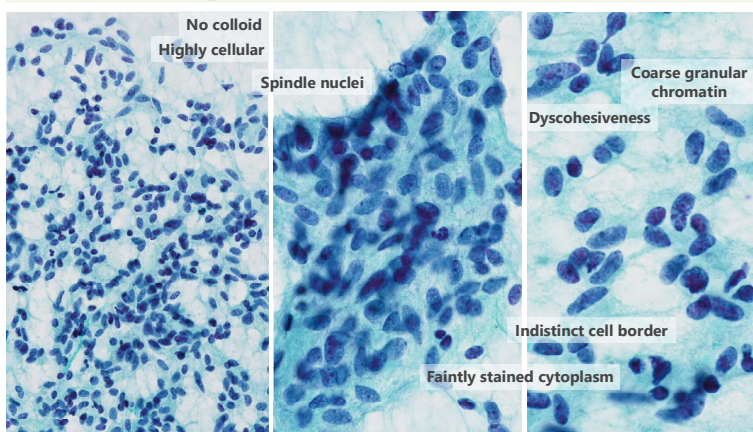
Hyalinizing trabecular tumor



8th Case



Spindle cells



Sample Reports (TBSRTC)

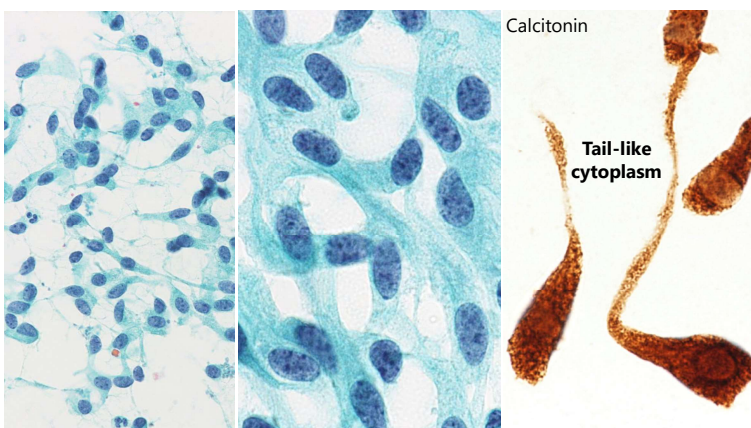
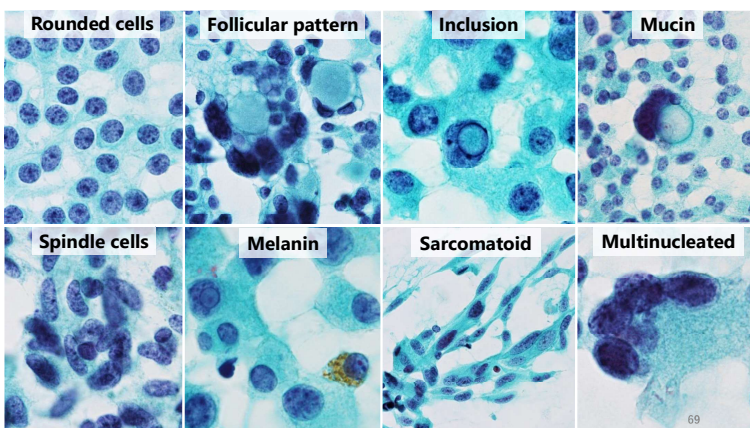
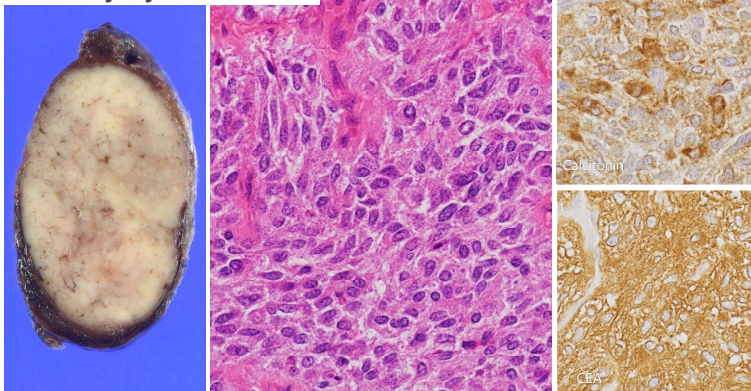
Example 3

SUSPICIOUS FOR MALIGNANCY.

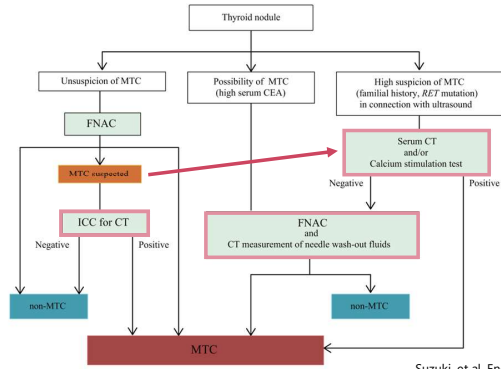
Suspicious for medullary thyroid carcinoma.

Note: Correlation with **serum calcitonin level** or re-aspiration for **immunohistochemical studies** or **needle washout for calcitonin measurement** might be helpful for definitive diagnosis if clinically indicated.

Medullary thyroid carcinoma



Diagnostic algorithm of MTC



Suzuki, et al. Endocr J. 2017;64:1099-

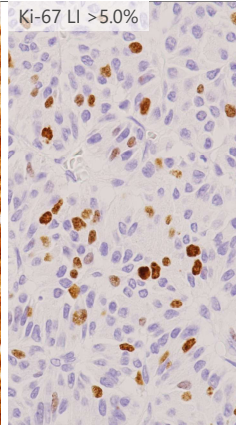
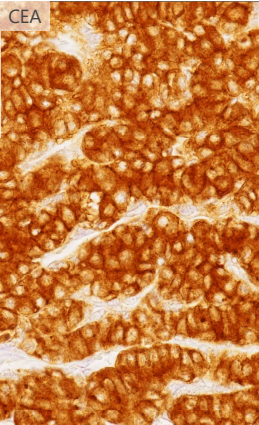
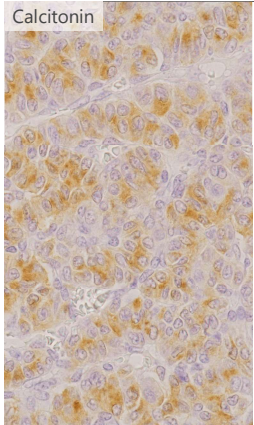
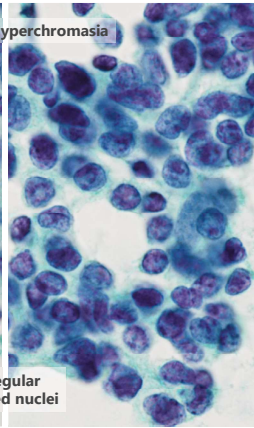
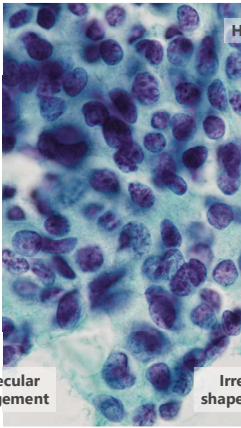
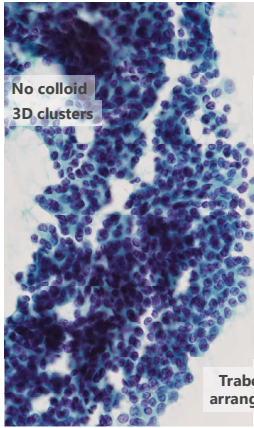
Serum calcitonin and CEA levels

採取日時:	2021/04/13(火) 11:44:07		
項目名	結果	3対	所見
検体検査			
Calcitonin	1450		
CEA	29.6		

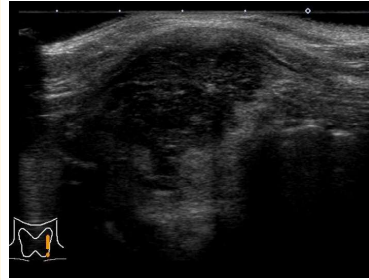
9th Case



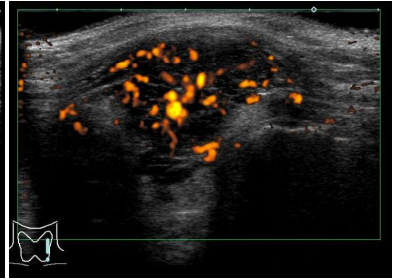
Irregular shaped nuclei



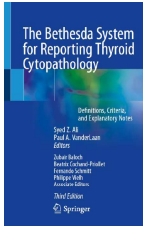
Case 9



Irregular shaped, hypoechoic, nodule



Increased vascular signal



Sample Reports (TBSRTC)

Example 1

MALIGNANT.

Most consistent with differentiated **high-grade thyroid carcinoma**.

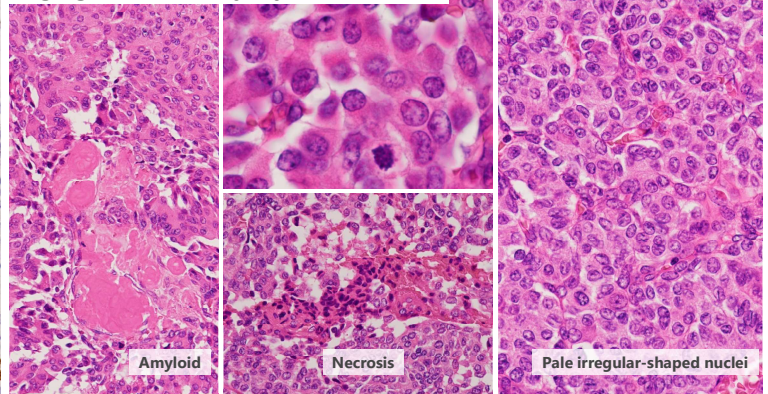
Note: Highly cellular aspirate with atypical follicular cells, necrosis, and scant colloid, most consistent with differentiated high-grade thyroid carcinoma. However, a poorly differentiated thyroid carcinoma cannot be excluded.

Example 2

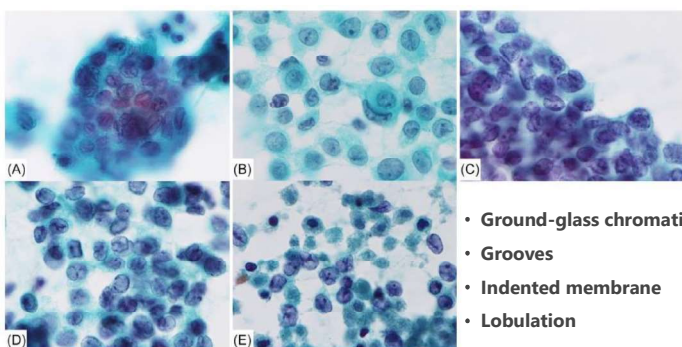
MALIGNANT.

PTC with focal poorly differentiated features, suggestive of differentiated high-grade thyroid carcinoma.

High-grade medullary thyroid carcinoma



High-grade MTC with papillary-like nuclear features



- Ground-glass chromatin
- Grooves
- Indented membrane
- Lobulation

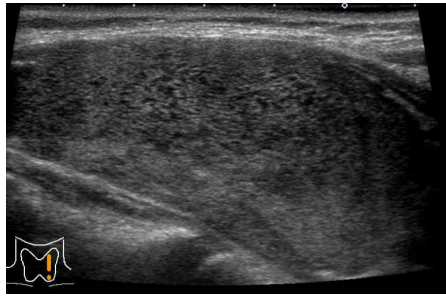
Yamano N, et al. Diagn Cytopathol. 2024;52:58-64.

10th Case

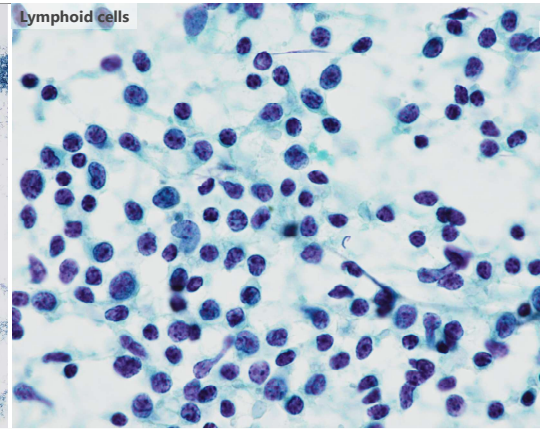
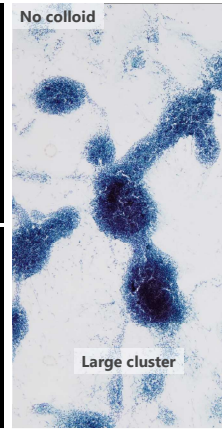
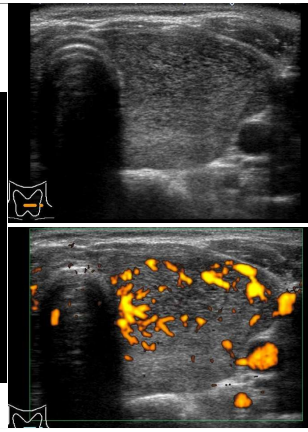


Lymphoid cells

Case 10



Diffuse enlargement



Sample Reports (TBSRTC)

Example 7

(FNA of a nodule in a patient with a long-standing history of Hashimoto thyroiditis)

ATYPIC OF UNDETERMINED SIGNIFICANCE. AUS-Other.

Numerous relatively monomorphic lymphoid cells.

Note: The findings are atypical and raise the possibility of a lymphoproliferative process arising in the background of the patient's long-standing chronic lymphocytic thyroiditis. Immunophenotyping studies could not be performed since only smears were made from the aspirate. Repeat FNA with aspirate collected for **flow cytometry** would be helpful in reaching a more definite diagnosis.

Light chain restriction rate using flow cytometry in thyroid lymphoma cases

	Total	MALTL	DLBCL	FL
Aspirated materials (n)	99	80	16	3
Light chain restriction	73 (73.7%)	60 (75.0%)	11 (68.8%)	2 (66.7%)
Resected materials (n)	104	86	16	2
Light chain restriction	72 (69.2%)	61 (70.9%)	9 (56.3%)	2 (100%)

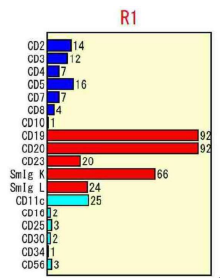
MALTL, mucosa-associated lymphoid tissue lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma

Suzuki A, et al. Endocr J. 2019;66:1083-1091

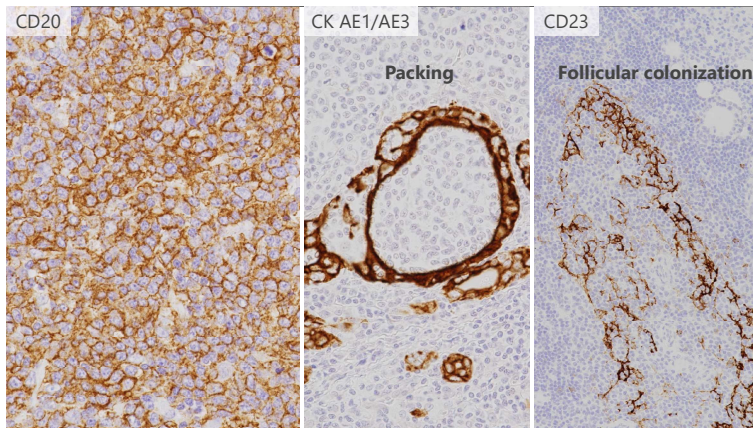
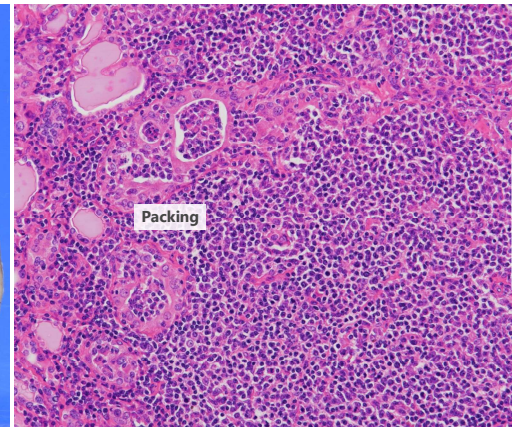
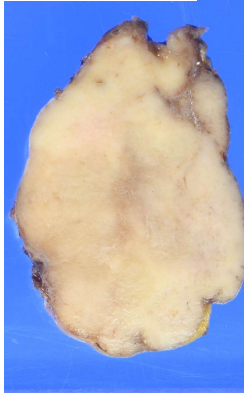
Flow cytometry using aspirated materials

Decreased T lymphocytes

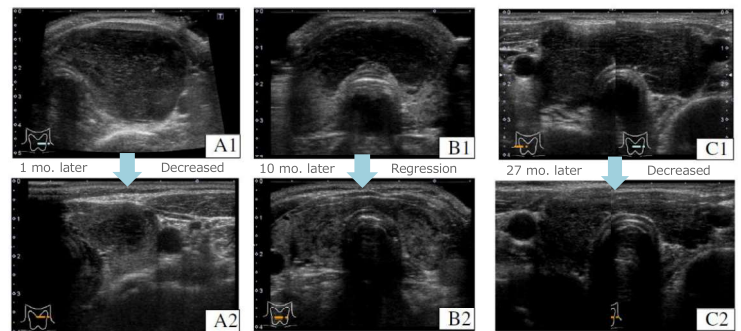
Kappa / lambda ratio = 2.75



MALT lymphoma

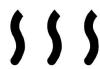


Thyroid lymphomas may be followed up without chemotherapy



Nakao T, et al. Thyroid Research 2018;11:8.

Just visit our website "Kobe Thyroid Cytology Club" and download the handouts of today's lecture.



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