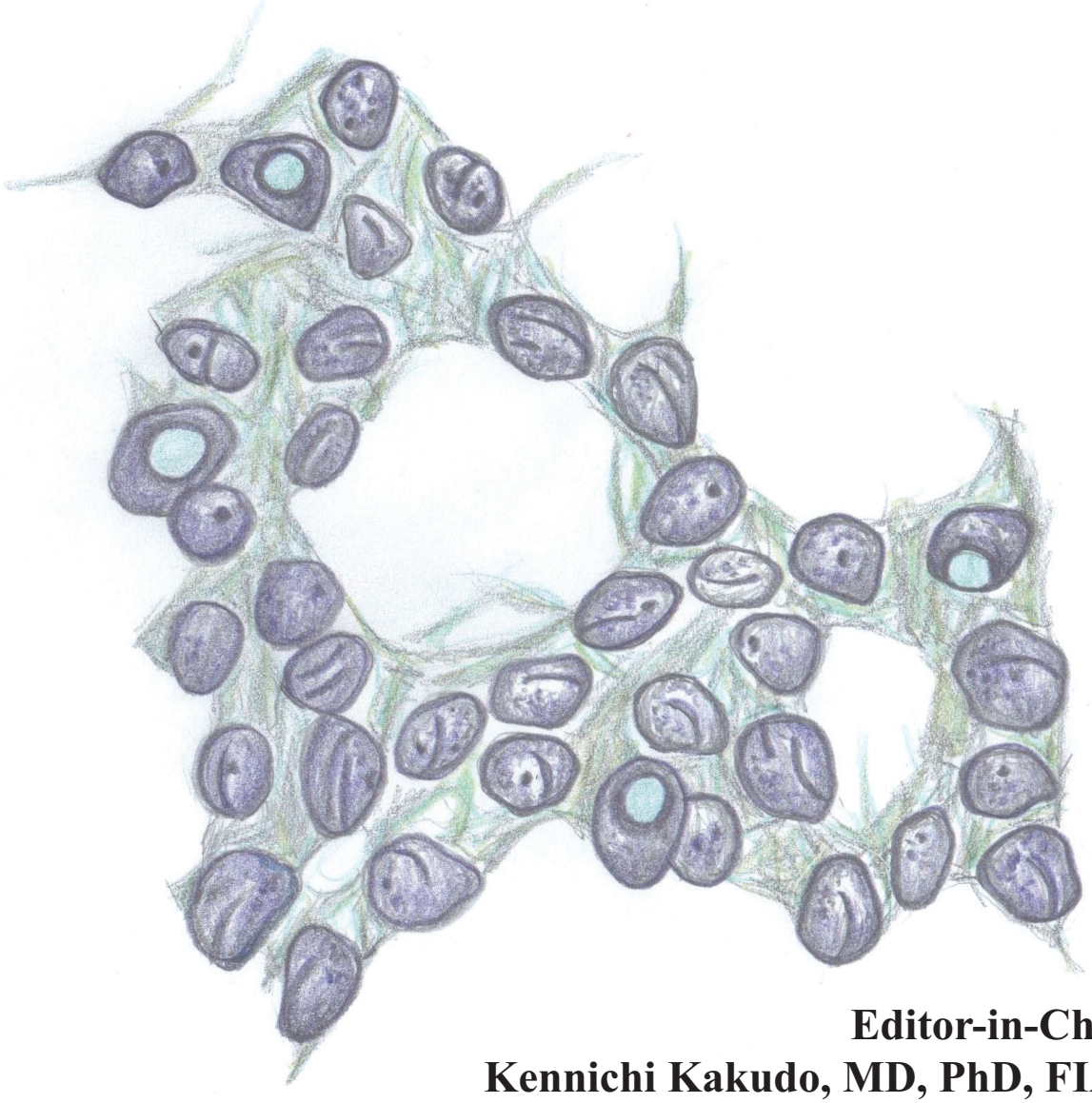
Thyroid FNA Cytology

Differential Diagnoses & Pitfalls



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Thyroid FNA Cytology: Differential Diagnoses and Pitfalls

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Preface to Print Edition
Thyroid FNA Cytology: Differential Diagnoses and Pitfalls

We are happy to provide you a print edition of, "Thyroid FNA Cytology: Differential Diagnoses and Pitfalls". As there is a file size limit in the eBook edition, some important illustrations were deleted and all illustrations in the eBook edition were reduced in quality. To circumvent these conditions, the print edition was published. In this print edition, we provide you with all of the original illustrations in high quality and have incorporated some more illustrations which were deleted from the eBook edition.

The editors proudly announce that this is the first and only textbook for thyroid FNA cytology that incorporates borderline tumor categories in thyroid tumor classification, which are hyalinizing trabecular adenoma identified by Carney et al.(1), UMP (well differentiated tumor of uncertain malignant potential and follicular tumor of uncertain malignant potential) proposed by Williams (2), the recent reclassification of some indolent tumors currently classified as carcinoma into the borderline tumor category proposed by Kakudo et al. (3-7) and NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features), a nomenclature revision of non-invasive encapsulated follicular variant papillary thyroid carcinoma proposed by Nikiforov et al. (8-15).

The E-Book edition was the first English-language textbook of thyroid FNA cytology textbook published in Asia. In the print edition, we invited some more authors, and we would like to highlight the new supplementary chapters only available in this print edition. Finally, this print edition is a more comprehensive and international textbook than our eBook edition, "Thyroid FNA Cytology: Differential Diagnoses and Pitfalls". The editors of the print edition, "Thyroid FNA Cytology: Differential Diagnoses and Pitfalls" thank all authors sincerely and appreciate their great efforts and contributions to this book.

The eBook version (reduced size version) is also available from the S&S Publications and distributed by Smashwords (https://www.smashwords.com/books/view/655745).

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Preface to eBook Edition
Thyroid FNA Cytology: Differential Diagnoses and Pitfalls

Thyroid fine needle aspiration (FNA) cytology is the most widely used clinical test for patients with thyroid nodules. This can be attributed to its accuracy and reliability in identifying high-risk patients who should undergo surgical treatments. It has been nearly 10 years since the National Cancer Institute of the United States of America proposed a reporting system for thyroid FNA cytology (1). Following this recommendation, Italy, England, and Japan developed their own reporting systems comparable with the American (Bethesda) system (2-4). These diagnostic systems have contributed to significantly better performance in thyroid cytology and improved communication among the different cytology practices. All four diagnostic systems focus on the standardization of 1) diagnostic terminologies, 2) clinical management, and 3) risk of malignancy. However, there remain a few of pitfalls that are important to address for cytopathologists to achieve a good performance in their practice. This E-Book, "Thyroid FNA Cytology: Differential Diagnoses and Pitfalls", focuses on how to avoid such pitfalls in thyroid FNA cytology. Good performance in your practice can only be achieved when you become familiar with these pitfalls and differential diagnoses in detail. The thyroid experts included in this E-Book demonstrate how to bypass these pitfalls using beautiful case presentations and detailed differential diagnoses based on their rich experiences and evidences from the literature. We believe this approach is essential for establishing high level performance in thyroid FNA cytology, regardless of the diagnostic system used.

This E-Book is the first English textbook of thyroid FNA cytology published in Asia, and all authors are of Asian background. The editors thank all authors sincerely and appreciate their great efforts on and contribution to this E-Book.

Chief Editor: Kennichi Kakudo, MD, PhD, FIAC

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Book review

This book takes an unconventional but pragmatic approach of addressing many key issues in thyroid cytopathology through the use of case studies in many chapters. I believe this format is effective in engaging the reader to understand the subspecialty practice of thyroid cytopathology. The text is authored by many well-known thyroid cytologists and pathologists, mostly from Asia. The first few chapters discuss some key principles regarding thyroid cytopathology. The differences in the approaches to thyroid FNA cytology in various countries such as the USA, UK, Italy, and Japan are detailed nicely and are very insightful; they raise questions as to whether the differences are cultural or responses to external factors (e.g. medical-legal environment in the USA). While the expectation of having everyone practice in exactly the same manner globally may be too idealistic, better understanding of our similarities and differences bring us closer together.

The chapters based on case studies are organized systematically into sections on clinical summary, radiologic findings (with ultrasound images), cytologic findings, differential diagnosis, gross and histopathologic diagnosis, discussion, and references. The images are effective in addressing the main points of the authors. Sample chapter headings include *Diagnostic Criteria of AUS/FLUS, NIFTP (Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features) and Conventional Papillary Carcinoma, Hyalinizing Trabecular Tumor vs. Papillary Thyroid Carcinoma, Parathyroid Adenoma and Its Differential Diagnosis, and Poorly Differentiated Carcinoma vs. Well Differentiated Carcinoma.* In some chapters, the differential diagnoses are based on the cytologic findings, whereas in other chapters, they are based on the histologic findings of the resected lesion. In either case, pitfalls are discussed thoroughly.

The last chapters of this book cover the technical aspects of thyroid cytology. These include procedural complications, liquid-based cytology, immunocytochemistry, molecular diagnosis, FNA techniques, and staining procedures. As for the case study chapters, the images illustrate the authors' points very effectively. For some chapters, the technical procedures may be based primarily on the author's experience. Inquisitive readers are encouraged to broaden their scope by surveying the up-to-date references provided by the authors.

In summary, I recommend this book for residents and fellows in pathology training as well as those practicing thyroid cytopathology. The selection of chapter titles is excellent and addresses many common dilemmas in daily practice. Case examples are well illustrated and the thyroid cytology practitioners should find this book to be a valuable reference. While the reader may have to adjust to the writing style of some authors, the text is relatively easy to follow. Since some topics (e.g. diagnosis of AUS/FLUS) are controversial with many differing opinions, readers may want to use the text as a foundation and use the up-to-date references to build on their own understanding of the topics.

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List of Frequently Used Abbreviations in This Book

ATA:	The American Thyroid Association
ATC:	Anaplastic Thyroid Carcinoma (Undifferentiated Carcinoma)
AUS:	Atypia of Undetermined Significance
BRAF:	B-Raf Proto-oncogene, Serine/Threonine Kinase
CEA:	Carcinoembryonic Antigen
CNB:	Core Needle Biopsy (Core Biopsy)
CFO:	Cyst Flued Only
CT:	Computed Tomography
CV-PTC:	Cribriform Variant of Papillary Thyroid Carcinoma
FA:	Follicular Adenoma
FLUS:	Follicular Lesion of Undetermined Significance
FNA:	Fine Needle Aspiration
FNAC:	Fine-Needle Aspiration Cytology
FN/HCN:	Follicular Neoplasm/Hurthle Cell Neoplasm
FN/SFN:	Follicular Neoplasm/Suspicious Follicular Neoplasm
FT-UMP:	Follicular Tumor of Uncertain Malignant Potential
fT3:	free T3
fT4:	free T4
FTC:	Follicular Thyroid Carcinoma
FVPTC:	Follicular Variant Papillary Thyroid Carcinoma
HCN:	Hurthle Cell Neoplasm
HE:	Hematoxylin and Eosin
HT:	Hashimoto's Thyroiditis
IHC:	Immunohistochemical Stain
IL:	Indeterminate Lesion
ITET/CASTLE:	Intrathyroid Epithelial Thymoma/Carcinoma Showing Thymus-like Differentiation
LBC:	Liquid-Based Cytology
LT:	Lymphocytic Thyroiditis
MGG:	May Gruenwalds Giewsa
ML:	Malignant Lymphoma
MTC:	Medullary Thyroid Cancer or C Cell Carcinoma
N/C:	Nuclear/Cytoplasmic
NCI:	Nuclear Cytoplasmic Inclusions (Pseudoinclusions), Intranuclear Cytoplasmic Inclusions (Pseudoinclusions)
ND:	Non Diagnostic
NIFTP:	Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features
PAP:	Papanicolaou
PAX8:	Paired Box Gene 8
PDC:	Poorly Differentiated Carcinoma
PHPT:	Primary Hyperparathyroidism
PMC:	Papillary Microcarcinoma
PTC:	Papillary Thyroid Carcinoma
PTC-N	Papillary Thyroid Carcinoma Type Nuclear Features (Changes)
PTH:	Parathyroid Hormone
PTMC:	Papillary Thyroid Microcarcinoma

RAI:	Radioactive Iodine
ROM:	Risk of Malignancy
ROSE	Rapid On-site Evaluation
SM:	Suspicious for Malignancy
TBSRTC:	The Bethesda System for Reporting Thyroid Cytopathology
TG:	Thyroglobulin
TGD:	Thyroglossal Duct
TPO:	Thyroid Peroxidase
TSH:	Thyroid Stimulating Hormone or Thyrotropin
TTF1:	Thyroid Transcription Factor 1
UC:	Undifferentiated Carcinoma (Anaplastic Thyroid Carcinoma)
US:	Ultrasonography
WHAFFT:	Worrisome Histologic Alterations Following Fine needle aspiration of the Thyroid
WDT-UB:	Well Differentiated Tumor of Uncertain Behavior
WDT-UMP:	Well Differentiated Tumor of Uncertain Malignant Potential
WHO:	World Health Organization

Chapter 1

Factors Impacting Thyroid Fine Needle Aspiration Cytology and the Algorithm for Cytological Diagnosis

Kennichi Kakudo

1. The American Thyroid Association (ATA) Management Guidelines and Thyroid Fine Needle Aspiration (FNA) Cytology

The ATA guidelines for thyroid nodules and differentiated thyroid carcinomas are the most well-known and established guidelines, with a new edition published recently (1). Recommendations (R7 to R24) regarding FNA cytology are also included in the 2015 ATA guidelines (1). Recommendation 8 suggests performing FNA cytology if the thyroid nodule is larger than 1 cm and with intermediate or highly suspicious pattern on sonography. Diagnostic FNA cytology is not recommended for thyroid nodules that are either purely cystic or smaller than 1 cm (please refer to Supplemental Chapter 3). Thus, papillary microcarcinomas smaller than 1 cm in diameter are clinically followed without cytological confirmation of malignancy. According to the 2015 ATA guidelines, a higher risk of malignancy should be suspected in cystic FNA samples from the USA than those from other countries. This is because according to the ATA guidelines, cystic FNA samples are often taken from the solid portion (high-risk for cystic papillary thyroid carcinoma [PTC]) of the cystic nodule, and purely cystic nodules should be excluded from FNA examination. The author of this textbook wishes cytopathologists, particularly those practicing in other geographic areas, to bear in mind that the risk of malignancy of cystic FNA samples from the American system may be different from the reader's samples, in which a significant number of samples are from purely cystic lesions (extremely low risk of malignancy).

Furthermore, important improvements in the clinical management of AUS/FLUS (low-risk indeterminate) and FN/SFN (high-risk indeterminate) nodules have been included in the 2015 ATA guidelines. Although diagnostic surgery is the traditional and established standard for FN/SFN nodules in all clinical guidelines from Western countries, additional preoperative risk stratification is recommended for SN/SFN nodules in the 2015 ATA guidelines. According to Recommendation 16, the weak recommendation with moderate-quality evidence in FN/SFN cytology suggests molecular testing for supplementation of malignancy risk assessment data in lieu of proceeding directly with surgery, after consideration of clinical and sonographic features. Therefore, a diagnosis of FN/SFN on thyroid FNA cytology is no longer a compulsory order of immediate diagnostic surgery from cytopathologists to clinical doctors. In Recommendation 15, molecular testing was added as a supplement in risk assessment for AUS/FLUS nodules, in addition to the use of repeat FNA cytology and assessment of clinical and sonographic features. This triage of patients with AUS/FLUS or FN/SFN nodules is already a standard practice in Asian countries, and more than half of these patients with benign clinical tests are followed without surgical intervention. Higher risks of malignancy in surgically treated patients with AUS/FLUS or FN/SFN nodules have been reported in Korea (2, 3), China (4), and Japan (5-9), where risk stratification using cytological sub-classification, clinical tests, sonographic risk-stratification, and molecular analyses are usually performed for patients with indeterminate nodules. The increased role of conservative management using molecular testing and clinical/radiologic risk stratification are emphasized in the 2015 ATA clinical guidelines (1).

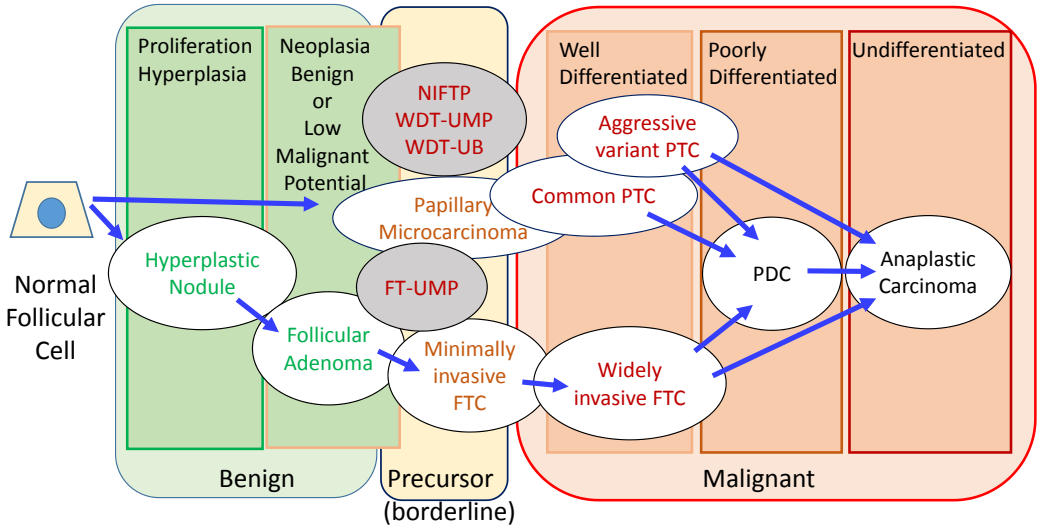

Figure 1. Progression and dedifferentiation of follicular cell neoplasia and precursor tumors in the multistep carcinogenesis theory. FTC: follicular thyroid carcinoma; FT-UMP: follicular tumor of uncertain malignant potential; NIFTP: non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC: papillary thyroid carcinoma; PDC: poorly differentiated carcinoma; WDT-UB: well-differentiated tumor of uncertain behavior; WDT-UMP: well-differentiated tumor of uncertain malignant potential.

2. The New Classification of Thyroid Tumors in the 4th Edition (2017) of the WHO Classification of Endocrine Organs

The WHO classification of tumors serves as an international standard for histopathologic diagnosis and clinical practice for neoplastic diseases in all organ systems. The 3rd edition of endocrine tumor classification is under revision, and the 4th edition WHO classification of endocrine organs will be published in 2017. The thyroid tumors included in the contents of the 4th edition (Table 1) are essentially the same as those of the 3rd edition, but with one significant change. The 4th edition introduces a precursor tumor category in the classification schema of follicular cell neoplasia to better adhere to the multistep carcinogenesis theory (Figure 1). This category is the non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), introduced by Nikiforov et al. in 2016, and was formerly named the well-differentiated tumor of uncertain malignant potential (WDT-UMP) by Williams in 2000, or the well-differentiated tumor with uncertain behavior (WDT-UB) by Liu *et al*. in 2011 (10-12). All 109 cases of NIFTP in a patient series by Nikiforov *et al*. showed a benign course, with average follow-up of more than 14 years after surgery alone (without RAI treatments) (10). NIFTP is an encapsulated, follicular pattern tumor characterized by the worrisome nuclear features of papillary carcinoma, and with no invasion. This type of tumor shows significant observer disagreement among pathologists (13-15), and is usually classified as a malignant tumor (encapsulated follicular variant PTC without invasion) in Western practice, resulting in it being the most popular (10-30%) variant of PTC. While the so-called encapsulated follicular variant PTC without invasion is a rare malignancy (<1%) in Asian practice, the majority of NIFTPs are classified as benign hyperplastic nodules or follicular adenomas when evidence of invasion is not discernible (12). The use of a lower cut-off threshold in judging PTC type nuclear features (PTC-N) by Western cytopathologists compared with Asian cytopathologists may be the cause for such an increased number of

malignant diagnoses (encapsulated follicular variant PTC), both histological and cytological, in Western practice. This was further demonstrated in recent publications from the USA, in which a significant number of malignancies in the indeterminate categories were shown to be NIFTP, and if NIFTP was no longer categorized as a malignant tumor, significant drops in the rates of malignancy were observed in the AUS/FLUS and suspicious for malignancy categories (16-18). Thus, there is a different diagnostic attitude regarding the diagnosis of PTC between Western and Eastern pathologists, contributing to significant inter-observer variation (11-15). Cytopathologists in Western countries must refine their cytological diagnostic criteria for PTC-N and adjust to the new WHO classification schema of PTC and precursor tumors (NIFTP).

Table 1. Classification of Thyroid Tumors in the 4th Edition

1	Follicular Adenoma
2	Hyalinizing Trabecular Adenoma/Tumor
2A	Other Encapsulated Follicular Patterned Thyroid Tumors
3	Papillary Carcinoma
4	Follicular Carcinoma
4A	Hurthle Cell Tumors
5	Poorly Differentiated Carcinoma
6	Undifferentiated Carcinoma
7	Squamous Cell Carcinoma
8	Medullary Carcinoma
9	Mixed Medullary and Follicular Cell Carcinomas
10	Mucoepidermoid Carcinoma
11	Sclerosing Mucoepidermoid Carcinoma with Eosinophilia
12	Mucinous Carcinoma
13	Ectopic Thymoma
14	Spindle Epithelial Tumor with Thymus-like Differentiation
15	Carcinoma showing Thymus-like Differentiation
16A	Paraganglioma
16B	Peripheral Nerve Sheath Tumors (including Schwannoma)
16C	Benign Vascular Tumors
16D	Angiosarcoma
16E	Smooth Muscle Tumors (including leiomyoma and leiomyosarcoma)
16F	Solitary Fibrous Tumor
17A	Langerhans Cell Histiocytosis
17B	Rosai-Dorfman Disease
17C	Follicular Dendritic Cell Tumor
17D	Primary Thyroid Lymphoma
18	Germ Cell Tumors
19	Secondary Tumors

3. Diagnostic Criteria and Observer Disagreement

Differences in the rates of thyroid tumor malignancy, proportions of histological types, and biological characteristics may exist among different geographic areas or patient populations. However, the author of this chapter emphasizes the importance of applying the diagnostic criteria of malignant thyroid tumors consistently throughout the world. From previous observer variation studies on the diagnostic criteria of PTC-N, possibly irreconcilable issues between the two types (Western and Eastern) of practice have been identified (13-15). These differences may also be observed not only in PTC type malignancies, but also in follicular adenoma (FA)/follicular thyroid carcinoma (FTC) tumors. Recently, Cipriani *et al*. from the USA reported that in a review of 66 FTC cases diagnosed over the past 50 years, 71% of the FTC diagnoses required reclassification, resulting in 36% of cases diagnosed as PTC, 8% as poorly differentiated carcinoma, and 27% as benign FA (19). The authors emphasized the importance of strict diagnostic criteria for thyroid tumors (19). In this chapter, issues that cause significant observer discrepancies in thyroid tumor diagnosis, resulting in difficulty in cytologic-histologic correlation studies and comparisons of data in the literature, will be highlighted. These reasons underlying such observer variations may also be applied to the diagnostic criteria of thyroid FNA cytology. Because the majority of thyroid malignancies in the current diagnostic schema do not recur or metastasize (20, 21), and a significant proportion of PTCs is proposed to be renamed NIFTP (precursor benign tumor) (10), the author of this chapter recommends applying stricter diagnostic criteria and retaining a more conservative attitude in the diagnosis of thyroid carcinomas. This is because there are several thyroid tumors currently classified as carcinomas, including papillary microcarcinoma, intrathyroidal PTC, encapsulated follicular variant PTC, and minimally invasive FTC, whose recurrence rates are less than 5% after initial surgery and cancer specific death rates are at negligible levels (1, 22, 23).

4. Diagnostic Algorithm for Thyroid FNA Cytology (Figure 2)

Assessment of cellularity and specimen adequacy is the first step in evaluation of FNA cytology specimens. Only adequate specimens must be processed for further cytological evaluation; however, special care must be paid to rare atypical cells in compromised specimens (sparse cellularity, air-drying artifact, bloody sample, poor fixation, or crush artifact) (please refer to Chapter 5). Thus, in such cases, assessment of the presence of atypical cells should be indicated as inadequate, followed by a statement pointing out the presence of atypical cells, clarifying that PTC cannot be ruled out, and that the specimen may be categorized into the low-risk indeterminate category (Figure 2), such as indeterminate B: others in the Japanese system or AUS (PTC type atypia in suboptimal specimen) in the American system (please refer to Chapters 2 and 5). If rare, but conclusive, malignant cells are found in a poor(low quality) specimen, the specimen maybe classified in the suspicious for malignancy, but not malignancy, category (Figure 2). In adequate smear samples, the following features are searched for: nuclear atypia (24, 25) (presence or absence of papillary carcinoma type nuclear atypia, neuroendocrine carcinoma type nuclear features, high-grade nuclear features, and atypical lymphocytes) (Figures 3-4), and architectural abnormalities, such as nuclear crowding and overlapping in follicular or trabecular clusters due to loss of cellular polarity, and dispersed cells or microfollicles due to loss of cellular cohesiveness (Figures 5-7). The microfollicle is emphasized in the Bethesda text book and the microfollicle consists of groups of 6-12 follicular cells in a small circle; sometimes with a small amount of thick luminal colloid (Figures 6 and 7) (24). These features are further graded depending on morphological features (mild, moderate, and marked) into benign, low-risk indeterminate, suspicious for malignancy, and malignancy categories for the PTC lineage (Figures 3 and 4), and benign, low-risk

indeterminate, and high-risk indeterminate categories in the FA/FTC lineage (Figures 6-7) (please refer to the scoring system by Kameyama in Chapter 20) (8, 25). These algorithms, shown in Figures 2, 3 and 5, are summarized in Figure 8.

Sample preparation, fixation, and/or staining methods may require some modifications for evaluation of these morphological features, an example of which is specimen adequacy for more than 180-320 follicular cells in LBC samples in comparison to more than 6 cell clustes in conventional smear (24, 26); please refer to Chapter 27 for liquid based cytology and Chapter 31 for different staining methods.

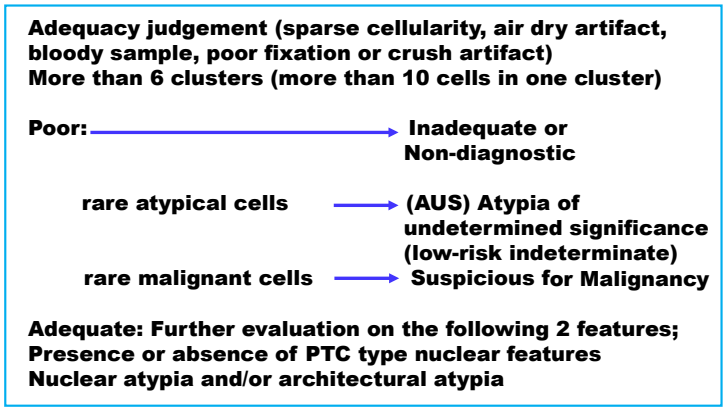

Figure 2. An adequate sample must contain at least 6 clusters composed of more than 10 cells. Special care must be paid to the possible presence of rare atypical cells in compromised specimens. In such cases, the assessment for the presence of atypical cells should be pointed out as being inadequate, followed by a statement indicating the presence of atypical cells or in the low-risk indeterminate category, such as indeterminate B: others in the Japanese system or AUS (PTC type atypia in suboptimal specimen) in the American system. If rare, but conclusive, malignant cells are found in a poor specimen, then the specimen should be classified into the suspicious for malignancy category.

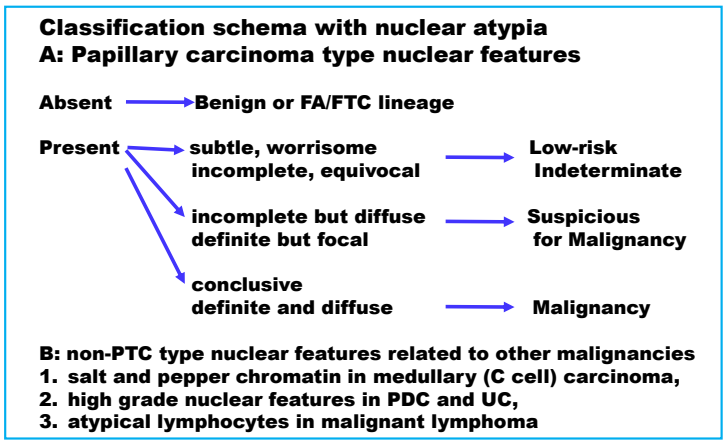

Figure 3. The next step is an assessment of the presence or absence of PTC type nuclear features. These are graded into four classes (negative, worrisome, definite but focal, and definite). Other types of nuclear features related to thyroid malignancy may also be evaluated here. They are 1) salt and pepper chromatin in medullary (C cell) carcinoma (please refer to Chapters 15 and 16), 2) high grade nuclear features in PDC and UC (Please refer to Chapter 21), and 3) atypical lymphocytes in malignant lymphoma (please refer to Chapter 14).

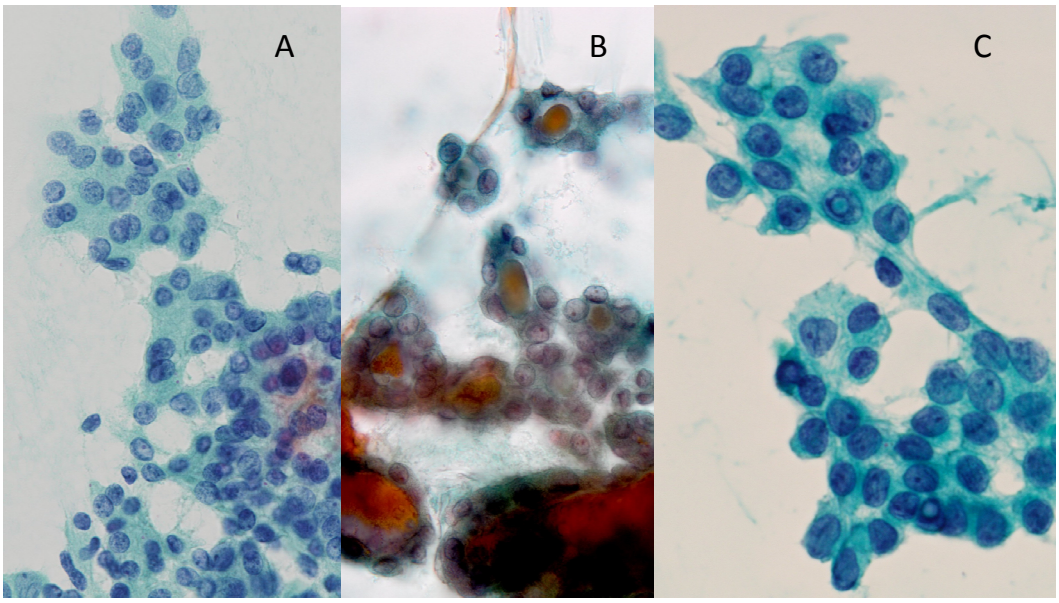

Figure 4. Papillary thyroid carcinoma type nuclear features. A: Subtle PTC type nuclear features, including nuclear enlargement and nuclear irregularity with questionable grooves. B: Incomplete PTC type nuclear features, such as pale (ground glass) nuclear chromatin with distinct small nucleoli in addition to nuclear enlargement. C: Fully developed PTC type nuclear features are seen, such as nuclear grooves and intranuclear cytoplasmic pseudo inclusions. (Conventional smear, Papanicolaou stain, A and B: x200, C: x400)

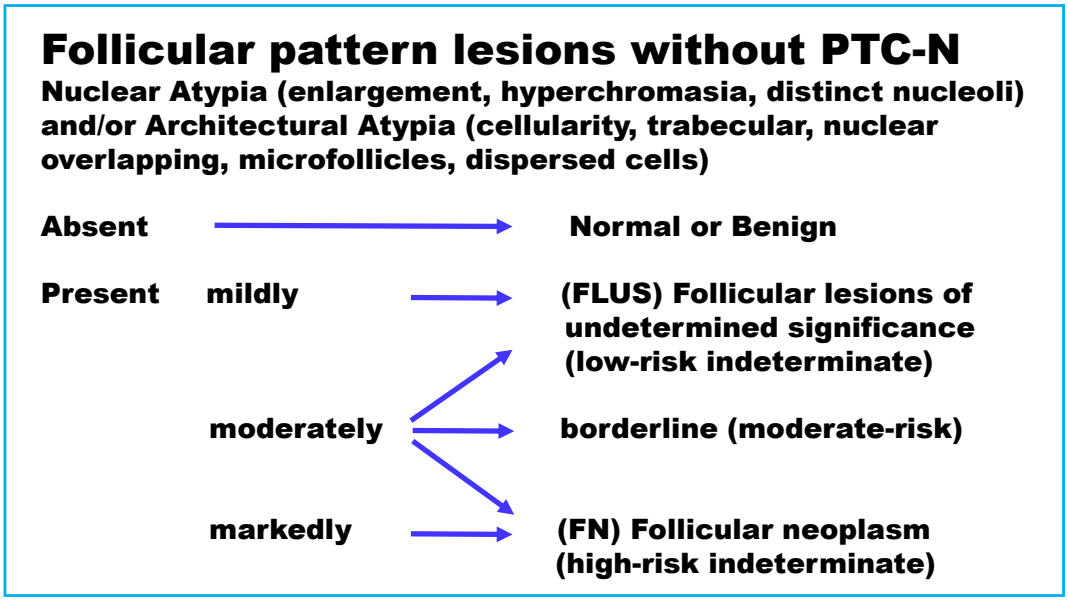

Figure 5. Follicular pattern lesions without PTC type nuclear features are graded into three classes, benign, low-risk indeterminate (FLUS in the American or indeterminate A1, favorable benign in the Japanese system), and high-risk indeterminate category (indeterminate A3, favorable malignant in the Japanese system or FN in the American, Thy 3f in the British or TIR3B in the Italian systems).

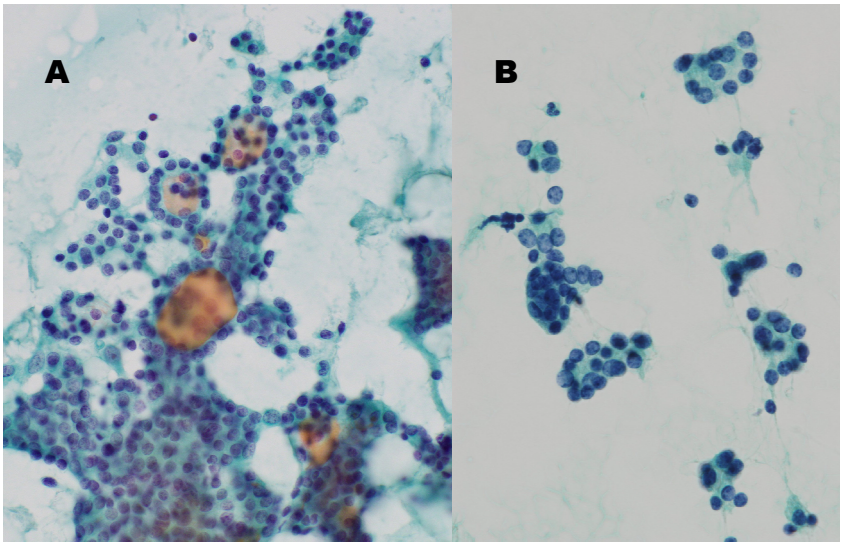

Figure 6. Architectural abnormalities in follicular pattern lesions (FA/FTC lineage). A: Large trabecular clusters show nuclear crowding and overlapping with small round nuclei. Cellular cohesion is fairly preserved and isolated cells are minimally found. Few macro-follicles containing colloid (orange red) are also seen. B: There are small clusters forming microfollicles with distorted cellular polarity. Note papillary thyroid carcinoma type nuclear features are not seen. (Conventional smear, Papanicolaou stain, A: x200, B: x400).

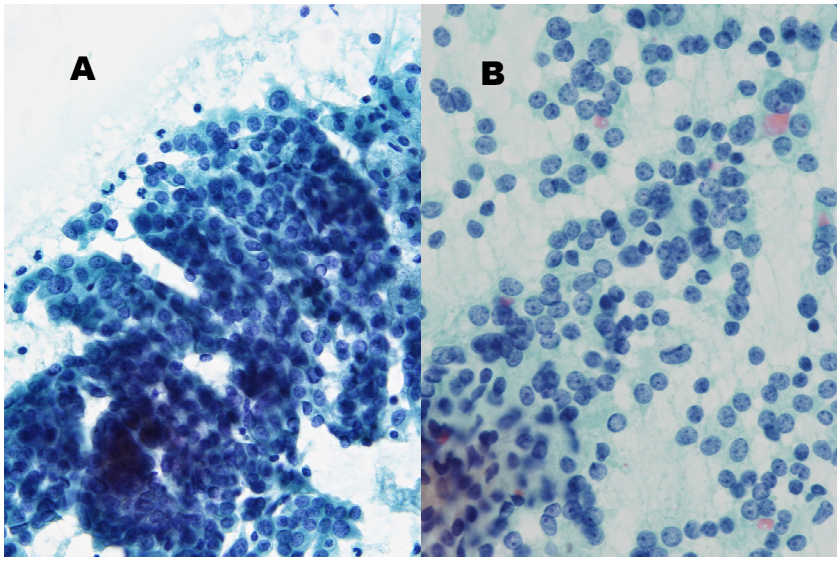

Figure 7. Architectural abnormalities in follicular pattern lesions (FA/FTC lineage). A: Nuclear crowding and overlapping are markedly seen in 3-dimensional, thick trabecular clusters. B: Predominantly dispersed cells are shown as a loss of cellular cohesiveness. Few micro-follicles containing colloid (orange red) are also seen. (Conventional smear, Papanicolaou stain, A: x200, B: x400).

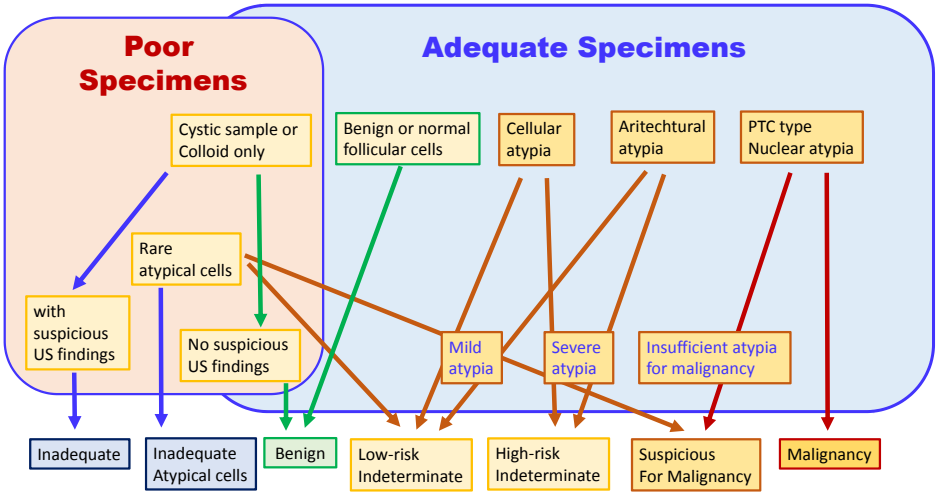

Figure 8. Algorithms for thyroid FNA cytology assessment, composed of three steps: 1) adequate judgement, 2) nuclear atypia, and 3) architectural abnormality.

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Chapter 2

Comparison of Diagnostic Systems: The American, British, Italian, and Japanese Reporting Systems of Thyroid FNA Cytology

Kennichi Kakudo, Zhiyan Liu and Kaori Kameyama

1. History of Diagnostic Systems in Different Countries

In the 2000s, the most popular reporting system of thyroid fine needle aspiration (FNA) cytology was the one recommended by the Papanicolaou society published in 1996 (1). It had a single indeterminate category (Follicular Neoplasm: FN), with many cytopathologists modifying it to their own institutional systems, which may have led to significant problems for clinical doctors on how to decide the clinical management of their patients. In 2008, the National Cancer Institute of the United States proposed a new reporting system for thyroid FNA cytology, the American (so-called Bethesda) system, in which standardization of terminologies, clinical managements and risks of malignancy were established (2). This diagnostic system sub-classified the indeterminate category into low-risk (AUS/FLUS) and high-risk (FN) categories (2, 3). Following this recommendation, the United Kingdom Royal College of Pathologists (the British system) (4) and Italian Societies of Endocrinology and the Italian Society for Anatomic Pathology and Cytology joint with the Italian Division of the International Academy of Pathology (the Italian system) (5) updated their diagnostic schema to be comparable with the American system. These were again updated in 2014 (6, 7). The Japan Thyroid Association (JTA) published its clinical guidelines for thyroid nodules in 2013 (8), which included a reporting system for thyroid cytology (the Japanese system), based on diagnostic systems used in high volume thyroid centers in Japan (9, 10). This system is characterized by more self-explanatory terminologies, and its principle of sub-classification (follicular pattern and papillary carcinoma lineages) of the indeterminate category, differing from other systems.

2. Differences among the Four National Systems (Table 1)

All four national reporting systems are comparable with one another, as shown in Table 1 (11, 12). However, there are slight, but significant, differences among them. First, cystic samples with fewer than 6 follicular cell clusters are classified into the non-diagnostic (Inadequate) category in the American system (2, 3). It is because the 2015 ATA guideline does not recommend FNA cytology to purely cystic nodule therefore cystic cytology samples in the American system usually have solid part suspicious for PTC. On the contrary, these samples are classified into benign category in the Japanese system (9), because majority of them are from pure cystic nodules. Repeat examination of all cystic samples with fewer than 6 follicular cell clusters is not justified in the TIR 1C category in the Italian system (6, 11) and the Thy 1C category in the British systems (7) due to its extremely low-risk nature (equal to or less than benign category). (Please refer to Supplemental Chapter 3) It is also stated in the 2015 ATA guideline, although an FNA specimen found to have abundant colloid and few epithelial cells may be considered nondiagnostic, this is also likely a benign biopsy. Second, the American system recommends limiting the percentage of cases diagnosed as AUS/FLUS (low-risk indeterminate category) to less than 7%, stating that overuse of this low-risk category as a wastebasket should be avoided (2). These strict target numbers for the low-risk and high-risk categories were not emphasized in the other reporting systems, although a proportion of less

than 20% of indeterminate diagnoses was recommended by the Papanicolaou society in 1996, which has been maintained as a common standard in all systems (1). The third characteristic is the different diagnostic criteria of the high-risk indeterminate (TIR 3B) category in the Italian system compared with the American and British systems. A significant degree of nuclear atypia serves as an inclusion criterion of the high-risk category (TIR 3B), and the risk of malignancy of the low-risk category (TIR 3A) in the Italian system was reported to be slightly lower (5-10%) than those (5-15%) of the American and British systems (6, 11) (please refer to Supplemental Chapter 1). The fourth is the manner in dividing the indeterminate category. In the Japanese system, the indeterminate category is divided into the follicular adenoma (FA)/follicular carcinoma (FTC) lineage and the PTC lineage, differing in principle from the other three diagnostic systems, where the indeterminate category is divided into low-risk (TIR 3A in the Italian, Thy3a in the British, and AUS/FLUS in the American systems) and high-risk (TIR 3B in the Italian, Thy 3b in the British, and FN in the American systems) categories, regardless of presence or absence of PTC type nuclear features (PTC-N). This difference was further demonstrated when a significant number of PTC type malignancies were found in both the low-risk and high-risk categories in the Italian, British, and American systems (2-7), whereas the majority of PTC cases were found in the indeterminate B: others (PTC-lineage) category in the Japanese system (9, 13-15). Sugino *et al*. reported that the risk of malignancy in the indeterminate A category was 283/779 (36.3%), and only 61/235 cases (26.0%) of PTC were classified as indeterminate A. On the other hand, they reported that while the risk of malignancy in the indeterminate B (Others) category was 202/270 (74.8%), and the majority of PTC cases (174/235, 64.4%) were classified into the indeterminate B (15) category. In the Japanese system, the distinction between PTC type and FTC type malignancies can be more accurately achieved in cytology due to application of stricter criteria for PTC-N in both the histological and cytological diagnoses by Asian pathologists (16-22).

Encapsulated non-invasive follicular pattern lesions with subtle (incomplete and questionable) nuclear changes of PTC are traditionally classified into the benign category in Asia, either as hyperplastic nodules or follicular adenomas (17-22). This diagnostic attitude by Asian pathologists has helped accommodate a recent reclassification and renaming of the non-invasive encapsulated follicular variant of PTC into the benign precursor tumor category NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) by Nikiforov *et al*. (23), as is the case with previously proposed borderline tumor terminologies, such as well-differentiated tumor of uncertain malignant potential (WDT-UMP) by Williams (24) and well-differentiated tumor with uncertain behavior (WDT-UB) by Liu *et al*. (20, 25) (please refer to Chapters 1 and 6).

3. How to Subclassify Indeterminate Thyroid Nodules, and the Principle of the Japanese System (Figure 1)

The American, Italian, and British systems subclassify the indeterminate category into low-risk and high-risk categories (Table 1). Their morphological criteria were established regardless of presence or absence of PTC type nuclear features. As a result, a significant proportion of the malignancies in both the low-risk and high-risk categories are PTCs (2-7). There are a number of explanations as to why PTCs are found in the follicular pattern lesions of the indeterminate category (FN in the American system, Thy 3f in the British system, and TIR 3B in the Italian system). The most accepted explanation is that this is due to the lax criteria for PTC-N in the histological diagnosis of encapsulated non-invasive follicular variant PTC; the presence of subtle PTC-N in this variant is not uncommon, and may lead to diagnosis of FN rather than PTC by cytology (2-4). The authors of this chapter believe it is important to separate the two different lineages (FA/FTC and PTC) using stricter criteria for PTC type

Table 1. Comparison of the Italian, British, American (Bethesda), and Japanese reporting systems of thyroid cytopathology

Diagnostic Category/ National Systems/ Risk of Malignancy	Itary	Risk of Malignancy by Fadda et al reference No. 9	British	American (Bethesda)	Risk of Malignancy by Ali et al reference No. 2	Japanese (Japan Thyroid Association)	Risk of Malignancy after triage by Kakudo et al reference No.7
Non Diagnostic	TIR 1	Not Defined	Thy 1	I. Non Diagnostic	Not Defined	Inadequate (Non-Diagnostic)	<10%
Non-Diagnostic-Cystic	TIR 1C	Low	Thy 1c:	I. Non Diagnostic	Not Defined	Benign	<1%
Non-Neoplastic/Benign	TIR 2	<3%	Thy 2/Thy 2c	II. Benign	0-3%	Normal or Benign	<1%
Low-Risk Indeterminate Lesion	TIR 3A	<10%	Thy 3a: Neoplasm Possible-Atypia/Non-Diagnostic	III. (AUS/FLUS) Atypia of Undetermined Significance /Follicular Lesion of Undetermined	5-15%	Indeterminate A: Follicular Neoplasms (Follicular Pattern Lesions) A1: Favor Benign, A2: Borderline, A3: Favor Malignant B: Others (Non-Follicular Pattern Lesions and PTC	A1: 5-15%, A2: 15-30%, A3: 40-60%, B: 40-60%
High-Risk Indeterminate Lesion	TIR 3B	15-30%	Thy 3f: Neoplasm Possible-Suggesting Follicular Neoplasm	IV. (FN/SFN) Follicular Neoplasm /Suspicious for Follicular Neoplasm	15-30%		
Suspicious of Malignancy	TIR 4	60-80%	Thy 4: Suspicious of Malignancy	V. Suspicious of Malignancy	60-75%	Malignancy Suspected (Not Conclusive for Malignancy)	>80%
Malignant	TIR 5	>95%	Thy 5: Diagnostic of Malignancy	VI. Malignant	97-99%	Malignancy	>99%

nuclear features, because the two types of well-differentiated follicular cell carcinomas have different molecular alterations in their carcinogenesis, which should be useful for molecular diagnosis. In addition, encapsulated follicular variant PTCs that have subtle PTC-N belong to the FA/FTC lineage, and do not harbor BRAF mutation or RET/PTC rearrangements (20, 26, 27) (please refer to Chapters 6 and 29). This distinction should also be useful for deciding clinical management, because their treatment strategies are different (28).

In the Japanese system, follicular pattern lesions without PTC type nuclear features (Indeterminate A: Follicular Neoplasm) are further sub-classified into A1: favor benign, A2: borderline, and A3: favor malignant (Figure 1), with a scoring system developed by Kameyama *et al*. (14) using three parameters (cellularity, nuclear overlapping, and nuclear atypia). Several studies from Japan have reported successful stratification of resection rates and risks of malignancy using this system (13-15, 29). Cases with PTC type nuclear features are also risk-stratified into three categories (Figure 1), Indeterminate B (40-60% risk), Malignancy suspected (more than 80% risk), and Malignancy (more than 99% risk), using strict criteria of PTC type nuclear features. With use of these criteria, Kameyama *et al*. were successful in differentiating PTC and FTC in their indeterminate categories (14).

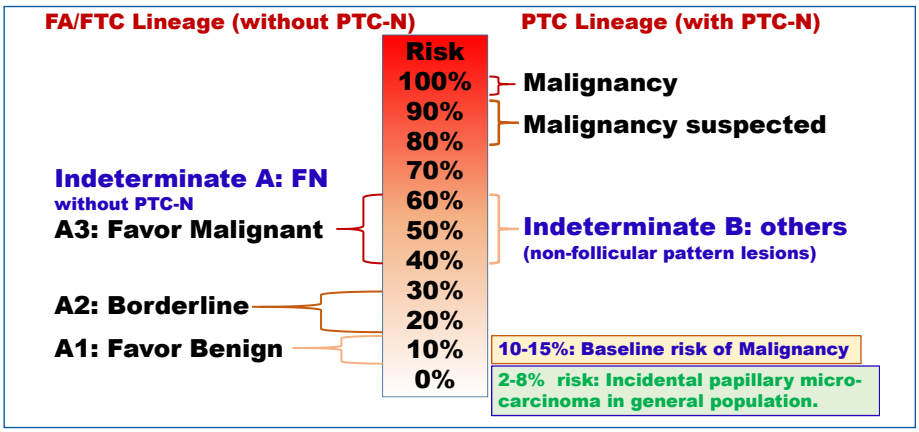

Figure 1. Risks of malignancy in Indeterminate A (Follicular Neoplasm: FA/FTC Lineage) and B (Others: PTC Lineage). On the left side, follicular pattern lesions without PTC type nuclear features (Indeterminate A: Follicular Neoplasm) are sub-classified into A1: favor benign, A2: borderline, and A3: favor malignant. Their risks of malignancy were reported to be 5-15%, 15-30%, and 40-60% using three parameters (cellularity, nuclear overlapping, and nuclear atypia). On the right side, cases with PTC type nuclear features are also risk-stratified into three categories, Indeterminate B (40-60% risk), Malignancy suspected (more than 80% risk), and Malignancy (more than 99% risk). These numbers are higher than those of the other three reporting systems, because strict criteria of PTC type nuclear features were applied for the cytological diagnosis, not just the histological diagnosis.

4. Clinical Management of Patients with Indeterminate Nodules

The American and Italian systems recommend a diagnostic lobectomy for all patients with high-risk (FN in the American system and TIR 3B in the Italian system) indeterminate nodules (1-4, 6, 30). In this regard, FNA may be thought of as a screening test selecting patients for surgery with higher probability of malignancy, although this clinical management has been reported to result in overtreatment for the majority (more than 75%) of patients, because they had benign nodules. Advising diagnostic surgery for all patients with high-risk indeterminate nodules may result in a high proportion (60-80%) of surgery and a 15-30% risk of malignancy in surgically-treated patients with high-risk indeterminate nodules (31-

33). It should be noted that all cases with indeterminate thyroid nodules (Thy 3a, Thy 3f, and Thy 4) in the British system are referred to so-called multidisciplinary team discussions to determine more appropriate clinical management (5, 7). In the JTA clinical guidelines, patients with indeterminate thyroid nodules are also recommended to undergo further triage with other clinical tests to minimize unnecessary diagnostic surgeries for those who actually have benign nodules (8, 9). This is a completely different approach from the clinical management of the American and Italian systems. If all patients with indeterminate cytology are advised to undergo diagnostic surgery immediately and unselectively, then the efforts of sub-classification of indeterminate A (FN), as in the Japanese system, or the use of multidisciplinary meetings, as in the British system, should not be necessary. Alternatively, emphasis should be placed on stricter diagnostic criteria of the high-risk (FN) category to reduce the proportion of this category and to avoid diagnostic surgery in patients with benign follicular pattern lesions (34, 35). Abele and Levine suggested that compared with their experience of 5%, the 15% national rate of the high-risk indeterminate category (FN) was in large part due to overdiagnosis (34), and a stricter approach is essential if patients with high-risk indeterminate nodules are sent to the operation room immediately and unselectively. The Japanese and British systems have set up a different strategy to reduce the overtreatments of patients, demonstrating that integrated clinical examination and watchful follow-up of thyroid nodules can spare many patients with benign nodules from diagnostic surgery. The authors of this chapter believe that this process may also assuage cytopathologists' anxiety over how to reduce the rate of missing FTC type malignancies in the benign category (9). This is because FTC cases with mild cellular abnormality and the absence of an altered architectural pattern, cell crowding, and/or a microfollicle formation may be placed in the indeterminate A1 (FN: favor benign), and these patients can be followed up without surgical intervention and be advised to undergo diagnostic surgery only when other clinical tests reveal malignant characteristics. This ultimately helps reduce missed diagnoses of FTC cases with mild cellular abnormality (please refer to Chapters 19 and 20).

5. **Which Reporting System Has Better Performance?**

The performance of these reporting systems likely depends on the manner of triaging patients with thyroid nodules as well as the decision making process of clinical management of patients with indeterminate nodules. Reports from Asian countries have demonstrated that the application of strict triage criteria preoperatively using integrated clinical tests for patients with indeterminate cytology may result in a low resection rate and a high proportion of malignancies in patients with indeterminate cytology (13-15, 22, 29). In clinical practice, if avoidance of missing a malignancy is the highest priority, as opposed to minimization of patient overtreatment, diagnostic surgery should be advised for patients with indeterminate nodules, because histological examination is ultimately necessary to determine whether the nodule is benign or malignant. Under such circumstances, higher resection rates and lower malignant risks have been reported in those with indeterminate nodules (31, 34, 35). Whatever reporting system is chosen to be used, the clinical management of patients with thyroid nodules is ultimately decided between the clinical doctors (endocrinologists and endocrine surgeons) and the patient, which significantly impacts the resection rates of thyroid nodules and their risks of malignancy. Although these numbers are measures of performance, they are dependent on the clinical guidelines applied to the patients. Thus, the thyroid FNA cytology reporting system remains only one of the decisive factors for obtaining a good performance in clinical practice of thyroid tumors. The increased role of conservative management using molecular testing and clinical/radiologic risk stratification is emphasized in the most recent edition of 2015 American Thyroid Association clinical guidelines, and all international

diagnostic systems for reporting thyroid cytology come close more and more, and, I believe, they will have only negligible differences soon (28).

Conclusion

An alternative approach for establishing good performance in thyroid cytology is a second opinion consultation with experts to establish more definitive diagnoses. This textbook, Thyroid FNA Cytology, Differential Diagnoses and Pitfalls, is designed to provide helpful consultation and guarantees better performance in the differential diagnoses of difficult cases. It also presents high quality evidence and helpful instructions on how to avoid the pitfalls of cytology practice, regardless of the reporting system used.

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Chapter 3

Pitfalls in the Diagnosis of Papillary Thyroid Carcinoma

Xin Jing and Claire W. Michael

Clinical History

A 10 year-old male presented with a two-year history of an enlarged neck, which was concerning for thyroid mass. He denied weight change, chills, excessively warm, diarrhea, constipation, sweatiness, anxiety, and palpitations. His mother stated that he had difficulty keeping up with his siblings and tired a little more easily.

Clinical Tests

TSH measured 1.6 (reference range: 0.30-5.50 mU/L), thyroid peroxidase antibody measured 35 (reference range: 0-30 IU/mL), and free T4 measured 1.39 (0.76-1.70 ng/dL).

Ultrasound Findings

The right thyroid contained a complex cyst measuring 2.1 cm (transverse) x 3.2 cm (superior-inferior) x 1.3 cm (anterior-posterior). Color Doppler demonstrated vascularity in the periphery. Central vascularity was not evident. Multiple non-shadowing punctate echoes were present throughout the complex cyst (Figure 1).

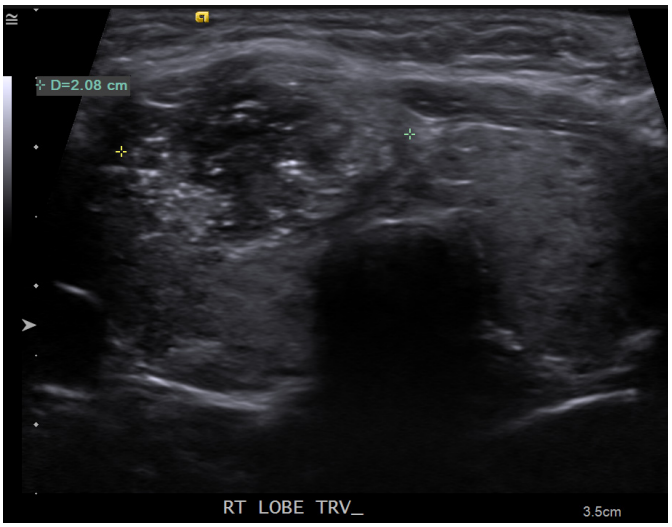


Figure 1. Ultrasound examination of the neck reveals a right thyroid nodule.

Cytological Findings

An ultrasound-guided fine needle aspiration (FNA) of the right thyroid nodule was performed with preparations of Diff-Quik- and Papanicolaou-stained conventional smears. Review of the Diff-Quik-stained conventional smears showed a cellular aspirate consisting of lymphocytes and follicular cells, which were arranged as single cells and/or irregular fragments/sheets (Figure 2). Some of the latter had a syncytial configuration with unevenly distributed nuclei (Figure 3). Various shaped nuclei (round, oval, or elongated) and nuclear

enlargement were evident. Some cells contained abundant cytoplasm, mimicking Hurthle cells (Figure 4). Detailed nuclear features were better appreciated upon examining the Papanicolaou-stained conventional smears, including an irregular nuclear membrane, pale chromatin, and distinct nucleoli (Figures 5 and 6). In addition, intranuclear grooves were occasionally seen (Figure 7). However, no intranuclear pseudoinclusions (NCI) were identified.

Differential Diagnoses

1. Benign hyperplastic nodule
2. Lymphocytic (Hashimoto's) thyroiditis
3. Follicular neoplasm/Hurthle cell neoplasm
4. Suspicious for papillary thyroid carcinoma (PTC)
5. PTC, including its variants

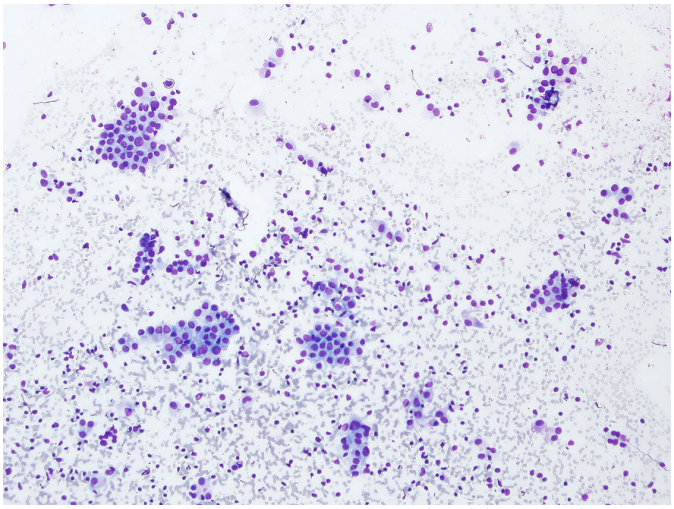


Figure 2. The aspirate is cellular with background lymphocytes, and single and irregular sheets of follicular cells. (Conventional smear, Diff-Quik stain, x100)

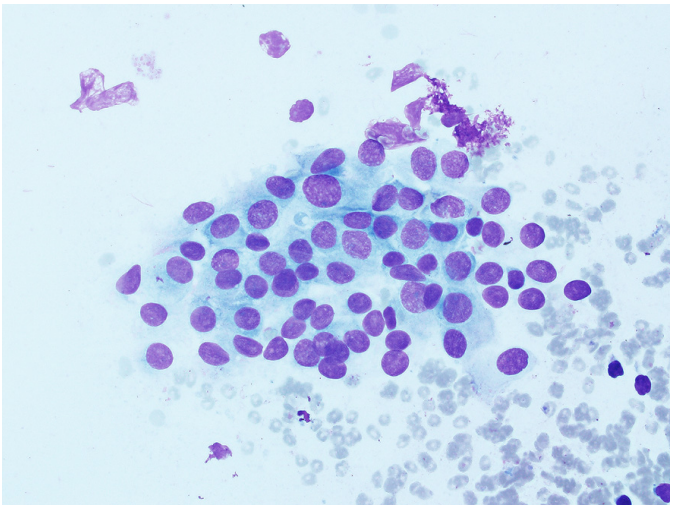


Figure 3. Syncytial sheets with unevenly distributed nuclei. (Conventional smear, Diff-Quik stain, x400)

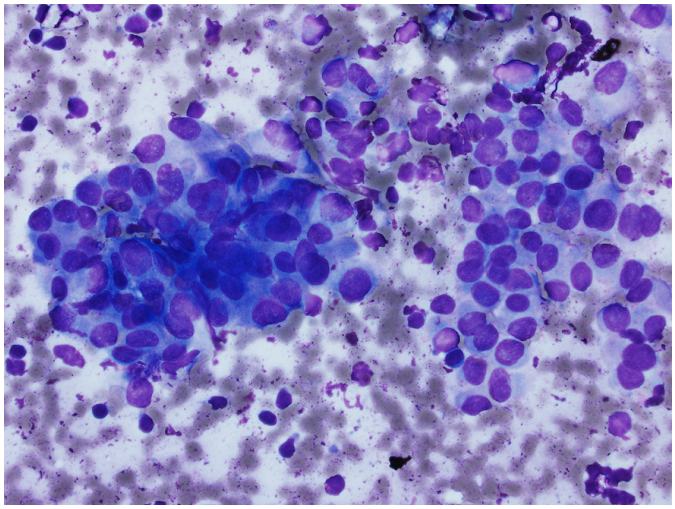
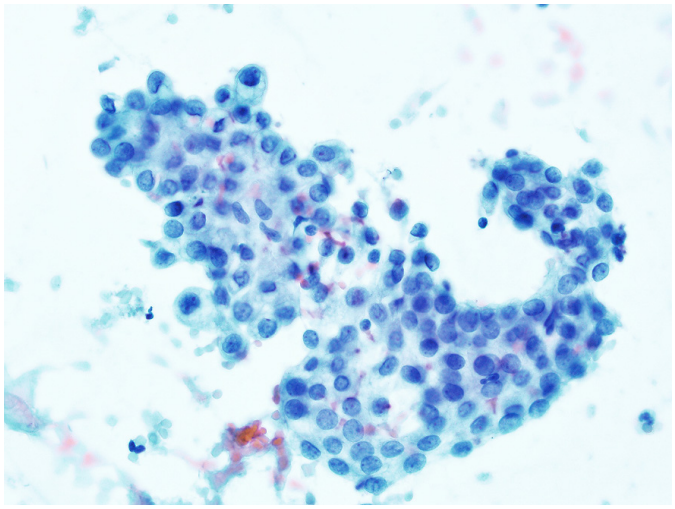
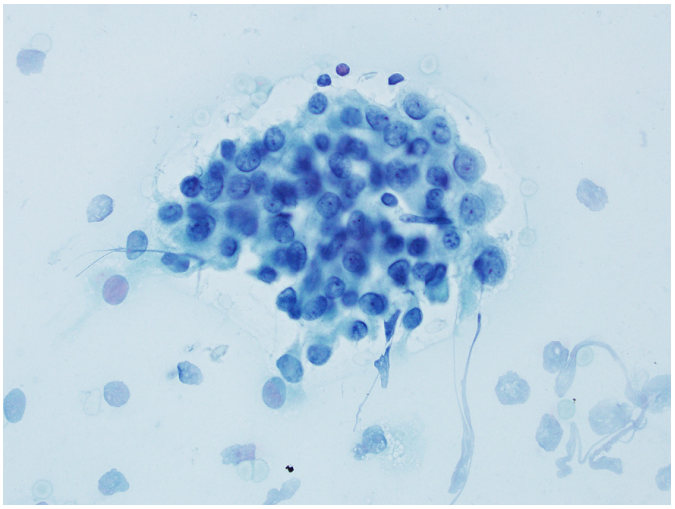


Figure 4. Various shaped nuclei (round, oval, or elongated) and nuclear enlargement are evident. Some cells contain abundant cytoplasm, mimicking Hurthle cells. (Conventional smear, Diff-Quik stain, x400)





Figures 5 and 6. Irregular nuclear membrane, pale chromatin and distinct nucleoli are appreciated. (Conventional smear, Papanicolaou stain, x400)

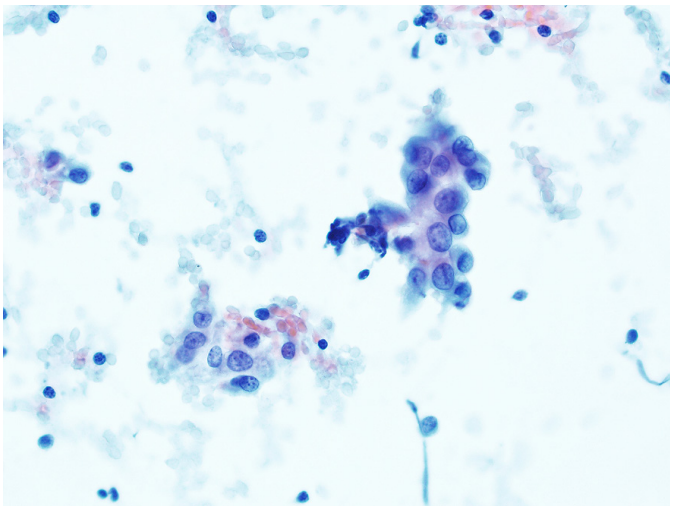


Figure 7. Intranuclear grooves are noted. (Conventional smear, Papanicolaou stain, x400)

Discussions

It has been widely accepted that FNA is a useful triage method in distinguishing neoplastic/malignant nodules from non-neoplastic/benign nodules of thyroid. Greater than 90% of diagnostic accuracy has been reported while utilizing FNA to detect PTC (1). Cytomorphological features associated with PTC have been well defined and The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) provides diagnostic criteria of PTC along with imaging illustrations and explanations. Briefly, the cytomorphological features of PTC include hypercellularity, papillae and/or syncytial tissue fragments, nuclear enlargement, oval or irregular shaped nuclei with crowding/overlapping/molding, intranuclear longitudinal grooves and NCIs, powdery chromatin, marginally located micronucleoli, psammoma bodies, and multinucleated giant cells (please refer to Chapters 4 and 5) (Tables 1 and 2) (2). It is noteworthy to mention that none of these features itself is specific for PTC. We have encountered benign hyperplastic nodule with monolayer sheets and/or papillary fragments of follicular cells, intranuclear grooves, and/or rarely NCIs; Hurthle cell-containing nodules (i.e. Hashimoto's thyroiditis and Hurthle cell neoplasm) with NCIs; and benign hyperplastic nodule with suboptimal preparation of smears showing foci of pale nuclei that mimic pale nuclei with powdery chromatin. Similarly, Kini reported three aspirates obtained from Hashimoto's thyroiditis that contained NCIs (3) (please refer to Chapter 13). Faquin *et al*. identified nuclear enlargement, nuclear grooves, fine chromatin, and distinct nucleoli, as well as rare nuclear crowding and NCI in cyst-lining cells (4) (please refer to Chapters 5 and 7). Other investigators also suggested that the presence of occasional intranuclear grooves should be interpreted as a non-specific finding (5-7). Overall, extreme cautions should be excised in the assessment of specimens with single or a few of the PTC-related features in order to avoid misinterpretation of these specimens as PTC. In addition, it is not uncommon that NCIs may be easily appreciated in other malignant neoplasms involving the thyroid, i.e., medullary thyroid carcinoma and metastatic melanoma to the thyroid. (please refer to Chapters 15 and 16)

There are limited literatures focusing on diagnostic pitfalls associated with FNA cytology of PTC. Generally, the presence of overlapping cytological features between PTC and non-PTC, as well as the over-interpretation of certain PTC-associated features are contributing factors to misdiagnosis of PTC. We previously performed a retrospective review of 22 thyroid aspirates with a histology-proven false diagnosis of PTC and identified several

pitfalls attributed to the misdiagnosis. The pitfalls included misinterpretation of papillary-like tissue fragments and/or monolayer sheets with honeycomb arrangement as syncytial fragments/sheets (please refer to Figure 6 in the Chapter 4), over-interpretation of suboptimal intranuclear grooves or rare NCIs, while other PTC-associated features were minimal or absent, and misinterpretation of the elongated or spindle cells that actually represented atypical cyst lining cells (8) (please refer to Chapter 7). Others have reported cases of histology-proven Hashimoto thyroiditis being over-interpreted as PTC (please refer to Chapter 13). The authors of these studies demonstrated the pitfalls leading to over-diagnosis of PTC, including powdery chromatin, occasional nuclear grooves or pseudoinclusions, and a paucity of background lymphocytes. Furthermore, it was indicated that appreciation of lymphocytes infiltrating follicular groups is a helpful approach to avoid over-diagnosis of Hashimoto thyroiditis as PTC (9, 10). In addition, one study retrospectively reviewed three cases in which cytologic evaluation raised suspicion PTC and the subsequent thyroidectomy revealed solitary papillary hyperplastic nodule. The retrospective review of the FNA specimens showed worrisome cytologic findings including broad flat sheets, 3-dimensional clusters, nonbranching papillae with transgressing vessels, as well as mild to moderate nuclear pleomorphism and occasional intranuclear grooves. The authors pointed out that the presence of short nonbranching papillae, watery and inspissated colloid plus lack of NCIs may be useful features of distinguishing solitary papillary hyperplastic nodule from PTC (11). Last but not the least, Pusztaszeri *et al*. reported a case of histology-proven primary Langerhans cell histiocytosis of the thyroid in which FNA specimen was interpreted as suspicious for PTC due to the finding of cells with nuclear enlargement, pale chromatin, and prominent nuclear grooves (12).

Besides aforementioned over-interpretation phenomenon, under-interpretation of variants of PTC poses a challenge to practicing cytopathologist as the classic features associated with PTC may appear subtle in some of these variants (please refer to Chapters 6, 9 and 10). Among all variants of PTC, the follicular variant is the most common one, in which FNA smear may display predominantly architectural atypia manifested by a microfollicular pattern, while PTC-associated nuclear features are inconspicuous. It is not uncommon that such variant is interpreted as follicular neoplasm rather than PTC (please refer to Chapters 4 and 6). Nonetheless, there has been an on-going discussion of reclassifying non-invasive follicular variant of PTC, which however, is beyond the scope of current discussion (please refer to Chapters 4-6).

Histological Diagnosis

A total thyroidectomy was subsequently performed. Gross examination of the right thyroid lobe revealed a 2.6 cm nodule, which abutted the anterior and isthmus margins (Figure 8). Microscopic examination demonstrated morphological features consistent with PTC, mixed follicular and Hurthle cell variant (Figure 9).

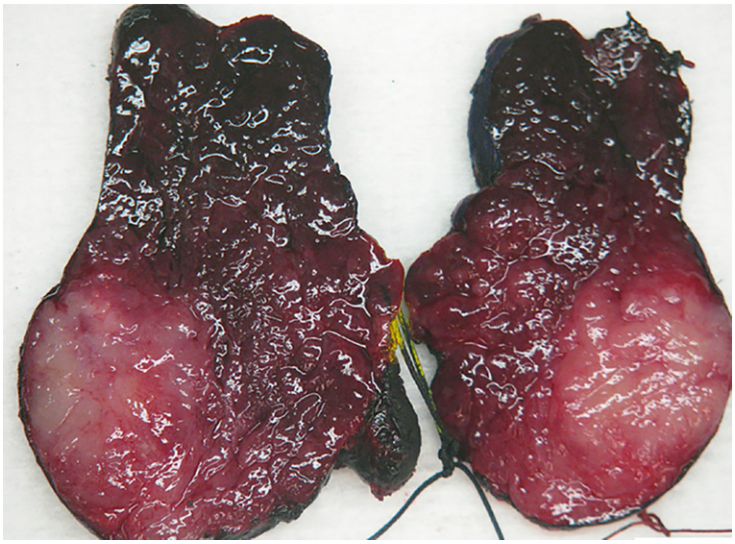


Figure 8. Gross examination of the right thyroid lobe revealed a 2.6 cm nodule.

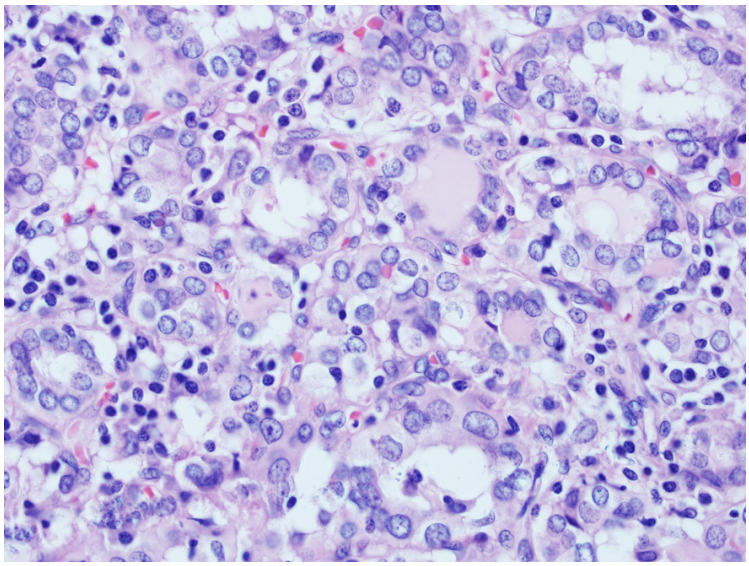


Figure 9. Microscopic examination identified morphological features of PTC, follicular and Hurthle cell variants. (H&E stain, x400)

Table 1. Differentiating features between PTC and benign non-neoplastic thyroid nodules

Features	PTC	BFH	LT/HT
Papillary-like fragments	syncytial arrangement with nuclear crowding/overlapping/molding	honeycomb arrangement with evenly spaced nuclei	honeycomb arrangement with evenly spaced nuclei
Syncytial-type sheets	moderate to abundant, diffuse	rare, focal	rare, focal
Microfollicles	prominent in FV variant	minor portion	minor portion
Hurthle cells	may be present	may be present	may be present
Lymphocytes	may be present	may be present	prominent, polymorphous population
Colloid	various amounts, may show a bubble-gum appearance	various amounts, homogenous, hard or watery	various amounts, homogenous, hard or watery
Psammomata bodies	may be present	may be present	may be present
Multinucleated giant cells	may be present, numerous nucleoli	rare	may be present, few nucleoli
Nuclei	oval, elongate or irregular shaped, variation in size, markedly enlarged, Irregular contour, pale chromatin	uniformed round or oval-shaped, slightly enlarged, smooth contour, fine chromatin	uniformed round or oval-shaped,, slightly enlarged, smooth contour, fine chromatin
Intranuclear grooves	thick/longitudinal, accompanied by other architectural/nuclear atypia	isolated, thin and/or incomplete	isolated, thin and/or incomplete
Intranuclear pseudoinclusion	Present along with other architectural/ nuclear atypia	rare and an isolated finding	rare and an isolated finding

PTC: papillary thyroid carcinoma; BFH: benign follicular nodule; LT/HT: Lymphocytic/Hashimoto's thyroiditis; FV: follicular variant

Table 2. Differentiating features between PTC and other neoplastic/malignant thyroid nodules

Features	PTC	FN/HN	MTC
Architecture	papillae and/or syncytial sheets, single cell microfollicles seen in FV	microfollicles, trabeculae, single cells Hurthle cell type may show transgressing vessels	various, commonly dispersed single cell
Cells	enlarged cells with various amount of cytoplasm may have histocytoid or squamoid appearance	uniformed, normal to slightly enlarged Hurthle cells may show marked pleomorphism	plasmacytoid, spindled, small blue cell, etc.,
Nuclei	oval, elongate or irregular shaped, variation in size, markedly enlarged, irregular contour, pale chromatin	uniformed round or oval-shaped, slightly enlarged, smooth contour, fine chromatin. Hurthle cells may show size variation and prominent nucleoli	round, oval or spindled, salt and pepper chromatin, inconspicuous nucleoli
Intranuclear grooves	thick/longitudinal, accompanied by other architectural/nuclear atypia	isolated, thin and/or incompleteay	none
Intranuclear pseudoinclusion	present along with other architectural/nuclear atypia	rare and an isolated finding	common
Background materials	bubble-gum colloid may present	scant amount or no colloid	amyloid may present
Positive immunostaining	TTF1 and thyroglobulin	TTF1 and thyroglobulin	calretinin, synaptophysin, chromogranin, CD56, CEA

PTC: papillary thyroid carcinoma; FN/HN: follicular/Hurthle cell neoplam; MTC: medullary thyroid carcinoma; FV: follicular variant

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Chapter 6

The New Tumor Entity "NIFTP (Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features)" and Conventional Papillary Carcinoma

Zhiyan Liu, Shinya Satoh and Kennichi Kakudo

Brief Clinical Summary

The patient was a 72-year-old female who has a history of stroke. During follow up, she was found to have a nodule in the right lobe of the thyroid. She was referred to our hospital for a further check-up, and under ultrasound guidance, a fine needle aspiration (FNA) was performed for the 18 mm thyroid nodule (Figure 1).

Ultrasound Findings

Ultrasound detected a well-circumscribed nodule in the right lobe of the thyroid (Figure 1). The nodule was solid with minor cystic change. Neither irregular margin suggestive of invasion into thyroid parenchyma nor invasion to thyroid capsule was found. No calcification was identified in the nodule. A clinical diagnosis of a benign adenomatous nodule was made based on the ultrasound images.

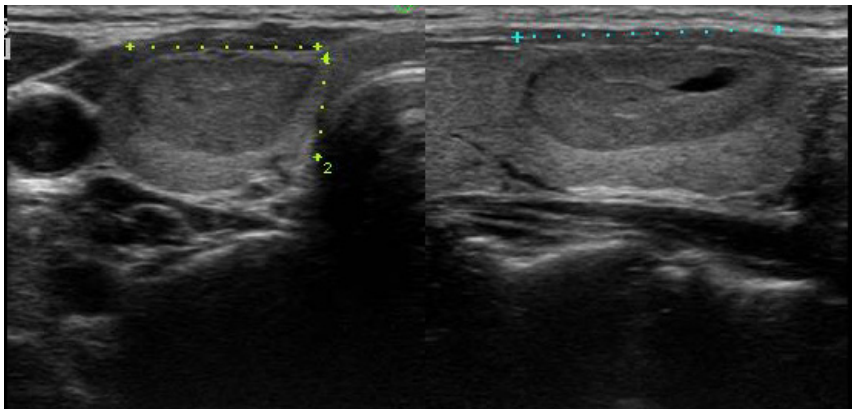

Figure 1. Ultrasound images show a well-demarcated thyroid nodule.

Cytological Findings:

A moderate number of follicular cells in follicular pattern clusters were seen in the Papanicolaou-stained conventional smear (Figures 2-6). No macrophages suggesting cystic change were noted in the smear background. These follicular cell clusters appeared in loosely cohesive with moderate nuclear overlapping (Figures 2-4) or in large trabecular clusters (Figure 5). Many isolated cells with ill-defined pale cytoplasm were also noted (Figure 4). The tumor cell nuclei were irregular in shape (Figures 3 and 5), and moderately enlarged, and they had a few grooves with fine powdery chromatin (Figures 2-6). Nuclear crowding, overlapping, and molding were conspicuous as shown in the Figure 5. A definite nuclear cytoplasmic

inclusion (NCI) body was found in only one sample (Figure 6), but small questionable nuclear inclusions or vacuoles (red arrows in Figures 3 and 4) and a few of nuclear grooves (yellow arrows in Figures 3 and 4) were worrisome nuclear features, suggesting papillary thyroid carcinoma (PTC) type malignancy. Nucleoli were small and inconspicuous. Neither psammoma bodies nor necrosis was identified in the smear background.

List of Differential Diagnoses

1. Benign, follicular adenoma
2. Benign, atypical follicular adenoma (FA)
3. Benign, Hashimoto thyroiditis
4. Indeterminate A, follicular neoplasm (FN by the Bethesda system, TIR 3B by Italian system or Thy 3f by British system)
5. Indeterminate B, others, PTC cannot rule out (AUS by the Bethesda system, TIR 3A by the Italian system or Thy 3a by the British system)
6. Suspicious for PTC, follicular variant
7. Malignant, PTC, follicular variant
8. Malignant, PTC, conventional

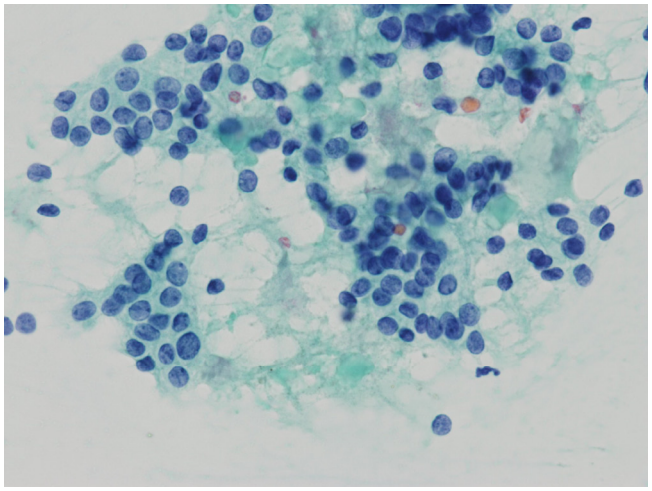

Figure 2. Moderate nuclear enlargement is seen in microfollicular or loosely arranged clusters. (Conventional smear, Papanicolaou stain, x400)

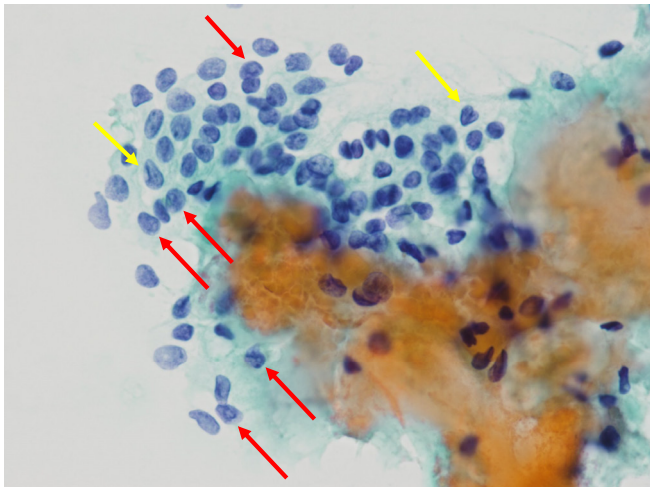

Figure 3. Small nuclear vacuoles (red arrows) and grooves (yellow arrows) are shown in loosely cohesive follicular cells. (Conventional smear, Papanicolaou stain, x400)

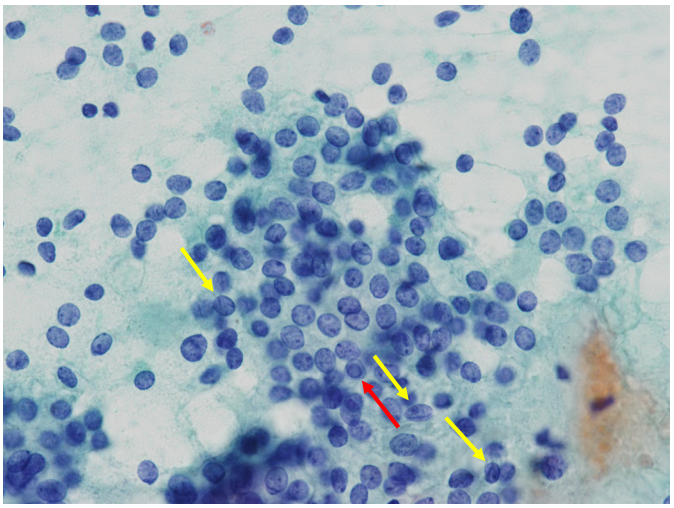

Figure 4. Note a small nuclear vacuole or inclusion (red arrow) and grooves (yellow arrows) in a loosely cohesive large cluster of follicular cells. Numerous isolated cells are also seen in the smear background. (Conventional smear, Papanicolaou stain, x400)

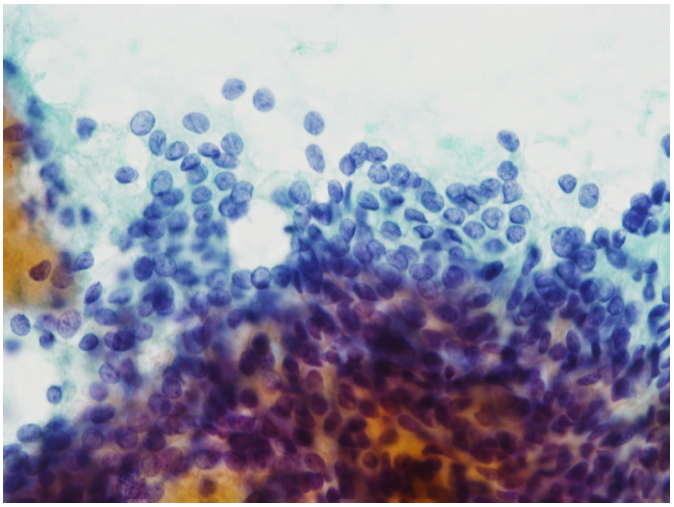

Figure 5. A large follicular cell cluster forms trabecular arrangement. Nuclear crowding, molding and irregularity are shown. (Conventional smear, Papanicolaou stain, x400)

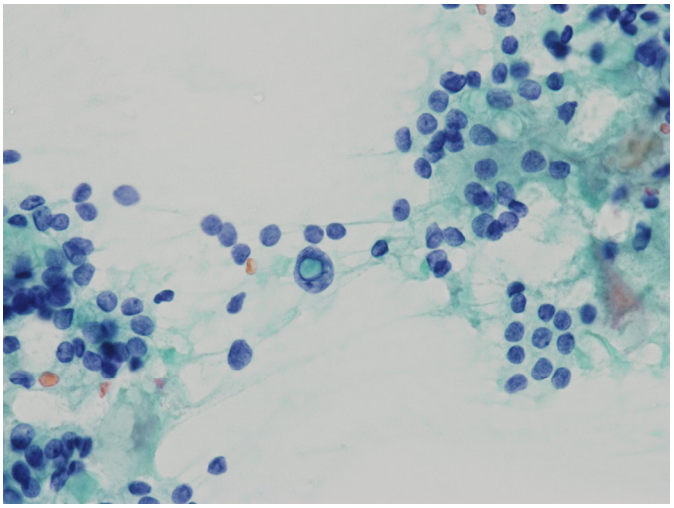

Figure 6. A large nucleus with a cytoplasmic inclusion is shown in the center. This is the only nuclear inclusion identified in the samples. (Conventional smear, Papanicolaou stain, x400)

Differential Diagnosis:

Differential diagnoses include atypical FA, atypical follicular cells in Hashimoto thyroiditis, conventional PTC, follicular variant PTC, well differentiated tumor of uncertain malignant potential (WDT-UMP), NIFTP, and follicular thyroid carcinoma (FTC).

Hashimoto thyroiditis can be ruled out by the absence of lymphocytes in the smear background. Characteristic oxyphilic change (Hurthle) of follicular cells in Hashimoto thyroiditis is absent (please refer to Chapter 13).

Moderate nuclear enlargement, nuclear shape irregularity, and small nuclear vacuoles in this case were worrisome nuclear features of PTC type malignancy. NCIs are seen in more than 80% of conventional PTC (please refer to Chapters 3 and 4), however, they are not specific for PTC type malignancy because they are also seen in C cell (medullary) carcinomas (please refer to Chapters 15 and 16), benign hyalinizing trabecular adenomas (please refer to Chapter 12), and in some cases of adenomatous nodules and FA (please refer to Chapters 3 and 4). The NCI of PTC are larger than one third of the nuclear diameter and have distinctive sharp contour by a rim of condensed chromatin (please refer to Chapters 3 and 4), which was rarely found in this case. The minimum number of NCIs necessary for a PTC diagnosis is uncertain because the threshold varies among observers and a significant observer variation exists. For PTC, NCIs should be observed in many tumor cells and is found easily when examining. However those nuclear changes as shown in the Figures 3 and 4 are incomplete nuclear features for PTC type malignancy. Therefore it may be appropriate to classify this case in either indeterminate B, others, PTC cannot be ruled out (AUS by the Bethesda system, TIR 3A by the Italian system or Thy 3a by the British system) or indeterminate A, follicular neoplasm (FN by the Bethesda system, TIR 3B by the Italian system or Thy 3f by the British system). It is also acceptable but not advisable to classify it in suspicious for PTC (TIR 4 or Thy 4), follicular variant, or pattern B of suspicious for malignancy by the Bethesda system, because it's clinical management is usually different from that of indeterminate categories. A conservative approach of classifying cases with mild PTC-N, which are intermediate between the indeterminate category and suspicious categories, into indeterminate category is recommended. Classification of NIFTP or WDT-UMP in suspicious for malignancy category has been reported in a high proportion from several academic centers (1-4), and it should be minimized because of benign nature of this lesion. One typical NCI (Figure 6) is not sufficient for a diagnosis of malignant. A diagnosis of malignancy, such as conventional PTC, should not be applied to this case.

Histological Diagnosis: NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features), WDT-UMP (well differentiated tumor of uncertain malignant potential), or non-invasive encapsulated follicular variant papillary carcinoma of the thyroid

An 18 mm well-circumscribed nodule was found in the right lobe of the thyroid gland (Figure 7). Small areas of hemorrhage and cystic change were noted on the cut surface (Figure 7). It was a capsulated, follicular patterned lesion with thin a fibrous capsule (Figures 8A and 8B). Neither invasive growth beyond the tumor capsule (Figure 8) nor papillary growth was identified (Figures 8-10). Moderately increased nuclear size and an irregular nuclear contour similar to the cytological features were well demonstrated in the histological samples (Figures 8-10). An irregular nuclear contour and ground glass (powdery chromatin) nuclei were more clearly shown in the Figures 9 and 10. Incomplete NCIs or degenerative vacuoles were seen as indicated with blue arrows in the Figures 9 and 10. No enlarged lymph nodes suggesting metastasis were found during surgery, and prophylactic lymph node dissection was not carried out.

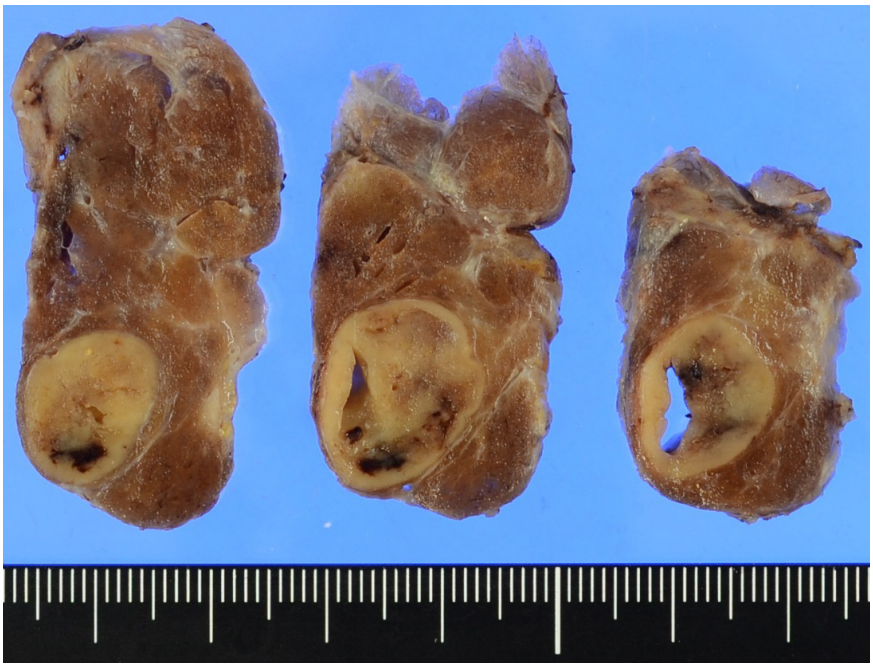

Figure 7. Gross appearance of the thyroid tumor (cut surface after formalin fixation), showing an encapsulated nodule, 18 mm in diameter, ivory-white in color, and solid with hemorrhage and cystic change.

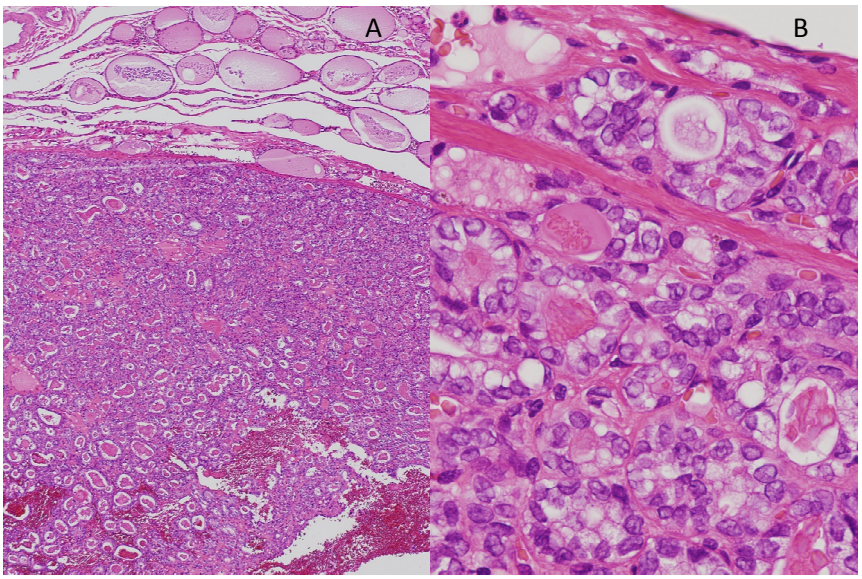

Figure 8. Low (A, x100) and high (B, x400) magnifications of the tumor, showing the well encapsulation by a thin fibrous capsule. Note follicular but not papillary growth pattern. These follicles are composed of atypical follicular cells with large irregular nuclei.

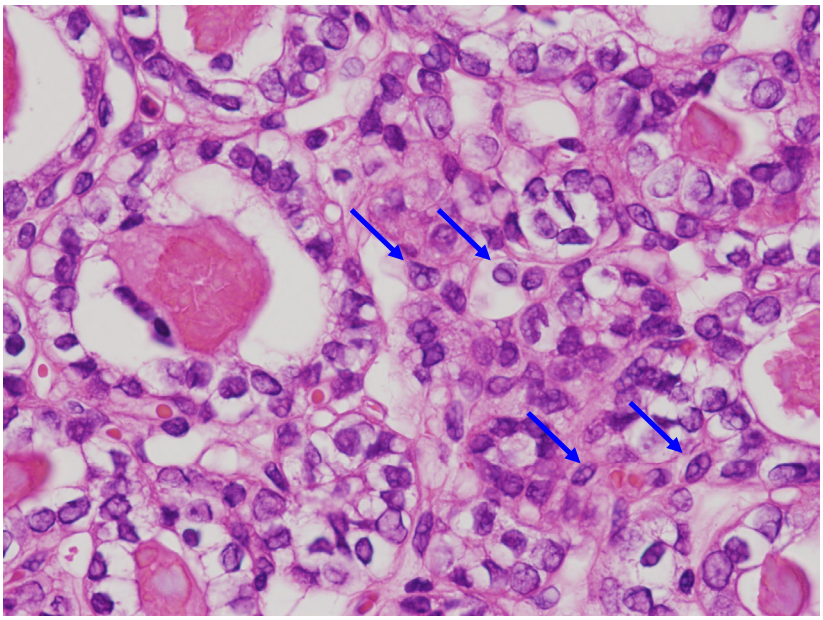

Figure 9. Incomplete nuclear inclusions or vacuoles are indicated by blue arrows. Note the irregular nuclear contour and hyperchromatic nuclear chromatin (x400).

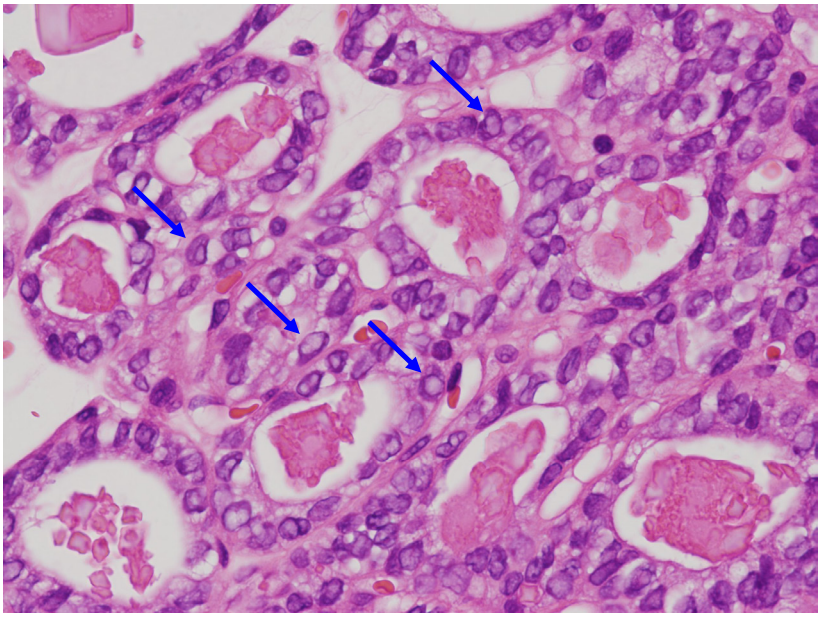

Figure 10. Blue arrows indicate nuclear vacuoles in irregular nuclei. Note the pure follicular growth pattern (x400).

Explanatory Notes:

PTC is a malignant follicular cell tumor characterized by distinctive nuclear features. Follicular variant PTC (FVPTC) is the most common sub-type of PTC, which is characterized by PTC type nuclear features (PTC-N) and a follicular (non-papillary) growth pattern. There are debates on diagnostic criteria of this variant and observer variation between benign FA and malignant FVPTC has been reported to be significant (5-7). The Memorial Sloan-Kettering Cancer Center group has clarified that there are three sub-types of FVPTC that have different genetic profiles and different biological behaviors (8-10). None of the 57 cases of non-invasive