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History of Thyroid Cytology in Japan and Reporting System Recommended by the Japan Thyroid Association

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Abstract

The present paper introduces the history of thyroid cytology and the traditional clinical managements of patients with indeterminate cytology in Japan because most literatures on this subject have been published in Japanese and limited publications are available in English. The Japan Thyroid Association has recently published a guideline for clinical practice for the management of thyroid nodules and this paper introduces its diagnostic system for reporting thyroid cytology. There are three aspects slightly different from the existing internationally recognized reporting systems. First is the so-called 'cyst fluid only' samples which contain only few or no follicular cells, and those samples are classed to 'benign category' in the Japan Thyroid Association reporting system for thyroid cytology. The second is the sub-classification of so-called 'indeterminate' category that is divided into 'follicular neoplasm' and 'others'. The third is the so-called sub-classification of 'follicular neoplasm' into 'favor benign' (low-risk), 'borderline' (moderate-risk) and 'favor malignant' (high-risk), which has been adapted from the high volume thyroid disease centers in Japan. This is because diagnostic surgery for all patients with follicular neoplasms is not a standard practice in Japan and most Japanese clinicians apply further risk stratification to identify higher-risk patients who should undergo surgery. The Japan Thyroid Association reporting system uses self-explanatory terminologies and provides a flexible choice of either a simple 6-tier (without stratification of follicular neoplasm), comparable to other internationally recognized reporting systems, or a more complicated 8-tier system for further risk stratification of patients. The reporting system is believed to be useful to reduce the number of unnecessary surgical procedures, particularly for those patients with benign nodules.

Keywords: Thyroid, fine needle aspiration, cytology, diagnosis, indeterminate, risk stratification

Introduction

The Japan Thyroid Association (JTA) has recently published a guideline for clinical practice for the management of thyroid nodules and this paper introduces its diagnostic system for reporting thyroid fine needle aspiration (FNA) cytology (Table 1) (1). There are only limited publications in English on thyroid cytology from Japan. This paper first introduces the history of thyroid FNA cytology in Japan and then the traditional clinical managements of patients with indeterminate cytology so that readers may understand why the JTA has published a national diagnostic system in thyroid cytology.

Table 1: Cytological reporting system recommended in the Japanese guideline for management of the thyroid nodules in 2013

Diagnostic Category	Risk of Malignancy
Inadequate (non-diagnostic)	10%
Normal or benign	<1%
Indeterminate	
A. Follicular neoplasms (follicular pattern lesions)	
A-1: favor benign	<15%
A-2: borderline	15-30%
A-3: favor malignant	40-60%
B. Others (atypia in non-follicular pattern lesions)	40-60%
Malignancy suspected (not conclusive for malignancy)	>80%
Malignancy	>99%

Thyroid FNA cytology plays an important role for decision-making in clinical management of patients with thyroid nodules. However debates continue regarding the indeterminate category (2). Follicular neoplasm is a major group of the indeterminate category because cytological features alone are insufficient to separate it into benign or malignant reliably (2-14). The patients with follicular neoplasm in this schema are advised to have a diagnostic surgery by most Western clinical guidelines and majority of the patients have undergone thyroid lobectomy (2-14). However, this surgical approach is proper only to a small group of patients, because usually fewer than 20% of patients are found to have malignancy (2-14), and even absence of histological malignancy has been reported in some patients [15]. As a result, this clinical management turns out to be an over-treatment for majority (usually more than 80 %) of the patients and this unnecessary procedure should be minimized for patients with benign thyroid nodule (1, 2, 8, 15).

History of thyroid FNA cytology in Japan

Shortly after Soderstrom in Sweden described his study on thyroid FNA cytology in 1952, thyroid FNA cytology was introduced to Japan (16,17). Dr Toriya published his first report on

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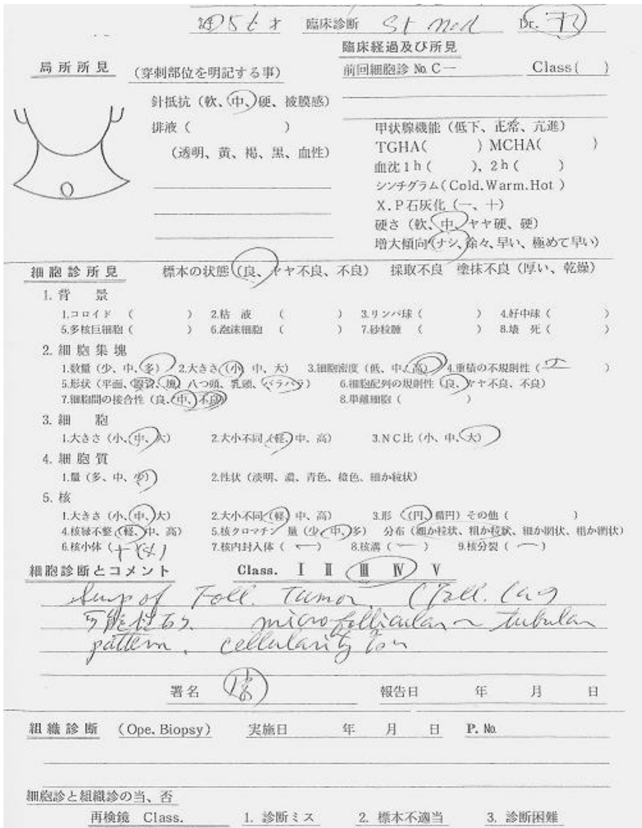

臨床診断 Dr.
臨床経過及び所見
局所所見 （穿刺部位を明記する事）
前回細胞診 No. C－ Class（ ）
針抵抗（軟、中、硬、被膜感）
排液（ ）
（透明、黄、褐、黒、血性）
甲状腺機能（低下、正常、亢進）
TGHA（ ）MCHA（ ）
血沈 1 h（ ），2 h（ ）
シンチグラム（Cold. Warm. Hot）
X. P 石灰化（－、＋）
硬さ（軟、中、ヤヤ硬、硬）
増大傾向（ナシ、徐々、早い、極めて早い）
細胞診所見 標本の状態（良、ヤヤ不良、不良） 採取不良 塗抹不良（厚い、乾燥）
1. 背景
1.コロイド（ ） 2.粘液（ ） 3.リンパ球（ ） 4.好中球（ ）
5.多核巨細胞（ ） 6.泡沫細胞（ ） 7.砂粒体（ ） 8.壊死（ ）
2. 細胞集塊
1.数量（少、中、多） 2.大きさ（小、中、大） 3.細胞密度（低、中、高） 4.重積の不規則性（ ）
5.形状（平面、管状、塊、八つ頭、乳頭、バラバラ） 6.細胞配列の規則性（良、ヤヤ不良、不良）
7.細胞間の接合性（良、中、不良） 8.単離細胞（ ）
3. 細胞
1.大きさ（小、中、大） 2.大小不同（軽、中、高） 3.NC比（小、中、大）
4. 細胞質
1.量（多、中、少） 2.性状（淡明、濃、青色、橙色、細か粒状）
5. 核
1.大きさ（小、中、大） 2.大小不同（軽、中、高） 3.形（円、楕円）その他（ ）
4.核縁不整（軽、中、高） 5.核クロマチン 量（少、中、多） 分布（細か粒状、粗か粒状、細か網状、粗か網状）
6.核小体（ ） 7.核内封入体（ ） 8.核溝（ ） 9.核分裂（ ）
細胞診断とコメント Class. I II III IV V
署名 報告日 年 月 日
組織診断（Ope. Biopsy） 実施日 年 月 日 P. No.
細胞診と組織診の当、否
再検鏡 Class. 1. 診断ミス 2. 標本不適当 3. 診断困難

Fig. 1A: A representative Japanese cytology report signed by Dr. Miyauchi in the early 1980s. The dates of order and cytological diagnosis, and the ID number and name of the patient were omitted for anonymity purpose. This case is an example of class 3.5 (between classes 3 and 4), follicular neoplasm (tumor). This case was diagnosed as high possibility of follicular carcinoma because of the findings of microfollicular and tubular growth patterns and high cellularity. In this report, He described the information of specimen adequacy, the findings (colloid, cystic, psammoma body type calcification, necrosis, and lymphocytes) in the smear background, and the features of cell clusters, cells, cytoplasm, and nuclei.

Clinical findings:
Sex: M or F; Age: years; Clinical Diagnosis: Attending doctor:
Previous FNA cytology No: Diagnosis (Class:):
Nodule location (with drawing and marking where the FNA samples from)
Needle resistance (soft, medium, hard, presence of tumor capsule)
Cystic (volume drained: ml); color (water clear, yellow, brown, black, bloody)
Thyroid function status (hypo-, normal, hyper-thyroid function)
TGHA (thyroglobulin antibody) ( ); MCHA (microsomal antibody) ( ),
ESR (erythrocyte sedimentation rates): 1 h ( ), 2 h ( ),
RAI scintigraphy (cold, warm, hot nodule); calcification with X ray (-,+),
Palpation nodule: (soft, elastic, elastic hard, stony hard)
Nodular size change (no change, slow growing, gradual growing, rapidly growing)
Cytological Findings:
Adequacy of sample (good, fair, inadequate), sampling error, preparation error (thick, dry artifact)
I. Smear background:
1. Colloid ( ); 2. Mucous ( ); 3. Lymphocytes ( ); 4. Granulocytes ( ); 5. Multinucleate giant cells ( ); 6. Foamy cells ( ); 7. Psammoma bodies ( ); 8. Necrosis ( )
II. Cell clusters:
1. Number (few, moderate, many); 2. Size of clusters (small, medium, large); 3. Cell density (mild, moderate, marked) 4. Over-lapping (mild, moderate, marked); 5. Shape (flat sheet, tubular, crowding, branching, papillary, dispersed); 6. Cellular polarity (preserved, fair, poor); 7. Cell adhesion (tight, fair, poor) 8. Isolated dispersed cells ( )
III. Cells:
1. Size (small, medium, large); 2. Anisocytosis (mild, moderate, marked); 3. Nuclear/Cytoplasmic ratio (small, medium, increased)
IV. Cytoplasm:
1. Amount (narrow, medium, wide); 2. Staining characteristics (clear, dense, cyanophilic, orangephilic, granular)
V. Nucleus:
1. Size (small, medium, large); 2. Anisonucleus (mild, moderate, marked); 3. Shape (round, oval, others); 4. Irregular nuclear membrane (mild, moderate, marked); 5. Increased chromatin (mild, moderate, marked); 6. Chromatin pattern (fine granular, coarse granular, fine reticular, coarse reticular); 7. Nucleoli ( ); 8. Intranuclear cytoplasmic inclusions ( ); 9. Nuclear grooves ( ); 10. Mitoses ( )
Cytological diagnosis: **Class: I, II, III, IV, V**
Comments:
Signature; date of report:
Histological diagnosis: (operation, biopsy), Date of report, Sample No:
Cytological-histological correlation: (agree, not-agree)
Revised cytological diagnosis: class
Interpretation of disagreement:
Missinterpretation of cytological observation, sampling error, difficult case

Fig. 1B: The English version of Figure 1A. More than 30 cytological parameters and 15 clinical parameters were recorded in Japanese (Fig. 1A).

thyroid FNA cytology in Japanese with an English abstract, as early as in 1972, from a thyroid disease center, Ito Hospital, Tokyo, Japan (18), where more than 1000 surgeries for thyroid diseases are carried out every year. His cytological diagnoses were more descriptive, and he used more surgical pathology terminologies in his reports including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), undifferentiated carcinoma (UC), medullary (C cell) carcinoma, chronic thyroiditis, cyst, adenomatous nodule (AD), and follicular adenoma (FA). His diagnostic system was well recognized in thyroid FNA at that time (16-19), although Papanicoloau classification (classes 1-5) was widely used in exfoliative cytology such as gynecological smear, urine, sputum, and body fluid specimens. He started his sub-classification of indeterminate category (favor benign and favor malignant) in 1991. In 2005, Dr Toriya reported his study results on the cytology-histology correlation of 1702 cases of surgically treated patients in Japanese (20). Of the cases, there were 68 (4.0%) cases in the indeterminate category including 39 cases of benign and 29 cases of malignant, and the risk of malignancy in the indeterminate category was 42.6%. He further divided the indeterminate category into two sub-categories (favor benign and favor malignant) in the report. Of the 28 cases of favor malignant sub-category, there were 16 cases of malignancy (4 PTCs and 12 FTCs) and the risk of malignancy was 57.1%. Of the 40 cases of favor benign sub-category, there were 13 cases of malignancy (3 PTCs and 10 FTCs) and the risk of malignancy was 32.5%. His 7 tiered cytological diagnosis (inadequate, benign, indeterminate (favor benign), indeterminate (borderline), indeterminate (favor malignant), suspicious for malignancy, and malignant) has still been maintained in the Ito Hospital until now. Fujisawa et al. reported their recent data from surgically treated patients in the Ito Hospital and the risks of malignancy of indeterminate sub-categories were 16.7% (9/54) in favor benign, 50% (5/10) in borderline, and 60% (10/20) in favor malignant, respectively (21).

Dr. Miyauchi started his practice of thyroid FNA cytology in another famous thyroid disease center, Kuma Hospital, Kobe, Japan in 1980, where more than 1000 surgeries for thyroid diseases have been carried out every year. An example of the cytological reports signed by Dr Miyauchi is shown in the Figure 1A in

Japanese and IB in English. Judging from his hand writings in the Figure 1A, this case was an example of follicular neoplasms and with his comments of microfollicular tubular pattern and high cellularity, he suggested a high probability of follicular carcinoma. His cytology report included the age, sex, previous cytological examination and clinical diagnosis of the patient as well as the thyroid autoantibodies, thyroid function, location and size of nodule with or without calcification, elasticity, and recent enlargement of the nodule. He scored more than 30 cytological parameters indicated with circles or plus or minus, and correlation with the final pathology report, and possible reasons and interpretation of discrepancy (Fig. 1).

Dr. Miyauchi's practice was remarkable in the following four points. 1) He first judged the adequacy of samples and only adequate samples were evaluated. 2) His diagnosis of thyroid FNA cytology was expressed from class 1 to class 5 similar to Papanicolaou classification, but having a risk stratification different from Papanicolaou classification for exfoliative cytology. The adequate samples were then classified into 10-tiered risk stratification according to the probability of malignancy as class 1: normal and no risk of malignancy; class 2: benign lesions and fewer than 2% risk of malignancy; class 3: about 50% of risk of malignancy; class 4: more than 80% risk of malignancy; and class 5: more than 95% risk of malignancy. The class 1 was divided into 1C and 1F two groups; the 1C with colloid background consistent with colloid nodule and the IF with foamy cells consistent with cystic change. The class 3 (indeterminate category) was further divided into three sub-classes similar to the Ito hospital diagnostic system, but different diagnostic terminologies were used including class 2.5 (between classes 2 and 3), class 3, and class 3.5 (between classes 3 and 4). He further created one more intermediate class (class 4.5) between class 4 and class 5. Based on his cytological and histological correlation data from surgically treated 537 cases, which was presented in the 45th Annual Meeting of the Japan Thyroid Association held at Hamamatsu in 2002, the risks of malignancy in his 10-tier classification are shown in the Figure 2. A gradual increase of malignancy rate is clearly represented from class 2 (14/119 cases: 11.8%), class 2.5 (6/35 cases: 17.1%), class 3 (10/23 cases: 43.5%), class 3.5 (20/23 cases: 87.0%), class 4 (27/28 cases: 96.4%), class 4.5 (37/37 cases: 100%) to class 5 (252/252 cases: 100%). For the follicular pattern lesions (other types of malignancy were excluded), there were 22 patients with FTC and 163 patients with benign nodular diseases (22). A gradual increase of malignancy rate was from 8.7% (class 2: benign), 12.1% (class 2.5: follicular neoplasms, favor benign), 25.0 % (class 3: follicular neoplasms, borderline), 50.0% (class 3.5: follicular neoplasms, favor malignant) to 50.0% (class 4: suspicious for malignant), which has confirmed that cytological sub-classification of the follicular neoplasms and the indeterminate category successfully stratifies the patients for their risk of malignancy (22). One more important observation in this analysis was that only 55 (39.9%) out of the 138 patients with follicular neoplasms underwent surgery, the rate of surgery was low (33/93 cases, 35.5%) in favor benign and high (6/7 cases, 85.7%) in favor malignant, indicating that this sub-classification had a good function to significantly reduce the number of unnecessary surgery, particularly for the patients with benign nodule in favor benign category. The results have also been confirmed by Fujisawa's report that only 93/197 (47.2%) cases of indeterminate category were surgically treated (21). 3) Dr. Miyauchi further applied bacterial studies and measurements of thyroglobulin, calcitonin and parathyroid hormone using needle washout for more robust diagnoses [23, 24]. His results were reported in 1983 in Japanese with the English abstract and this report might be the first in literature which have shown that the bacteriological and hormonal tests of the FNA samples improve the accuracy of diagnosis dramatically (24). 4) He classified samples with cyst fluid only (fewer than six groups of follicular cells) to benign (class 1F). It was because he was a thyroid surgeon and he himself conducted physical examination, image diagnosis, FNA sampling, thyroid surgery and follow-up of the patients, and the cytological diagnosis was only one piece of information for him to decide patients' management. Therefore, a good consensus was established among his colleagues that benign diagnosis from cyst fluid only sample might occur in rare cystic PTCs and they further agreed and accepted that the most responsible person of false negative diagnosis should be those who performed FNA sampling rather than the cytopathologists. It is because the false-negative diagnosis in cyst fluid only samples was due to sampling error but not due to the miss interpretation of FNA samples by cytopathologists. The benign diagnosis on cyst fluid only FNA is maintained in Kuma Hospital and Ito Hospital at present, adapted by other cytopathologists and by the present reporting system of thyroid FNA cytology in the guideline for clinical practice for the management of thyroid nodules in Japan, 2013 (1).

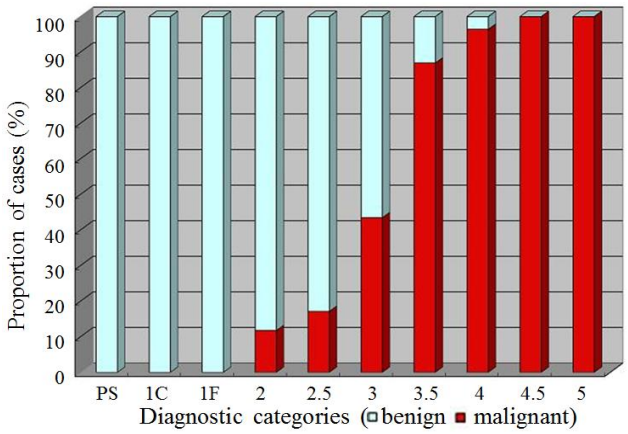

Fig. 2: The risk of malignancy for each class in the 10-tiered classification of thyroid FNA in Kuma hospital, based on the analysis of 537 cases of surgically treated thyroid nodules in 2000. The red and blue bars represent malignant and benign diagnosis, respectively. Note a gradual increase of malignancy rate from class 2 (11.8%), class 2.5 (17.1%), class 3 (43.5%), class 3.5 (87.0%), class 4 (96.4%), class 4.5 (100%) to class 5 (100%). PS, poor sample (inadequate or non-diagnostic); 1C, class 1 with colloid background; 1F, class 1 with cystic change (foamy cells); 2, class 2; 2.5, class 2.5; 3, class 3; 3.5, class 3.5; 4, class 4; 4.5, class 4.5; and 5, class 5.

History of thyroid FNA cytology and the Japanese Society of Clinical Cytology

The Japanese Society of Clinical Cytology (JSCC) was established in 1962 as an organization to promote cytological diagnosis in clinical practice and provide education and training as well as research opportunities. JSCC is one of the member societies of the International Academy of Cytology (IAC) and will organize the 19th International Congress of Cytology in Yokohama, Japan in 2016. This organization provides certification of cytopathologist to those who have passed board examinations, which started in 1968. In the early days, many clinical doctors examined cytological samples by themselves, and JSCC welcomed those clinical doctors as board-certified cytopathologists. JSCC also provided several sub-specialties in its microscopy examination focusing on a certain organ system, such as gynecology, breast and

thyroid, respiratory system, urology, and gastro-intestinal tract in addition to the general pathology. There were 2606 JSCC board-certified cytopathologists and 162 Fellows of IAC in 2013. More than half of the cytopathologists are also certified in pathology or oral (dental) pathology by the Japanese Society of Pathology. The other half has specialized in various clinical medicines and engages their clinical practice, such as obstetrics and gynecology, thoracic surgery, internal medicine, laboratory medicine, oncology and hematology, urology, oral surgery, thyroid surgery or breast surgery, etc. The cytopathology certification for clinical doctors has been given after passing a written examination on general pathology and a microscopy examination focusing on one certain organ system. In total, 33 had passed the cytopathologist board examination on breast and thyroid, and board-certified as a JSCC cytopathologist. However, JSCC ceased this subspecialty type of board examination in 2012 and started a new cytopathology board examination in 2013, which requires general knowledge of cytological diagnosis in all organ systems and three years of training experience in the cytology laboratory which covers all fields of cytological diagnosis. The only exception is for those applicants with dental license. JSCC started organ-specific board examination for dentists in 2012 and the microscopy examination is limited on head and neck lesions in addition to a written examination on general pathology. Seventeen dentists passed the examination in 2012, and in total 40 dentists are JSCC cytopathologist (dental)-certified.

The thyroid cytology is one of the most popular areas in the JSCC Annual Meeting. There were one symposium, one seminar and 14 poster presentations on thyroid cytology in the 52th JSCC Fall Meeting, held in Osaka, 2013.

Clinical management for the indeterminate category in Japan

Upon your cytological report of indeterminate A (follicular neoplasm), surgeons and endocrinologists in Japan usually apply other clinical examinations useful for decision-making in clinical management of the patient (1, 25-28). It is because FNA cytology alone does not efficiently select patients with thyroid nodules for surgery and because the risk of malignancy of follicular neoplasm is within the range of baseline, which is estimated about 10-20% in Western countries and 12.4-15.9% in Japan by Mori et al., Suehiro et al., and Miki et al. (6, 7, 8, 29-31).

Japanese surgeons and endocrinologists regard the reported risk of malignancy (15-30%) in patients with follicular neoplasm to be not high enough for surgical treatment to all patients without further selection, while surgery is always recommended to the patient with follicular neoplasm by the most guidelines in Western countries (2-14). Though, for a part of follicular lesions with benign clinical and ultrasound characteristics in the British Thyroid Association (BTA) and atypia of unknown significance/follicular lesion of undetermined significance (AUS/FLUS) in Bethesda system, a clinical follow-up without immediate surgery and repeat FNA may be considered [12, 32, 33]. In this respect, FLUS in Bethesda system is almost same to the sub-category of A-1, favor benign, in Japanese system (Table 2) (12, 22).

In Japan, further selection for surgical treatments is considered to all patients with follicular neoplasm, which should be based on the combined information of physical examination, change in nodular size, ultrasound image, blood flow Doppler ultrasound, and serum thyroglobulin level (1, 22, 25-28), The diagnostic roles of ultrasound and color Doppler are also emphasized from Western countries (33-36). It has been recommended that surgical treatment should not be indicated to the patient based on the cytological diagnosis alone, particularly on those with A-1: follicular neoplasm, favor benign. Clinical follow up is one of the choices in Japan for patients with indeterminate A: follicular neoplasms, when other clinical tests indicate high probability of benign characteristics of the nodule. Clinical management for follicular neoplasm in Japan is very different on this particular point from the other guidelines [1].

Table 2: Cytological classification of thyroid cytology recommended by Japan Thyroid Association Guideline for the Management of Thyroid Nodules, 2013 and comparison with Papanicolaou, Bethesda and UK diagnostic systems.

JTA	Papanicolaou	Bethesda	UK
Inadequate	Inadequate	ND	Thy1
Normal or benign	Benign nonneoplastic	Benign	Thy2
Indeterminate			
A. Follicular Neoplasms		FN	Thy3f
A-1: favor benign	Cellular follicular lesions	FN	Thy3f
A-2: borderline	FN (favor benign)	FN	Thy3f
A-3: favor malignant	FN (favor malignant)	FN	Thy3f
B. Others		AUS	Thy3a
Malignancy suspected	SM	SM	Thy4
Malignancy	Malignant	Malignant	Thy5

JTA: Reporting system recommended by the Japan Thyroid Association guideline; Papanicolaou: Papanicolaou Society recommendation in 1996; Bethesda: The Bethesda system for reporting thyroid cytology; UK: Reporting systems by the United Kingdom Royal College of Pathologists; ND: Non-diagnostic; FN: Follicular neoplasm; AUS: Atypia of undetermined significance; and SM: Suspicious for malignancy.

The Japanese reporting system of thyroid cytology tries to solve several issues by this characteristic sub-classification of follicular neoplasm and set up a sub-category of indeterminate A-1: follicular neoplasms, favor benign. We hope this category may help establish a proper clinical management of the patients with follicular neoplasm 1) to select patients for surgery more efficiently (reduce number of unnecessary surgery) and 2) to minimize the missing malignancy (normofollicular type FTC and macrofollicular type FTC as well as FTC with mild cellular abnormality) in benign category. Concerning about indeterminate B, a clinical follow-up without immediate surgery and repeat FNA is recommended, which is similar to AUS in Bethesda system (12).

Irrespective of what diagnostic terminology is used in cytology reports, all diagnostic systems in the world try to triage patients for surgical treatment or clinical follow-up. Unfortunately the terminologies for the indeterminate category are differently defined and used, which certainly be a significant source of confusion among cytopathologists and clinicians. The JTA tries to use more descriptive terminologies (follicular neoplasm and others) with more explanatory sub-categories (favor benign, borderline, and favor malignant), so that clinicians may understand the risk of malignancy and the histological type of cytological indeterminate nodules more precisely, which is essential for appropriate clinical management for patients.

Reporting system of FNA cytology in the guideline for clinical practice for the management of thyroid nodules in Japan, 2013

The diagnostic category and the risk of malignancy proposed in the Japanese system of thyroid cytology are shown in the Table 1. Most diagnostic categories of thyroid cytology in the guideline for clinical practice for the management of thyroid nodules in Japan have been adapted from the Papanicolaou Society recommendation published in 1996 (3).

They are:

(I) Inadequate (non-diagnostic):
There are two types of specimens classed in this category including the samples with 1) no or few follicular cells (fewer than six groups of follicular cell clusters), and 2) those with artifacts (crush artifact, poor fixation, air dry, and bloody samples).

(II) Normal or benign:
Cases with: 1) normal follicular cells, consistent with adenomatous nodule (a significant proportion of follicular adenoma of normofollicular and macrofollicular type may be included); 2) degenerated oxyphilic follicular cells and lymphocyte background, consistent with Hashimoto's disease (chronic thyroiditis); and 3) abundant colloid or foamy histiocytes, consistent with benign colloid nodule or cyst (even with follicular cells fewer than 6 groups).

(III) Indeterminate: A. Follicular neoplasms (follicular pattern lesions, possibly neoplastic)
The most important criteria of follicular neoplasm are the cellular aspirates suggesting neoplastic change with exclusion of papillary carcinoma type nuclear features. This group may be sub-classified into the following three sub-categories depending on the cellular atypia, loss of cellular cohesiveness, loss of cellular polarity, and structural abnormalities such as trabecular, tubular and microfollicular growth pattern.
A-1: favor benign
A-2: borderline
A-3: favor malignant

(IV) Indeterminate: B. Others
This category consists of all the histological types of lesions except for the follicular neoplasm in the indeterminate category, which includes the cases with equivocal features of papillary carcinoma, suggestive features for chronic thyroiditis and malignant lymphoma, and questionable features for C cell carcinoma, poorly differentiated carcinoma, undifferentiated carcinoma, and intrathyroidal epithelial thymoma/carcinoma showing thymus-like differentiation and metastatic carcinoma.

(V) Malignancy suspected (not conclusive for malignancy)
Suspicious cases for any types of malignant tumors are included.

(VI) Malignancy
Definite and conclusive features for all of the histological types of malignancy are included.

Modifications on the Papanicolaou Society recommendation have been made only on the indeterminate category, and the indeterminate category is divided into two groups (groups A and B). The group A is termed as indeterminate A: follicular neoplasms, when the samples have atypia in follicular pattern lesions but without PTC-type nuclear features. Possible thyroid diseases in this group include AN, FA, follicular tumor of uncertain malignant potential (FT-UMP), FTC (both minimally invasive and widely invasive type), FV-PTC (both encapsulated and infiltrative), and poorly differentiated carcinoma (PDC).

Further sub-classification of the indeterminate A is encouraged in the Japanese reporting system. This sub-classification is not a definite diagnosis, but a risk stratification of the patients as shown in the Figure 2, which is useful in decision-making of clinical management (clinical follow-up or diagnostic surgery).

Concerning about the indeterminate B: others (atypia in non-follicular pattern lesions), this group covers all indeterminate categories except for group A.

As to benign category, the Japanese system of thyroid cytology is different from the other national guidelines in one aspect: the cyst fluid only samples with fewer than six groups of follicular cells are classed to benign category. This has been recommended in the 1996 guideline of the Papanicolaou society (3). This diagnostic approach to cyst fluid only samples is kept in the Japanese reporting system of thyroid cytology, because the risk of malignancy in patients with cyst fluid only is very low and repeat cytology to all patients may be harmful to patients' psychology as well as to medical economy. Most of the Western guidelines have made protective statements on this type of samples (2-14). The different approaches, benign or inadequate, to the same type of samples may be not due to different risk of malignancy of cyst fluid only samples among those countries, but probably due to the different practice patterns and social backgrounds. Japanese cytopathologists understand the possibility of rare cystic PTC cannot be excluded, but at the same time the risk of malignancy is lower than 1%, which is equal to or lower than that of benign category. Japanese cytopathologists, radiologists, thyroid surgeons and endocrinologists all agree that image diagnosis is a powerful tool to select patients with suspicious for cystic PTC for repeat FNA, thereby minimizing the number of unnecessary repeat FNAs (1).

Conflict of interest

None of the authors have any potential conflicts of interest associated with this research.

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