



The Use of Fine-Needle Aspiration (FNA) Cytology in Patients with Thyroid Nodules in Asia: A Brief Overview of Studies from the Working Group of Asian Thyroid FNA Cytology

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Ultrasound-guided fine-needle aspiration (FNA) cytology is the most widely used screening and diagnostic method for thyroid nodules. Although Western guidelines for managing thyroid nodules and the Bethesda System for Reporting Thyroid Cytopathology are widely available throughout Asia, the clinical practices in Asia vary from those of Western countries. Accordingly, the Working Group of Asian Thyroid FNA Cytology encouraged group members to publish their works jointly with the same topic. The articles in this special issue focused on the history of thyroid FNA, FNA performers and interpreters, training programs of cytopathologists and cytotechnicians, staining methods, the reporting system of thyroid FNA, quality assurance programs, ancillary testing, and literature review of their own country's products. Herein, we provide a brief overview of thyroid FNA practices in China, India, Japan, Korea, the Philippines, Taiwan, and Thailand.

Key Words: Thyroid; Cytology; Fine-needle aspiration; Asia; History; Methods; Survey

Fine-needle aspiration (FNA) cytology has been widely accepted as a safe, cost-effective, and accurate tool for the preoperative diagnosis of thyroid nodules. In the past, aspirations were performed only with the manual aid. Since FNA under ultrasound guidance proved to be more accurate for the detection of thyroid cancer, FNA should be performed under ultrasound guidance using a 23-, 25-, or 27-gauge needle for cytological evaluation.^{1,2} The wide use of FNA cytology for thyroid nodules has significantly decreased the rate of unnecessary surgery for benign thyroid nodules over the last three decades.^{1,3}

Although North American and European guidelines for managing thyroid nodules and the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) are available throughout Asia, the clinical practices in Asia vary from those of Western countries in terms of disease incidence, diagnostic methods, availability of diagnostic tests, conservative management approach,

national health insurance system, and governmental regulations on health care. Moreover, there is considerable variation among Asian countries due to the different rates of economic development and kinds of healthcare systems. Asian countries have increasingly reported their experiences of FNA of thyroid nodules using TBSRTC. Despite these efforts, Asian data on thyroid FNA have not been very well-organized so far. Accordingly, the Working Group of Asian Thyroid FNA Cytology established in 2016 has encouraged group members to publish their work jointly.⁴

In this special issue, seven articles from China, India, Japan, Korea, the Philippines, Taiwan, and Thailand jointly focused on the same topic regarding the history of thyroid FNA, FNA performers and interpreters, the training programs of cytopathologists and cytotechnicians, staining methods, the reporting system of thyroid FNA, quality assurance programs, and ancillary testing, added by the comprehensive review of publications released

Table 1. A brief overview of the history of thyroid FNA cytology in Asian countries

	China	India	Japan	Korea	Philippines	Taiwan	Thailand
1950s	1950s: Introduction of cytology	-	1952: Introduction of thyroid FNA	-	-	-	-
1960s	-	1965: First attempt of needle biopsy of thyroid	1962: Japanese Society of Clinical Cytology was founded.	-	-	-	-
1970s	1970-1980s: FNA was applied to thyroid. 1972: First Chinese FNA book-Atlas of clinical cytology	1970: Indian Academy of Cytologists 1975: First publication on FNA by Gupta <i>et al.</i>	1972: First report of thyroid FNA cytology by Toriya, Ito Hospital	1977: Thyroid FNA was introduced by a physician. Korean Thyroid Study group was founded.	-	1979: Tien-Chun Chang, an endocrinologist at National Taiwan University Hospital, started thyroid FNA	-
1980s	1985: Chinese Academy of Cytology was founded and the first National Clinical Cytology Conference was held.	1987: First paper on thyroid FNA cytology by Rege <i>et al.</i>	-	1981: Cytology training program for pathologists and cytototechnicians 1986: The Korean Society for Cytopathology was founded.	Late 1980s: Thyroid FNA started at the Philippine General Hospital. 1987: Aspiration cytology unit was established in the Department of Pathology, University of the Philippines.	1981: First article on thyroid FNA was published in a local journal by Tien-Chun Chang. 1988: Taiwan Society of Clinical Cytology was founded. 1989: Articles on thyroid FNA were published in international journals.	Endocrinologists started experience with thyroid. 1986: Pathologists started to interpret thyroid FNA.
1990s	1990s: Some of the hospitals started US-guided thyroid FNA.	-	1990s: Wide introduction of US-guidance for thyroid FNA	1996: Cytology proficiency testing has been performed since 1996.	1990s: Private hospitals in the Metro Manila started practice of thyroid FNA.	1995: First color atlas of thyroid and parathyroid cytology	-
2000s	2007: Cytology Operational Manual and Quality Control Standards were proposed by the Cytology Section of the Chinese Pathology Association.	-	-	2006: Korean management guidelines for patients with thyroid nodules and thyroid cancer 2007: Korean Endocrine Pathology Study Group was founded. 2008: Korean Thyroid Association (KTA) was founded.	-	-	-
2010s	-	2011: Endocrine Society of India management guidelines for patients with thyroid nodules	2013: The Japan Thyroid Association Guidelines for the management of thyroid nodules	2010: Revised KTA management guidelines 2016: 2016 Revised KTA management guidelines	2010: Radiologists, endocrinologists, and cytopathologists started US-guided thyroid FNA.	-	2000: Thai Society of Cytology was founded. 2015: Guidelines for the diagnosis and treatment of thyroid cancer

FNA, fine-needle aspiration; US, ultrasound.

from the individual countries.⁵⁻¹¹ Herein, we provide a brief overview of contemporary thyroid FNA practices based on the review articles from seven Asian countries.

HISTORICAL ASPECTS OF THYROID FINE-NEEDLE ASPIRATION

In the late 1920s, Hayes Martin and Edward Ellis performed aspiration biopsies using an 18-gauge needle for the cytological evaluation of thyroid lesions in the Memorial Hospital of New York.¹² In 1952, thyroid aspiration cytology using a fine needle (diameter of 0.4–0.8 mm) was introduced by Nils Söderström in Sweden.¹³ Thyroid FNA was used in routine practice as an accurate test for distinguishing between benign and malignant thyroid nodules in Sweden since the 1950s. In the United States, FNA was not successfully used for the diagnosis of thyroid nodules before 1970s because of the clinician's preference for surgical biopsies, a lack of familiarity with the FNA procedure, and concerns about tumor seeding along the needle tract.^{14,15} After that time, thyroid FNA was reintroduced in the United States and became widely available in the 1980s.¹⁴

In Asia, thyroid FNA was introduced in China and Japan in the 1950s.^{9,10} In Korea, India, and Taiwan, thyroid FNA was introduced in the 1970s.^{5-7,11} Table 1 summarizes the brief history of thyroid FNA in seven Asian countries.⁵⁻¹¹

PERFORMERS AND INTERPRETERS OF THYROID FINE-NEEDLE ASPIRATION CYTOLOGY

Since thyroid FNA was initially introduced by clinicians in most countries, interpretation of FNA cytology were mostly done by clinicians in the past, including endocrinologists, surgeons, and radiologists. In recent years, thyroid FNA has been performed under ultrasound guidance by clinicians in Japan, Korea, the Philippines, Taiwan, and Thailand. Chinese clinicians prefer an intraoperative frozen section rather than FNA for the diagnosis of thyroid nodules.⁹ Thyroid FNA is more frequently performed through palpation rather than ultrasound in India, Thailand, and the Philippines because of limited or delayed access to sonography.^{5,8,11} Table 2 summarizes the current practices of thyroid FNA performers and interpreters in seven Asian countries.⁵⁻¹¹

STAINING METHODS OF THYROID FINE-NEEDLE ASPIRATION CYTOLOGY SAMPLES

The most widely used staining method for thyroid FNA specimens was Papanicolaou stain. Hematoxylin and eosin stain was favored by most Chinese pathologists.⁹ In India and Thailand, thyroid FNA samples were stained with a combination of two classical stains: alcohol-fixed smears were stained with Papani-

Table 2. Thyroid FNA performer and interpreter

Country	Sampling	Interpretation
China	Primarily performed in endocrinology department in 1970–80s. After 1987, thyroid FNA began to be popular in the pathology department. Thyroid FNA is not yet well accepted in China. Most general hospital use frozen section as a diagnostic method instead of thyroid FNA.	Primarily performed in endocrinology department in 1970–80s. After 1987, thyroid FNA began to be interpreted mainly by pathologists.
India	Blind, palpation-guided FNAs performed by cytopathologists US-guided FNA performed by clinicians or radiologists Palpation-guided FNA appears to be the most commonly used technique.	Interpretation done by pathologists Rapid on-site evaluation done in few academic institutions
Japan	US-guided FNA usually performed by clinicians	Pathologists and clinicians with a board certification in cytopathology
Korea	US-guided FNA usually performed by clinicians	Pathologists (cytopathologists) only interpret the thyroid FNA.
Philippines	Thyroid FNA procedure under US-guidance is performed by pathologists and clinicians.	Majority of pathologists report the diagnosis of cytology. All interpretations are rendered by the pathologist.
Taiwan	Radiologists are the major performer of thyroid FNA. US is used in most cases.	Pathologists are the main diagnostician. Before 1995, clinicians used to be both the performer and the interpreter of thyroid FNA.
Thailand	FNA procedure is universally performed by clinicians. In academic environment, trainees are frequently responsible to perform FNA.	Almost all cases of thyroid FNA cytology are signed out by certified pathologists. Cytotechnologists are not involved in thyroid FNA. Few endocrinologists sign out thyroid FNA in academic centers. Rapid on-site evaluation is rarely performed.

FNA, fine-needle aspiration; US, ultrasound.

colaou stain and air-dried smears were stained with modified Giemsa stain (e.g., May-Grünwald-Giemsa stain or Diff-Quik stain).^{5,8} Table 3 summarizes the staining methods for thyroid FNA cytology specimens.⁵⁻¹¹

REPORTING SYSTEM OF THYROID FINE-NEEDLE ASPIRATION CYTOLOGY

The reporting system of thyroid FNA cytology has improved significantly over the past 10 years with the introduction of TBSRTC.^{1,3} TBSRTC consists of six diagnostic categories in order to facilitate communication among cytopathologists and their clinical colleagues and to provide the risk of malignancy for each diagnostic category.³ After the introduction of TBSRTC, the system has been most widely accepted in China, India, Korea,

Table 3. Staining methods for thyroid fine-needle aspiration cytology specimens

Country	Staining method
China	Wrights staining is popular in endocrine and clinical laboratory department. H&E stain is common in pathology department.
India	Combination of Romanowsky (May-Grünwald-Giemsa stain) and Papanicolaou stains is most widely used. H&E stain in few institutions
Japan	Papanicolaou stain is the most widely used. Giemsa stain or Diff-Quik stain
Korea	Papanicolaou stain is the most widely used. H&E or Giemsa stain are used in some institutions.
Philippines	Papanicolaou stain Diff-Quik stain H&E stain in cell blocks
Taiwan	Papanicolaou stain Liu stain
Thailand	Combination of Papanicolaou and Diff-Quik stains are most widely used.

H&E, hematoxylin and eosin.

Table 4. Reporting system of thyroid FNA cytology

Country	Before TBSRTC	After TBSRTC
China	No data	TBSRTC is the most widely accepted.
India	No data	TBSRTC is the most widely used.
Japan	General Rules for the Description of Thyroid Cancer (GRDTC): adapted from the 1996 Papanicolaou Society recommendations; published by the Japanese Society of Thyroid Surgery in 2005 and updated in 2006	GRDTC system is widely used. Japanese system for thyroid FNA cytology published by the Japan Thyroid Association (JTA) in 2013: used in several high-volume thyroid surgery centers TBSRTC is rarely used.
Korea	Not standardized and varied, but mostly followed guidelines of the Papanicolaou Society of Cytopathology	TBSRTC is the most widely accepted.
Philippines	Based on histopathologic terminology of thyroid disorder	TBSRTC is the most widely used.
Taiwan	All investigators used different diagnostic categories.	TBSRTC or the 6-tier system corresponding to each Bethesda category
Thailand	Not standardized and varied, e.g., thyroid FNA reporting was based on specific diagnosis of the lesions.	TBSRTC is the most widely accepted.

FNA, fine-needle aspiration; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology.

the Philippines, and Thailand.^{5,6,8,9} Other reporting systems for thyroid FNA cytology used in Asia were the General Rules for the Description of Thyroid Cancer by the Japanese Society of Thyroid Surgery, the Japanese System for Thyroid FNA Cytology by the Japan Thyroid Association, and the 6-tier System of Taiwan.^{7,10} Table 4 summarized the reporting system of thyroid FNA cytology before and after the introduction of TBSRTC.⁵⁻¹¹

NON-DIAGNOSTIC THYROID FINE-NEEDLE ASPIRATION

Although ultrasound-guided thyroid FNA has high sensitivity and specificity in distinguishing benign from malignant thyroid nodules, in 1%–40% of cases, thyroid FNA is insufficient for diagnosis and is categorized as non-diagnostic according to TBSRTC.¹⁶ The non-diagnostic FNA cytology by TBSRTC includes virtually acellular specimens (requiring the presence of at least six groups of well-visualized follicular cells with each group containing at least 10 well-preserved epithelial cells), cystic fluid only, and other specimens (obscuring blood, crushed artifacts, poor clotting artifacts, air drying artifacts, overly thick smears, etc.).³ In the Japanese system, thyroid FNA with “cystic fluid only” is classified as benign rather than non-diagnostic.^{10,17} In Taiwan, a paucicellular specimen with fewer than six groups of ten benign follicular cells is considered benign if it contains more than 50 follicular cells in total or consists of degenerative hemorrhagic cyst fluid and scant benign follicular cells.⁷

Table 5 summarizes the criteria and rate of non-diagnostic thyroid FNA.⁵⁻¹¹ A high rate of non-diagnostic aspirates was reported from several teaching hospitals in the Philippines and Thailand, which was linked to the training activity of unskilled residents and limited access to ultrasound guidance.^{8,11}

LIQUID-BASED CYTOLOGY AND ANCILLARY TESTS

In Korea, the use of liquid-based cytology in thyroid FNA was adopted in 2008 and became widely used since 2010.^{6,18} In Taiwan, liquid-based cytology in thyroid FNA was first introduced in 2014 and then became commonly used.⁷ However, liquid-based cytology has not been made widely available for thyroid FNA in other countries.^{5,8-11}

Core needle biopsy as an alternative to thyroid FNA has been

used mainly in Korea whereas in other countries, this biopsy is performed only in a few institutions.⁵⁻¹⁰

Immunocytochemistry generally has limited applications for the diagnosis of thyroid FNA in Asian countries. Although molecular testing has been useful for the diagnosis of indeterminate thyroid FNA, it is often not practical for most clinical laboratories and is generally not covered by health insurance in Asia.⁵⁻¹¹

Table 6 summarizes the ancillary tests in thyroid FNA cytology.⁵⁻¹¹

Table 5. Non-diagnostic thyroid FNA

Country	Criteria for non-diagnostic FNA	Incidence of non-diagnostic FNA
China	TBSRTC	3.6% at one institution
India	TBSRTC Different criteria in a study: 10 clusters are needed with each having more than 20 cells; in case of presence of tissue fragments, minimum number of fragments required is 8. Royal College of Pathologists guidelines in one study	7.4% (0.5%–25.7%) from 38 studies
Japan	General Rules for the Description of Thyroid Cancer system Japanese system	10% according to the Japanese system
Korea	TBSRTC	12.4% (0%–32.6%) from 12 institutions
Philippines	TBRSTC	1.3% and 23.1% from 2 studies
Taiwan	Variable but different from TBRSTC ^a	8% at one institution
Thailand	TBSRTC	12.7%–47.6% from three institutions

FNA, fine-needle aspiration; TBSRTC, the Bethesda System for Reporting Thyroid Cytopathology.

^aMost Taiwan pathologists consider that the specimen is negative, but not non-diagnostic when there are less than six groups but more than 50 follicular cells in total or a degenerative hemorrhagic cyst with scant benign follicular cells.

Table 6. Ancillary tests in thyroid FNA cytology

Country	Liquid-based cytology	Core needle biopsy	Immunocytochemistry	Molecular or other testing
China	Not commonly used	No data	No data	Amplification refractory mutation system for <i>BRAF</i> V600E is the most popular technique. Next generation sequencing is not well accepted.
India	Has been used in some institutions as addition to conventional smears	Limited applicability and acceptability	Limited applicability and acceptability	Limited applicability and acceptability
Japan	Used in some laboratories, but is not widely available	Rarely performed	No data	<i>BRAF</i> testing is uncommon practice and not covered by national health insurance system. Thyroglobulin and/or calcitonin in FNA needle washings is often used in thyroid or lymph node aspirates.
Korea	Became popular since 2010 Used in 68% institutions in 2016	Widely used	Not routinely used but can be applied in specific cases	<i>BRAF</i> testing is used. Thyroglobulin and/or calcitonin in FNA needle washings is often used in thyroid or lymph node aspirates.
Philippines	Not used	No data	Rarely performed	Not covered by health care insurance Referred to outsource/abroad facilities if patients agree to pay
Taiwan	Became popular since 2014	Rarely performed	In some institutions, immunocytochemical staining is used.	In some institutions, molecular testing is used.
Thailand	Rarely used	Very uncommon	Available, but rarely performed	Rarely used due to limited availability

FNA, fine-needle aspiration.

TRAINING PROGRAM

Asian pathologists receive a certification in pathology and cytopathology after completing residency training and passing board examinations, and usually practice both surgical pathology and cytopathology. Training programs for cytotechnicians have been well organized in Japan, Korea, and Taiwan. Certified cytotechnicians screen thyroid FNA cytology, but are not eligible to declare a final diagnosis without supervision by a pathologist. Table 7 summarizes the training programs for cytopathologists and cytotechnicians.⁵⁻¹¹

QUALITY CONTROL AND QUALITY ASSURANCE PRACTICES

Quality control in cytology includes all activities to improve the performance of the test from the time of specimen collection until the cytology report is completed. Quality assurance defined by the College of American Pathologists includes quality review activities and systematic monitoring of quality control results

Table 7. Training programs for cytopathologists and cytotechnicians

Country	Cytopathologist	Cytotechnician
China	No data	No data
India	No data	Indian Academy of Cytologists conducts exam for cytotechnicians and cytotechnologists. Few centers run cytotechnician and cytotechnologist training programs for certification. Only limited institutions have cytoscreeners.
Japan	Pathologists have dual boards of anatomical pathology and cytopathology. Clinicians also have board of cytopathology.	JSCC certification Candidate 1: medical technologist after 3-year course at a vocational school or 4-year course at a medical technology school, 1-year work experience requirements at the cytology laboratory of a teaching hospital Candidate 2: 4-year college graduate
Korea	Pathology residents must pass the exam in both fields of surgical pathology and cytopathology to get the pathology board. For board certificated pathologists, there is annual requirement for continuing cytology education activities.	Nationwide cytotechnician education program began under the auspices of the World Health Organization in 1981. After 2-year pathology or cytology laboratory practice as a technician, 1-year training program at a National Cancer Center and certification exam
Philippines	Formal cytopathology training programs are not offered. Conferences in cytopathology are embedded in the training program of anatomic pathology.	No training programs
Taiwan	At least 3 months of cytology screening and sign-out practice Pathology residents are required to attend a 2-week intensive course. Pathology residents should pass both exams of surgical pathology and cytopathology to get the pathology board. For board certificated pathologists, there is annual requirement for continuing cytology education activities.	One-year on-site training at a qualified training institution and a final exam There are 12 qualified institutions for cytotechnologist training in Taiwan.
Thailand	General cytopathology and thyroid cytology are the essential parts of the training program for anatomic pathology residents.	No data

JSCC, Japanese Society of Clinical Cytology.

to provide confidence that all quality control systems are functioning properly and quality requirements are fulfilled.¹⁹ Quality control materials in thyroid FNA should include the distribution of each diagnostic category, histologic outcomes of FNA diagnostic categories, rate of surgical follow-up, and risk of malignancy calculated using the total number of each diagnostic category with and without surgical follow-up.

Quality improvement programs in Asian countries are organized by local societies of cytology and/or pathology. Table 8 summarizes the quality assurance and quality control programs in thyroid FNA cytology.⁵⁻¹¹

CONCLUSION

The purpose of the recently established Working Group of Asian Thyroid FNA Cytology is to promote communication and share practices among pathologists, cytopathologists, and clinicians dealing with thyroid FNA in Asia. In this special issue, we presented for the first time a single volume collection of contemporary reviews on Asian practices of thyroid FNA. Despite

Table 8. Quality assurance and quality control programs in thyroid FNA cytology

Country	Internal program	Nationwide external program
China	No data	No data
India	No data	External Quality Assurance Programme of the Indian Academy of Cytologists Only straightforward diagnose are assessed for thyroid FNA quality control.
Japan	No data	No data
Korea	Accuracy assessment by cyto-histological correlations Annual reports on quality control of thyroid FNA have been published since 1996.	Cytology proficiency testing in the Korean Society for Cytopathology has been performed since 1996. National quality control program in the Korean Society of Pathologists began in 1999.
Philippines	Self-review Intradepartmental referral to another pathologist All thyroid surgeries with previous FNA done in the same hospital are reviewed.	In the process of developing an external quality assurance program in cytopathology
Taiwan	No data	Currently there is no authoritative quality assurance program for external evaluation.
Thailand	No data	External quality assurance program for Thai pathologists is set up and supported by the Thai Society of Cytology. No nationwide thyroid FNA cytologic-histological correlation program

FNA, fine-needle aspiration.

most countries adopting Western systems and guidelines and incorporated them into their national systems early, there remains local variation which should be considered when doing comparisons between Asian and Western countries, and among Asian countries. We hope that these reports from Asia will encourage further studies on thyroid FNA cytology to improve the diagnosis of thyroid nodules and subsequently provide optimal care for patients with thyroid nodules in Asia.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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