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

| Decades | China | India | Japan | Korea | Philippines | Taiwan | Thailand |
|---------|-------|-------|-------|-------|-------------|--------|----------|
| 1950s   | 1950s: Introduction of cytology | - | 1952: Introduction of thyroid FNA | - | - | - | - |
| 1960s   | - | - | 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 et al. | 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 Pege et al. | 1981: Cytology training program for pathologists and cytotechnicians 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. | - | - | - | - | - | - |
| 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. 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. In 1952, thyroid aspiration cytology using a fine needle (diameter of 0.4–0.8 mm) was introduced by Nils Söderström in Sweden. 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. After that time, thyroid FNA was reintroduced in the United States and became widely available in the 1980s.

In Asia, thyroid FNA was introduced in China and Japan in the 1950s. In Korea, India, and Taiwan, thyroid FNA was introduced in the 1970s. Table 1 summarizes the brief history of thyroid FNA in seven Asian countries.

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. 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. Table 2 summarizes the current practices of thyroid FNA performers and interpreters in seven Asian countries.

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. In India and Thailand, thyroid FNA samples were stained with a combination of two classical stains: alcohol-fixed smears were stained with Papanicolaou stain and air-dried smears were stained with hematoxylin and eosin.

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. | Interpretation done 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. | 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.
The reporting system of thyroid FNA cytology has improved significantly over the past 10 years with the introduction of TBSRTC. 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. After the introduction of TBSRTC, the system has been most widely accepted in China, India, Korea, the Philippines, and Thailand. 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. Table 4 summarized the reporting system of thyroid FNA cytology before and after the introduction of TBSRTC.

**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. 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.). In the Japanese system, thyroid FNA with "cystic fluid only" is classified as benign rather than non-diagnostic. In Taiwan, a paucicellular specimen with fewer than six groups of 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.

Table 5 summarizes the criteria and rate of non-diagnostic thyroid FNA.

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**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 or Diff-Quik stain |
| Taiwan  | Papanicolaou stain or 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 |
| 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.
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 2010.6,19 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                          | 7.4% (0.5%–25.7%) from 38 studies |
| Japan   | General Rules for the Description of Thyroid Cancer 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* | 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.

*Most 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 BRAF 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 | BRAF 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 | Widely used | Not routinely used but can be applied in specific cases | BRAF 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 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 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 |
|         | 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. | 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   | No data        | 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.
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 | Cytopathology proficiency testing in the Korean Society for Cytopathology has been performed since 1996. |
|         | Annual reports on quality control of thyroid FNA      | National quality control program in the Korean Society of Pathologists began in 1999.           |
|         | have been published since 1996.                       |                                                                                               |
| 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 |
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