Cytopathology Reporting using the New Bethesda System of Thyroid FNAC and Correlation with Histopathological Follow-up: A Three-Year Study of Routine Service at Rajavithi Hospital

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Background: *The new Bethesda system for reporting thyroid cytopathology (TBSRTC) was a major step towards standardization, reproducibility and clarity of communication in thyroid fine needle aspiration cytology (FNAC). This system is used worldwide, including in Thailand, and the Department of Pathology at Rajavithi Hospital has been using this system for three years.*

Objective: *To evaluate the Bethesda system for reporting thyroid cytopathology at Rajavithi Hospital and assess the malignancy risk and diagnostic accuracy of thyroid FNAC.*

Material and Method: *The author retrospectively reanalyzed the thyroid FNAC reports for three years (January 2013 to December 2015). The reports were reclassified into each Bethesda system classes, and the malignancy risks for each category were calculated and compared with the follow-up histopathology reports. The statistical parameters of diagnostic accuracy for FNAC were also analyzed.*

Results: *A final total of 13,371 reports were included as follows: non-diagnostic/unsatisfactory (ND/UNS) 32.2%; benign 46.9%; atypical follicular lesion of undetermined significance (AFLUS) 4.8%; follicular neoplasm or suspicious for follicular neoplasm (FN/SFN) 7.8%; suspicious for malignancy (SM) 4.4%; and malignant 3.9%. The rates of malignancy reported on 358 cases with follow-up histopathology were ND/UNS, 22.1%; benign, 2.8%; AFLUS, 46.2%; FN/SFN, 37.3%; SM 74.3%; and malignant 90.0%. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FNAC were 74.7%, 90.3%, 81.5%, 86.2% and 84.6%, respectively.*

Conclusion: *The thyroid FNAC interpretation, using the Bethesda system in routine service allowed a more specific cytological diagnosis. The distribution of cases using the Bethesda categories differed from previous studies, but the malignancy rate of ND/UNS and AFLUS case were higher, the overall accuracy rate was similar with high yield. The universal Bethesda classification is a useful application for general practice in institutes without specialist pathologists and may decrease interlaboratory disagreements and variability.*

Keywords: *Thyroid FNAC, Bethesda system, Cytology, Fine-needle aspiration*

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Thyroid lesions are common, with an incidence rate of 4.0% to 7.0% palpable lesions in the general adult population[1]. Over the past three decades, fine needle aspiration cytology (FNAC) has become the first-line diagnostic test for evaluating thyroid nodules[2]. It is a simple, rapid and cost-effective test which can reduce the rate of unnecessary thyroid surgery for patients with benign nodules and help in choosing appropriate surgery for those with cancer. However, FNAC has limitations; in particular, it lacks a standardized system for cytological reports. Pathologists have thus been using different terminology and diagnostic criteria, thereby creating confusion among clinicians in the interpretation of the cytopathology reports and definitive clinical management.

The Bethesda system for reporting thyroid cytopathology (TBSRTC) was established to resolve this problem. A conference was held in 2007 by a multidisciplinary group of thyroid experts, including pathologists, endocrinologists, surgeons and radiologists, in Bethesda, Maryland, USA in order to provide uniform, standard and international terminology for reporting thyroid fine needle aspirations. There are six diagnostic categories of

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lesions: non-diagnostic/unsatisfactory (ND/UNS); benign; atypical follicular lesion of undetermined significance (AFLUS); follicular lesion/suspicious for follicular neoplasm (FN/SFN); suspicious for malignancy (SM); and malignant (Table 1)[3]. These six diagnostic categories of the Bethesda system have individual implied risks of malignancy that influence management paradigms (Table 2)[3]. Few studies have been published on the implementation of the TBSRTC in Thailand.

The author aimed to evaluate the diagnostic yield of the Bethesda system in reporting thyroid FNAC and correlate it with histopathological results in patients who had undergone thyroid surgery at Rajavithi Hospital.

Material and Method

The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 182/2559). The author conducted a

Table 1. The Bethesda System for Reporting Thyroid Cytopathology[3]

The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories[3]
I. Non-diagnostic or Unsatisfactory Cyst fluid only Virtually acellular specimen Other (obscuring blood, clotting artifact, etc)
II. Benign Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical Context Consistent with granulomatous (subacute) thyroiditis Other
III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm Specify if Hurthle cell (oncocytic) type
V. Suspicious for Malignancy Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other
VI. Malignant Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinomaUndifferentiated (anaplastic) carcinoma Squamous cell carcinomawith mixed features(specify) Metastatic carcinoma Non-Hodgkin lymphoma Other

Table 2. The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management[3]

Diagnostic Category	Risk of malignancy (%)	Usual management
1. Nondiagnostic or Unsatisfactory	0.1 to 0.4	Repeat FNA with ultrasound guidance
2. Benign	0 to 3	Clinical follow-up
3. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5 to 15	Repeat FNA
4. Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15 to 30	Surgical lobectomy
5. Suspicious for Malignancy	60 to 75	Near-total thyroidectomy or surgical lobectomy
6. Malignant	97 to 99	Near-total thyroidectomy

FNA= Fine Needle Aspiration

retrospective review of all patients who had thyroid FNAC at the Rajavithi Hospital between January 2013 and December 2015. The FNAC diagnoses were collected and reclassified based on TBSRTC categories of lesions as follows: non-diagnostic or unsatisfactory (ND/UNS); benign; atypia of undetermined significance or follicular lesion of undetermined significance (AFLUS); follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN); suspicious for malignancy (SM); and malignant[3]. In the cases of multiple FNAC, the higher TBSRTC class was selected for analysis.

Class I: Non-diagnostic or unsatisfactory (ND/UNS)

A smear was categorized as non-diagnostic or unsatisfactory if it did not fulfil the adequacy criteria of the Bethesda system[3], which includes follicular cells less than six well-preserved groups. Thyroid cysts containing histiocytes but with little or no follicular cells were also interpreted as non-diagnostic.

Class II: Benign

The slides were reclassified as benign if they had cytomorphological features of colloid goiter/ adenomatoid goiter, thyroiditis such as Hashimoto's thyroiditis, thyrotoxicosis, de Quervain's thyroiditis, or granulomatous thyroiditis.

Class III: Atypia of undetermined significance/ atypical follicular lesion of undetermined significance (AFLUS)

Based on the guidelines of the Bethesda system, aspirates which were considered adequate and had some features of atypia but could not be categorized definitely into either of the benign, SN/SFN, SM, or malignancy categories were grouped under this class[3].

Class IV: Follicular neoplasm/suspicious for follicular neoplasm (FN/SFN)

This term was applied to cases with cytomorphological features of moderate to high cellularity, scant or absent colloid, with predominantly microfollicular or trabecular configuration of follicular cells in repetitive patterns. Aspirates with cytomorphological features of Hurthle cell neoplasm were also included in this classification.

Class V: Suspicious for malignancy (SM)

These groups consisted of the aspirates that had cytological features suggestive of, but not definite, papillary carcinoma, medullary carcinoma, lymphoma and other malignancy.

Class VI: Malignant

Aspirates that appeared clearly malignant were placed in this category.

Follow-up histology

The follow-up histopathology examinations (HPE) of these patients were also identified using retrospective computer searches, and then comparing them with pre-operative cytopathology. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of the FNAC as well as the malignancy risk for each category were calculated. In the benign category (Class II), the author used the total number of initial FNA diagnoses to calculate the malignancy risk, with previous studies[8]. For calculating statistical parameters ND/UNS, AFLUS and FN/SFN cases were excluded as non-definitive diagnoses and categories. "SFM" and "malignant" cases were grouped together.

Statistical analysis

Statistical analysis was carried out using SPSS for Windows Evaluation Version 17.0. The specific incidence of age and sex was calculated, and the ages at diagnosis were compared using the two-tailed Student t-test. Chi-square test was used for categorical variables, such as gender, to evaluate statistical differences. The differences in lesional size were compared using the Mann-Whitney U test, and a p-value <0.05 was considered statistically significant.

Results

Between January 2013 and December 2015, 1,371 patients underwent FNA at Rajavithi Hospital (with 1,694 cytology reports), consisting of 1,203 (87.7%) females and 168 (12.3%) males. The female: male incidence ratio was 7:1. The patients' ages ranged from 12 years with diagnosis of non-diagnostic to 91 years with nodular goiter. The mean age for all the patients at diagnosis was 48 years. The peak incidences of all thyroid lesions were between 51 to 60 years in males and 41 to 50 years in females. Furthermore, the mean ages of the malignant group were 58 years in males and 48 years in females, while the size of the lesions ranged from 1 to 18 cm. There was no significant difference in size of lesions between the benign and malignant groups.

Among these 1,371 patients with 1,694 reports, there were 661 reports (39.0%) with diagnosis of ND/

Table 3. Distribution of TBSRTC diagnostic category

Diagnostic category	Number of FNAC (%)	
	Total FNAC (%)	Repeated FNAC (%)
1) Nondiagnostic or unsatisfactory	661 (39.0)	442 (32.2)
2) Benign	717 (42.3)	643 (46.9)
3) Atypical follicular lesion of undetermined significance	76 (4.5)	66 (4.8)
4) Follicular neoplasm/suspicious for follicular neoplasm	121 (7.1)	107 (7.8)
5) Suspicious for malignancy	64 (3.8)	60 (4.4)
6) Malignant	55 (3.3)	53 (3.9)
Total	1,694	1,371

UNS, 717 (42.3%) benign, 76 (4.5%) AFLUS, 121 (7.2%) FN/SFN, 64 (3.8%) SM and 55 (3.2%) malignant (Table 3).

There were 1,103 single-aspirated and 268 multiple-aspirated cases (591 FNAC reports). In the multiple-aspirated cases, the author collected the more severe cytology reports for analysis. The distribution of cases in the six-tier Bethesda categories following re-aspiration were ND/UNS, 442 cases (32.2%); benign, 643 cases (46.9%); AFLUS, 66 cases (4.8%); FN/SFN,107 cases (7.8%); SM, 60 cases (4.4%); and malignancy, 53 cases (3.9%) as show in Fig. 1.

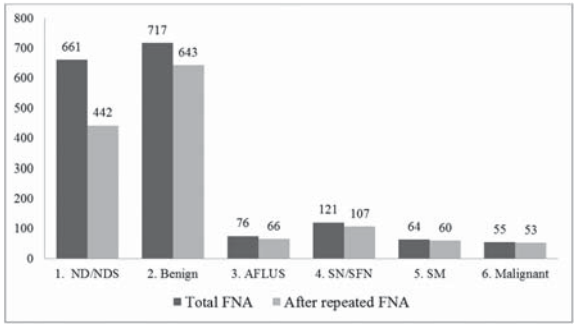

Fig. 1 Distribution of TBSRTC diagnostic category before and after re-aspiration. ND/UNS = non-diagnostic or unsatisfactory, AFLUS = atypia of undetermined significance or follicular lesion of undetermined significance, SN/SFN = follicular neoplasm or suspicious for a follicular neoplasm, SM = suspicious for malignancy.

Cyto-histologic correlation and malignancy risk

Out of 1,371 patients, 358 cases had undergone surgery, and all had histopathology reports. The original FNAC reports revealed 86 (24.0%) cases as ND/UNS, 130 (36.3%) cases as benign, 26 (7.3%) cases as AFLUS, 51 (14.2%) cases as FN/SFN, 35 (9.8%) cases as SM, and 30 (8.4%) cases as malignant. The author compared the TBSRTC FNA diagnoses of these cases with final histologic diagnoses and calculated the malignancy risk for each category. There were 121 total cases of malignant diagnosis on histopathology; as a result, the overall surgical malignancy risk was 33.8%.The rates of malignancy in each category according to TBSRTC were as follows: ND/UNS 22.1% (19/86); benign 2.8% (18/643); AFLUS 46.2% (12/26); SFN 37.3% (19/51); SM 74.3% (26/35); and malignancy 90.0% (27/30) (Table 4).

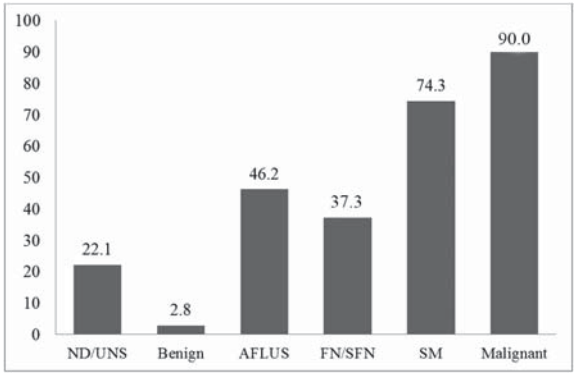

Fig. 2 Malignancy risk of each category according to TBSRTC.

Class I: Non-diagnostic or unsatisfactory (ND/UNS)

Out of the total FNA samples, 661 were ND/UNS. There were 151 repeat FNAC from these cases with 71 patients (47.0%) remaining ND/UNS. The distributions of other diagnoses on repeated FNAC were as follows: benign 69 (45.7%); AFLUS 5 (3.3%); SFN 1 (0.7%); SM 4 (2.6%); and malignancy 1 (0.7%).

Follow-up HPE of 86 cases revealed the following diagnoses: benign thyroid tissue 1; nodular goiter 52; chronic thyroiditis 1; follicular adenoma 13;

Table 4. Distributions of malignancy risk on follow-up surgical resection

Diagnostic category	FNAC cases	Malignant cases	Malignancy risk (%)
Non-diagnostic or unsatisfactory	86	19	22.1
Benign	643	18	2.8
Atypia of undetermined significance/follicular lesion of undetermined significance	26	12	46.2
Follicular neoplasm/suspicious for a follicular neoplasm	51	19	37.3
Suspicious for malignancy	35	26	74.3
Malignant	30	27	90.0
Overall	358	121	33.8

papillary thyroid carcinoma 9; follicular carcinoma 4; undifferentiated (anaplastic) carcinoma 3; well-differentiated tumor of uncertain malignant potential 2; and metastatic carcinoma or secondary carcinoma 1. Overall, 19 cases were diagnosed with malignancy, yielding a malignancy risk of 22.1%.

Class II: Benign

In the benign group (n = 717), the FNA procedures were repeated, and 643 cases were reclassified as benign according to class II criteria. Follow-up HPE reports were available for 130 cases, yielding the following diagnoses: nodular goiter, 76 cases; chronic thyroiditis: 3 cases; diffuse hyperplasia, 1 case; follicular adenoma, 31 cases; hurthle cell adenoma, 1 case; papillary thyroid carcinoma, 7 cases; follicular carcinoma, 6 cases; follicular variant of papillary carcinoma, 3 cases; poorly differentiated squamous cell carcinoma, 1 case; and malignant lymphoma, 1 case. There were 18 cases of malignancy in the histopathologic findings of the 643 benign FNA diagnoses; therefore, the overall malignancy risk was 2.8%.

Class III: Atypia of undetermined significance/ atypical follicular lesion of undetermined significance (AFLUS)

The present study categorized 76 FNA samples as AFLUS. Twenty of these cases were repeat FNA, and the following diagnoses were made: ND/UNS, 4 cases; benign, 8 cases; AFLUS, 3 cases; FN/SFN, 1 case; SFM, 2 cases; and malignant, 2 cases. From the total 66 cases (rearranged after repeat FNAC), 26 were followed by surgical resection, with the following diagnoses: nodular goiter, 10 cases; follicular adenoma, 4 cases; papillary thyroid carcinoma,8 cases; follicular carcinoma, 1 case; well differentiated thyroid carcinoma, 1 case; malignant lymphoma, 1 case; and metastatic carcinoma, 1 case. In conclusion, there were 12 malignant cases in all, yielding a 46.2% malignancy risk.

Class IV: Follicular neoplasm/suspicious for follicular neoplasm (FN/SFN)

One hundred and twenty-one FNA sample were classified as SFN, including Hurthle cell type, and 51 had follow-up histology. The following diagnoses were made: nodular goiter, 14 cases; chronic thyroiditis, 1 case; benign-parathyroid adenoma, 1 case; follicular adenoma, 11 cases; hurthle cell adenoma, 5 cases; papillary thyroid carcinoma, 6 cases; follicular variant of papillary thyroid carcinoma,1 case; tall cell variant of papillary thyroid carcinoma, 1 case; oncocytic variant of papillary thyroid carcinoma, 1 case; follicular carcinoma, 9 cases; and well differentiated thyroid carcinoma, 1 case. Based on 19 cases of malignancy, the malignancy risk was 37.3%.

Class V: Suspicious for malignancy (SM)

Of the 60 SM cases, thyroidectomy was performed on 35, of which 26 (74.3%) were malignant, with the following diagnoses: papillary thyroid carcinoma, 18 cases; undifferentiated (anaplastic) carcinoma, 1 case; follicular carcinoma, 3 cases; follicular variant of papillary thyroid carcinoma, 3 cases; and tall cell variant of papillary thyroid carcinoma, 1 case. The non-malignant cases in this category consisted of 8 cases of nodular goiter and 1 of follicular adenoma.

Class VI: Malignant

In this last category, 55 thyroid FNA samples were diagnosed as malignant. Cytologic interpretations were as follows: papillary thyroid carcinoma, conventional type, 36 cases; poorly differentiated carcinoma, 3 cases; anaplastic carcinoma, 5 cases;

papillary carcinoma, follicular variant, 1 case; papillary carcinoma, tall cell variant, 1 case; and other, 9 cases.

Thirty cases had follow-up HPE, and 27 (90.0%) were confirmed as malignant. The diagnoses of malignancy on resection were as follows: papillary thyroid carcinoma, 21 cases; undifferentiated (anaplastic) carcinoma, 3 cases; follicular variant of papillary carcinoma, 1 case; tall cell variant of papillary thyroid carcinoma, 1 case; and poorly differentiated squamous cell carcinoma, 1 case. The 3 non-malignant resection cases consisted of 2 cases of nodular goiter and one of follicular adenoma.

The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of the FNAC

Out of 358 follow-up histopathology cases, the benign: malignancy ratio was about 2: 1 (237/121). Most of the benign cases were nodular goiter 162 (68.5%) while the remaining benign thyroid lesions consisted of follicular adenoma, 61 (25.7%) cases; hurthle cell adenoma, 6 cases (2.5%);chronic thyroiditis, 5 (2.1%) cases; diffuse hyperplasia, 1 (0.4%) case; and benign thyroid tissue, 1 (0.4%) case. There was also 1 case of parathyroid adenoma (0.4%).

Among the malignant lesions, papillary thyroid carcinoma was the most common, including: conventional papillary carcinoma, 68 cases; follicular variant, 8 cases; tall cell variant, 3 cases; and oncocytic variant of papillary thyroid carcinoma, 2 cases. The second most common was follicular carcinoma, 23 (19.3%), followed by undifferentiated (anaplastic) carcinoma, 7 (5.8%). The other malignant lesions found were as follows: well-differentiated thyroid carcinoma, 2 (1.7%) cases; well-differentiated tumor of uncertain malignant potential, 2 (1.7%) cases; poorly differentiated squamous cell carcinoma, 2 (1.7%) cases; malignant lymphoma, 2 (1.7%) cases; and metastatic carcinoma or secondary carcinoma, 2 (1.7%) cases (Table 5).

From all these cytopathology and histopathology results, the author calculated the accuracy of FNAC. The results of various statistical parameters yielded a sensitivity (95% CI) of 74.7% (70.44% to 89.11%), specificity (95% CI) of 90.3% (79.17% to 91.05%), positive predictive value of 81.5%, negative predictive value of 86.2%, and diagnostic accuracy of 84.6%.

Discussion

The present study examined the data of patients with thyroid nodule who underwent FNAC and histological examination at Rajavithi Hospital. The general information about sex and age were similar to results reported by two other Thai-based population studies[6,7]. These findings reported the experience of Rajavithi Hospital in using the newly proposed Bethesda system for reporting thyroid cytopathology as a routine service. The distribution of cases differed from previous studies in some categories (Table 4), but although the malignancy rates of ND/UNS and AFLUS cases were higher than in previous studies, the overall

Table 5. Diagnoses and Distribution of Malignancies on Surgical Resection

Diagnosis on resection	n (%)
Benign lesion	237 (66.2)
Malignant lesion.	121 (33.8)
Papillary carcinoma, conventional	68
Follicular carcinoma	23
Follicular variant of papillary carcinoma	8
Undifferentiated (anaplastic) carcinoma	7
Tall cell variant of papillary carcinoma	3
Oncocytic variant of papillary carcinoma	2
Well-differentiated thyroid carcinoma, NOS	2
Well-differentiated tumor of uncertain malignant potential	2
Squamous cell carcinoma	2
Malignant lymphoma	2
Metastatic carcinoma	2
Total	358

Values are presented as n (%)

accuracy rate was similar with high diagnostic yield.

While it has been documented that FNAC has become the first-line diagnostic test for evaluating thyroid nodules[2] because it is a simple, rapid, and cost-effective test with high sensitivity and specificity, it also has its limitations, especially with regard to its lack of a standardized system of reporting. Pathologists have been using different terminology and diagnostic criteria, thus creating confusion among clinicians and even groups of pathologists.

The distributions of each TBSRTC classification and some the malignancy risks found in this study were similar to those of previous reports using the Bethesda or comparable systems in the last 10 years (Table 6, 7). Yassa et al[8] reported a 10-year study of thyroid cytopathology with ultrasound-guided FNAC and correlated them with follow-up histologic findings. After categorizing FNAC according to TBSRTC, they found the proportion and malignancy risks in each group were as follows: ND/UNS, 7.0% (malignancy risk 10.0%); benign, 66.0% (malignancy risk 0.3%); AFLUS, 4.0% (malignancy risk 24.0%); FN/SFN, 9.0% (malignancy risk 28.0%); SM 9.0% (malignancy risk. 60.0%); and malignant 5.0% (malignancy risk 97.0%). The cytologic diagnoses 'positive for malignancy' and 'no malignant cells' had 97.0% positive predictive value and 99.7% negative predictive value. Details of distributions and malignancy risks found in other international studies are shown in Table 6, 7.

In Thailand, a study[12] at King Chulalongkorn Memorial Hospital revealed the distribution of the six diagnostic categories as 47.3%, 42.1%, 2.5%, 2.8%, 2.1% and 3.2%, respectively. Rates of malignancy for 433 operated thyroid nodules were 17%, 14%, 39%, 22%, 84% and 93% for categories 1 to 6, respectively.

Additionally, the results of various statistical parameters, including sensitivity, specificity, positive predictive value, negative predictive value were comparable to the previous studies conducted in the past 15 years, including some studies of Thai populations (Table 8).

The number of cases in the diagnostic category of ND/UNS in this study was particularly high compared to previous published studies, but similar to the report from the study of King Chulalongkorn Memorial Hospital[12]. Both King Chulalongkorn Memorial Hospital and Rajavithi Hospital are academic centers, providing residency training with variations of FNA skills, although the curriculum for teaching these procedural skills may be different and even vary widely among the departments (internal medicine, Head and neck surgery, Otorhinolaryngology, etc).

Within this diagnostic category, 22.4% of cases had malignant diagnoses in the follow-up histology. Most of them were papillary carcinoma that initially presented with 'cystic fluid only' in 7 out of 9 cases. Because the term cystic fluid is only included in

Table 6. Distributions of each TBSRTC category among previous studiesin percentage

Diagnostic Category	Present Study	Yassa[8]	Yang[9]	Nayar[10]	JoVY[11]	Phanop[12]
ND/UNS	32.2	7.0	10.4	5.0	18.6	47.3
Benign	46.9	66.0	64.6	64.0	59.0	42.1
AFLUS	4.8	4.0	3.2	18.0	3.4	2.5
FN/SFN	7.8	9.0	11.6	6.0	9.7	2.8
SM	4.4	9.0	2.6	2.0	2.3	2.1
Malignant	3.9	5.0	7.6	5.0	7.0	3.2

Table 7. Comparisons of Malignancy risk among previous studiesin percentage

Diagnostic Category	Present Study	Yassa[8]	Yang[9]	Nayar[10]	JoVY[11]	Phanop[12]
ND/UNS	22.1	10.0	10.7	9.0	8.9	17.0
Benign	2.8	0.3	0.7	2.0	1.1	14.0
AFLUS	44.0	24.0	19.2	6.0	17.0	39.0
FN/SFN	35.2	28.0	32.2	14.0	25.4	22.0
SM	74.3	60.0	64.8	53.0	70.0	84.0
Malignant	90.0	97.0	98.4	97.0	98.1	93.0

Table 8. Comparisons of diagnostic accuracy of thyroid FNAC among previous studies over the last 15 years [6,7,16-20]

Reports	n	Malignant	Sensitivity	Specificity	PPV	NPV
Gharib and Goellner,1993	3144	32	83.0	92.0	83.0	92.0
Chang et al, 1997	662	25	65.0	98.0	92.0	95.0
Ogawa et al, 2001	226	67	76.0	73.0	85.0	60.0
Sclabas et al,2003	240	43	71.0	98.0	96.0	82.0
Morgan et al, 2003	253	13	55.0	94.0	70.0	67.0
Cheung e YS et al, 2007	179	8	54.0	100.0	100.0	75.0
Himakhun et al, 2009	469	22	82.0	100.0	100.0	90.0
Kantasueb et al, 2010	848	226	74.7	93.2	79.5	91.3
Present study	357	119	74.7	90.3	81.5	86.2

PPV = Positive predictive value, NPV = Negative predictive value

ND/UNS, cystic papillary carcinoma was the major pitfall of this category. These findings showed the significance and clinical value of the term 'cystic fluid only' in large thyroid nodules. In this contingency, follow-up with the sonographic correlation should be considered. A repeat aspiration with ultrasound guidance is recommended for ND/UNS and clinically or sonographically worrisome cystic fluid only cases[3]. In this study, there were 268 cases with follow-up FNAC. The maximum follow-up was six repeated FNAC per patient. Some of the cases in this category underwent ultrasound-guide FNAC.

Atypical follicular lesion of undetermined significance (AFLUS) is the most controversial category in this scheme. This present study revealed high malignancy rates compared to TBSRTC guidelines and previous published studies. The National Cancer Institute (USA) conference suggested that this category could represent a heterogeneous set of cases which limit its use to approximately 7.0% and its overall risk of malignancy of 5.0% to 15.0%[3]. However, this rate of malignancy is uncertain because only a minority of cases in this category have surgical follow-up. As more laboratories have adopted TBSRTC, some studies have shared their experiences with variable usage and higher malignancy rates than TBSRTC guidelines. Variable malignancy rates, ranging from 6% to 48.0% (average 32.7%) in AFLUS cases of retrospective studies have been reported in the review literature[13]. The average was similar (35.3%) in some prospective studies[13]. In this present study, AFLUS was diagnosed in 66 cases or 4.8% with a malignancy rate of 44.0% (11 out of 25) in cases with histologic follow-up.

Papillary carcinoma was the most common malignancy in this category. The author found that most of these cases had cytologic atypia of nuclear feature, suggestive of papillary carcinoma. The two most common findings consisted of irregular nuclear membrane (nuclear groove) and fine chromatin (Fig. 3, 4), which were evidence of malignant diagnosis. The limitations for definite diagnosis of these cases included poor smear quality and low cellularity specimens. These findings have been reported[14]. The higher rate of malignancy in the present study was possibly due to the small number of cases; however, these results implied that practical pathologists tend to use the term of under-diagnosis in FNA specimens.

According to TBSRTC, the recommended management for thyroid nodules with an initial AFLUS diagnosis is repeat FNA or observation but also depends on clinical correlation[3]. However, there are some guidelines from the American Association of Clinical Endocrinologists/Association Medici Endocrinologi/European Thyroid Association Task Force which favor surgery over observation and repeat FNA[15].

In the present study, there were 62 cases with initial diagnosis of AFLUS in the first FNAC, including 20 repeat FNAC cases and 42 single FNAC cases. Twenty-seven cases underwent surgery, with a malignancy rate of 50.0% (4/8) in cases with repeated FNAC versus 47.0% (9/19) in cases of direct surgery without repeat FNAC. These findings showed that repeat FNAC seems to be the proper management rather than direct surgery without it. However, this data reflects the treatment decisions of the clinicians at Rajavithi Hospital, who prefer direct surgery to repeat FNAC. It should be noted that, this interesting study had limitations due to the small sample sizes; therefore, a prospective study will be performed in the future with

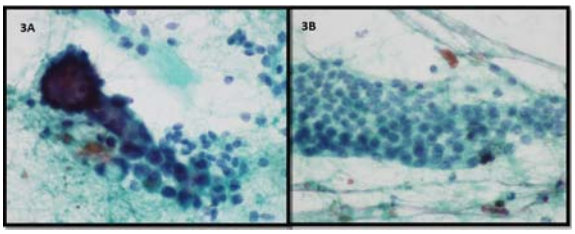

Fig. 3 3A and 3B Cytologic feature of AFLUS composed of irregular nuclear membrane (nuclear groove) and fine chromatin. The limitation for definite diagnosis of this case is poor smear quality.

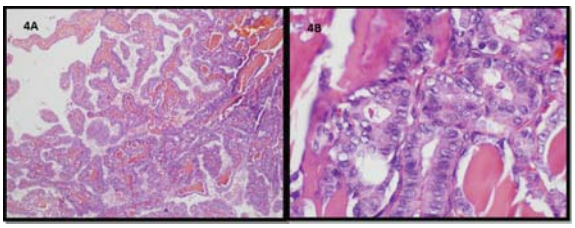

Fig. 4 4A and 4B) Follow-up histological examination reveals typical feature of papillary thyroid carcinoma, showing papillary fronds with central fibrovascular core, lined by atypical follicular cells with irregular nuclear membrane, nuclear groove, fine chromatin and occasionally intranuclear inclusion.

more collected AFLUS cases as well as clinical and radiographic correlation for analysis of AFLUS category. Ancillary research, such as cytogenetic and immunohistochemistry panels, has been proposed for AFLUS and SFM which include papillary carcinoma (BRAF mutation), medullary carcinoma (calcitonin, thyroglobulin, CEA, and chromogranin), anaplastic carcinoma (pan-cytokeratin), and metastatic carcinoma (TTF-1). These are to be done on cell block from FNAC[20,21]. However, the protocols should be carefully validated and cost-effectiveness should be considered. The accuracy rate of FNAC, including sensitivity, specificity, positive predictive value and negative predictive value of this study were 74.7%, 90.3%, 81.5% and 86.2%, respectively. The overall accuracy rate was similar to those of previous studies with high diagnostic yield. However, these statistical parameters vary in previous studies, depending on methods of statistical analysis (Table 8)[6-8,16-19].

The data of this study were retrieved from computer data bases of previous FNAC reports, which were diagnosed by general pathologists in routine service at Rajavithi Hospital. Most of these reports used terms of diagnosis based on TBSRTC classification. The author reviewed and/or used a well-matched category for re-classifying in some reports which were signed out with different terminology. As most cytopathologists are aware, there can be wide variation in diagnostic thresholds, especially in retrospective observational review by one pathologist. Furthermore, the limitation of FNA skills in the institute may also produce misdiagnosis. Therefore, prospective studies using this TBSRTC by groups of pathologist should provide further information.

This study reflects the usefulness of TBSRTC in this institute without specialist pathologists; furthermore, these statistical parameters of FNA diagnostic accuracy can be a point of reference for laboratory quality assessment.

Conclusion

This study showed the utility of TBSRTC system at Rajavithi Hospital in routine service. Even though its incidence of UD/UNS and AFLUS had a much higher proportion of distribution and malignancy rates compared to TBSRTC guidelines and some other published studies, the overall accuracy rate shows a high yield of diagnosis. This universal classification of the new standardized nomenclature is a useful application for general practice especially in institutes without specialized pathologists. This system simplifies interlaboratory agreements and facilitates implementation of institutional strategies for better management of patients.

What is already known on this topic?

The Bethesda System for reporting thyroid cytopathology (TBSRTC) was established to resolve the limitation, especially lack of a standardized system of cytology reports in Thyroid FNAC. This system has been used worldwide because it consists of six diagnostic uniform categories which have provided more reproducible results from different institutes. Each diagnostic categories of the Bethesda system has individual implied risks of malignancy that influence management paradigms. There were similar results for risk of malignancy reported by other applying this proposed Bethesda or comparable system. Few studies have been published on the implementation of the TBSRTC in Thailand.

What this study adds?

The present study shows data, reflecting the experience of Rajavithi hospital, using the newly

proposed Bethesda system for reporting thyroid cytopathology in routine service in this institute. Even though some categories (UD/UNS and AFLUS) are particularly higher proportion of distribution and malignancy rate compare to TBSRTC guideline and some published studies. But the overall accuracy rate shows a high yield of diagnosing similar to other pathology scoring system. This universal classification of the new standardized nomenclature is a useful application for general pathologist even in the institute without specialist pathologist.

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Potential conflicts of interest

None.

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