Original Article

The sensitivity and specificity of fine needle aspiration cytology in detecting thyroid malignancy according to Bethesda system at a teaching hospital in Saudi Arabia

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Abstract

Background: The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) aims to standardize the terminology and morphologic criteria associated with thyroid fine-needle aspiration cytology (FNAC) results while also providing corresponding risk assessments for malignancy. contributing to more consistent and standardized reporting of thyroid nodules and aiding clinicians in making informed decisions. Since then, it has been undergoing revisions and updates to further improve its utility and accuracy. **Materials and Methods:** This is a retrospective study conducted at a tertiary care center. All patients with a history of thyroid gland swelling who had previously undergone FNA were included. The procedure included cytopathologists performing FNAC for all cases of midline neck swelling. Demographic and histopathology data were correlated with the cytological diagnosis. **Results:** We included 288 cases. Of those, 234 (81.3%) were female and 54 (18.8%) were male. The presentation age range was 18–91 years. The most reported category was benign, which constituted 30.9% of the cases followed by malignancy (27.1%). As for thyroid lesions, papillary carcinoma was the most prevalent (43.6%). The correlation on cyto-histopathology was presented in every diagnostic category, showing high heterogeneity in diagnostic specificity and sensitivity. The overall diagnostic specificity and sensitivity were 56.05% (95% confidence interval [CI]: 47.92–63.95%) and 80.92% (95% CI: 73.13–87.25%), respectively. Positive and negative predictive values were 60.57% and 77.88%, respectively. **Conclusion:** Our data suggests that the TBSRTC system promotes similar sensitivity and specificity to those reported elsewhere. It standardizes reporting and improves communication between cytopathologists and clinicians.

Keywords: Bethesda system, cytology, histopathology, pathology, thyroid

Introduction

The term thyroid nodule has been defined by the American Thyroid Association (ATA) as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma."[1] With an estimated annual incidence rate of 0.1% in the United States, it is a common pathological condition that can be divided into benign and malignant types, affecting 3–7% of the population and suggesting that 300,000 new nodules are found each year.[2] The majority of these nodules are benign, but 5–15% of the general population can eventually develop cancer, depending on their age, sex, history of radiation exposure, family history, and other demographic and clinical factors.[3] Since the majority of patients with thyroid nodules are asymptomatic, some

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might develop compressive symptoms that include neck fullness, dysphagia, odynophagia, choking, and dyspnea.[4] Such symptoms were demonstrated to present in benign as well as malignant thyroid nodules.[5] Despite several investigations conducted to assess any potential relationship between compressive symptoms and thyroid lobe volume, the exact relationship remains to be fully elucidated.[6,7] Moreover, clinical and thyroid ultrasound (US) risk indicators for malignant illness are regularly assessed to decide whether further thyroid fine-needle aspiration (FNA) is necessary.[8] Because of its cost-effectiveness and minimal invasiveness, US-guided thyroid FNA with cytological evaluation is considered standard management.[9] However, there are limitations to fully relying on US-FNA cytology, including the nature of the results category (inadequate, indeterminate, or suspicious aspirates).[9] Additionally, several studies reported false-negative cytological results among patients.[10] As a result, doctors must interpret FNA results to determine whether or not more invasive testing is required. The problems are amplified toward the population of lower socioeconomic status, where they cannot afford higher investigations in private laboratories.[11] Furthermore, studies have been conducted on the efficacy of FNA in identifying thyroid malignancy, which has resulted in the creation of uniform guidelines and algorithms for clinical use.[12] To guarantee the best possible patient care, it is necessary to evaluate how well these guidelines apply and are dependable in various healthcare settings.[12] The literature currently in publication still has a clear gap about its effectiveness, particularly when it comes to Saudi Arabian healthcare. Saudi Arabia offers a distinct clinical landscape that may affect the diagnostic accuracy of FNA for thyroid malignancy detection due to its unique demographic and environmental features.[13] Despite the clinical significance of FNA accuracy, there is a paucity of research investigating its performance in detecting thyroid malignancies in Saudi Arabia. Therefore, this study will correlate the cytological diagnosis of thyroid lesions according to the Bethesda system and its histopathological results within a tertiary care hospital in Jeddah, Saudi Arabia. The aim of this study was to assess the efficacy of The Bethesda System for Reporting Thyroid Cytology (TBSRTC).

Materials and Methods

Ethical approval

The Unit of Biomedical Ethics Research Committee at the Faculty of Medicine, King Abdulaziz University, approved the study's aim, protocol, data collection sheet, and procedures under reference number 40–23. The study was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for retrospective studies.[14] Informed consent was waived due to the retrospective nature of this study. The study adhered to the Declaration of Helsinki. Patients' personal data were masked, and all information was kept private and anonymous.

Study design and setting

In this study, we conducted a retrospective chart review of our hospital electronic record on June 11, 2023. Cases admitted during the period of January 2023 to June 2023 were enrolled in our study. We included all patients who presented or were referred to King Abdulaziz University Hospital (KAUH), a tertiary care center in Jeddah, Saudi Arabia, that is publicly funded and operated to serve the entire community.

Study population and inclusion and exclusion criteria

All patients with a positive history of thyroid swelling who previously underwent FNA, regardless of the affected lobe of the gland, were included. All the patients with thyroid swelling who have been treated medically were excluded. No restrictions were applied to the patients' demographic characteristics. The following demographic variables were collected: Gender, age, and nationality. Clinical variables included the diagnosis category, which was subtyped into the following: nondiagnostic or unsatisfactory (ND – category 1), benign (category 2), atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS – category 3), follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN – category 4), follicular neoplasm, Hürthle cell type/suspicious for a follicular neoplasm, Hürthle cell type (FN/SFN – category 4), suspicious for malignancy (SFM – category 5), and malignant (category 6). These subtypes were constructed according to the consensus of the "National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Science Conference" in 2007 at Bethesda, Maryland, hosted by the NCI [Table 1]. Furthermore, our study included the details of the thyroid lesion based on histology, which included the following: colloid

Table 1: TBSRTC diagnostic categories

Classification	Diagnostic category
I. ND	Cystic fluid only
	Virtually acellular specimen
	Other (obscuring blood, collecting artifacts, 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. AUS/FLUS	
IV. FN/SFN	Specify if Hürthle 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 carcinoma
	Undifferentiated (anaplastic) carcinoma
	Squamous cell carcinoma
	Carcinoma with mixed features (specify)
	Metastatic carcinoma
	Non-Hodgkin's lymphoma
	Other

cyst/goiter, hyperplastic thyroid lesion, subacute granulomatous thyroiditis, lymphocytic (Hashimoto's) thyroiditis, follicular adenoma/carcinoma, Hürthle cell adenoma, papillary carcinoma, medullary carcinoma, and microscopic description of any relevant and important findings.

Study procedure

The procedure was as follows: Under consent, cytopathologists performed FNAC for all cases of midline neck swelling. FNAs were performed using a 22G needle, with or without an airtight syringe, using imaging guidance wherever necessary. Smears were fixed in 95% methanol while still wet and stained using the standard hematoxylin and eosin, Giemsa. and Papanicolaou stains. The TBSRTC was used to report the cytological diagnosis. When possible, the demographic characteristics and histopathology were correlated with the cytological diagnosis.

Data analysis

Microsoft Excel 2014 (Microsoft Corp., Redmond, WA, USA) served as the spreadsheet tool to conduct the data assembly and entry. Statistical analysis was made using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY) and SmartPLS 3 to test the relationship between the variables. The variables were classified as qualitative or quantitative. Qualitative variables were described in frequency tables with percentages, and quantitative data were described with a mean and standard deviation (SD). All data utilized graphical presentation in the form of line charts and illustrated graphs.

Results

Baseline clinical and TBSRTC data

We included 288 cases that fulfilled our enrollment criteria and extracted their data accordingly. The cases presented with various thyroid lesions. Of the cases, there were 234 (81.3%) female cases and 54 (18.8%) male cases, with a female-to-male ratio of 13:3. The age range was 18–91 years. The mean, median, and mode for patients' ages were 45.67, 44, and 22 and 38 years, respectively. The SD was 15.02. Furthermore, Saudi nationals constituted 88.2% of the cases. Regarding the diagnostic category, the most reported category was benign (category 2), which constituted 30.9% of the cases. This was followed by malignancy (category 5), which included 27.1% of the cases. Meanwhile, cases with AUD (category 3) included 12.2% of the whole sample. In respect to patients' demographic data, ND (category 1) cases were exclusively presented among females (n = 24). They presented a prevalence of 8.3% among the collected sample. The age group for ND (category 1) cases is 22–84 years. Meanwhile, benign (category 2) was present in 73 female patients in comparison to 16 male cases. Their age group was similar to the previous category (22–84 years). Malignancy (category 6) also had a higher female prevalence (n = 57) in comparison to male (n = 21). The age group for malignancy cases is 22–79 years. Detailed data on the other categories are presented in Table 2. Regarding the data on thyroid lesions, papillary carcinoma was the most prevalent lesion (43.6%). Papillary carcinoma was presented among cases aged 22–82 years. Their female-to-male prevalence was 89/30. A hyperplastic thyroid lesion was reported in 20.1% of the cases. Of those cases, 34 were female and 19 were male. The age group in which hyperplastic thyroid lesions occurred was 18–80 years. The third most prevalent lesion was follicular adenoma (14.2%). It was reported among 32 female patients in comparison to seven male patients. The age group for follicular adenoma was 18–91 years. Detailed data including colloid cyst/goiter, subacute granulomatous thyroiditis, lymphocytic (Hashimoto's) thyroiditis, follicular carcinoma, Hürthle cell adenoma, and medullary carcinoma are illustrated in Table 3. Moreover, of the 24 cases that were ND, histopathology revealed nine malignant cases. As for benign cases on cytopathology, there were 73 benign cases in histopathology in comparison to 16 malignant cases. There were 35 cases with AUS/FLUS diagnosis on cytopathology, of which, 21 and 14 were benign and malignant on histopathology, respectively. In terms of malignant cases, there were 78 cases diagnosed using cytopathology. On histopathology, 64 cases were confirmed to be malignant. Other detail data were numerically presented in Table 4 and illustrated in Figure 1.

Table 2: Frequency of thyroid lesion (based on FNAC according to TBSRTC)

Classification	Number of cases	Percentage	F/M	Age group (years)
I. ND	24	8.3	24/0	22–84
II. Benign	89	30.9	73/16	22–84
III. AUS/FLUS	35	12.2	29/6	24–91
IV. FN/SFN	25	8.7	23/2	18–70
V. FN/HCT	9	3.1	9/0	36–55
VI. SFM	28	9.7	19/9	23–80
VII. Malignant	78	27.1	57/21	22–79

Clinical sensitivity and specificity of the TBSRTC

Table 5 shows the statistical analysis for our data. As shown, the table provides various statistics and their corresponding 95% confidence intervals. Sensitivity (true positive rate): this metric indicates the proportion of true positive results among individuals who actually have the disease. In this case, the sensitivity is 80.92%, with a 95% confidence interval ranging from 73.13% to 87.25%. A higher sensitivity value suggests that the test is accurately identifying individuals with the disease. Specificity (true negative rate): specificity represents the proportion of true negative results among individuals who do not have the disease. In this context, the specificity is 56.05%, with a 95% confidence interval spanning from 47.92% to 63.95%. A higher specificity indicates that the test is effective at correctly identifying disease-free individuals. Positive predictive value (PPV): the PPV is the probability that a positive test result is correct, indicating the likelihood of having the condition given a positive result. Here, the PPV is 1.84%, with a 95% confidence interval from 55.83% to 65.13%. A low PPV suggests that a positive result may not necessarily mean the individual

Table 3: Thyroid lesion (based on histology)

Thyroid lesion	Number of cases	Percentage	F/M	Age group (years)
Colloid cyst	36	13.3	30/6	18–84
Colloid goiter	15	5.5	12/3	18–59
Hyperplastic thyroid lesion	55	20.1	34/19	18–80
Subacute granulomatous thyroiditis	1	0.4	1/0	46
Lymphocytic (Hashimoto's) thyroiditis	32	11.7	26/6	18–67
Follicular adenoma	39	14.2	32/7	18–91
Follicular carcinoma	22	8.1	16/6	24–82
Hürthle cell adenoma	16	5.9	15/1	29–67
Papillary carcinoma	119	43.6	89/30	22–82
Medullary carcinoma	5	1.8	4/0	39–53

Table 4: Cyto-histopathological correlation of thyroid lesion of our study

Cytopathology	Histopathological diagnosis		Total
	Benign	Malignant	
I. ND	15	9	24
II. Benign	73	16	89
III. AUS/FLUS	21	14	35
IV. FN/SFN	18	7	25
V. FN/HCT	5	4	9
VI. Suspicious for malignancy	11	17	28
VII. Malignant	14	64	78
Total	157	131	288

Table 5: Sensitivity and specificity assessment of our data

Statistic	Value	95% CI
Sensitivity	80.92%	73.13–87.25%
Specificity	56.05%	47.92–63.95%
Positive predictive value	1.84%	55.83–65.13%
Negative predictive value	0.34%	70.67–83.72%
Positive likelihood ratio	1.84%	1.51–2.24%
Negative likelihood ratio	0.34%	0.23–0.5%

has the disease. Negative predictive value (NPV): the NPV is the probability that a negative test result is correct, signifying the likelihood of not having the disease given a negative result. The NPV is 0.34%, with a 95% confidence interval spanning from 70.67% to 83.72%. A low NPV implies that a negative result may not conclusively rule out the presence of the disease. Positive likelihood ratio: this ratio represents how much more likely a positive test result is in individuals with the condition compared to those without the condition. Here, the positive likelihood ratio is 1.84, with a 95% confidence interval from 1.51 to 2.24. A higher positive likelihood ratio suggests that a positive result is more informative about the presence of the disease. Negative likelihood ratio: The negative likelihood ratio indicates how much less likely a negative test result is in individuals with the condition compared to those without the condition. In this case, the negative likelihood ratio is 0.34, with a 95% confidence interval ranging from 0.23 to 0.5. A lower negative likelihood ratio suggests that a negative result is more informative for ruling out the disease.

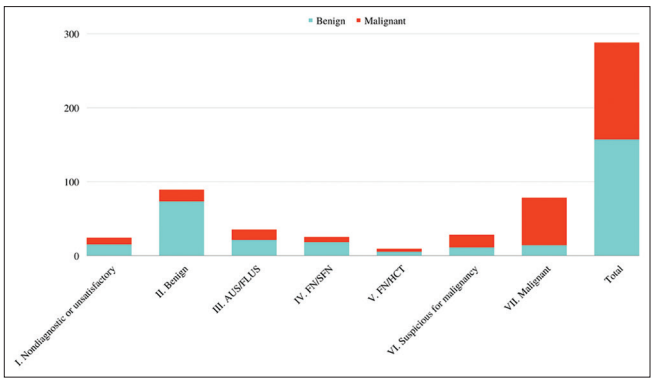

Figure 1: Prevalence of benign and malignant cases with respect to cyto-histopathological testing

Discussion

Study population and demographic data

To promote standardization in terminology and communication clarity, the NCI organized the "NCI Thyroid FNA State Science Conference." The Bethesda Thyroid Atlas Project was born out of the results reached after this meeting regarding terminology and morphologic criteria, which also served as the foundation for TBSRTC. Six diagnostic categories were suggested by TBSRTC.[15] In this study, we encompassed a diverse cohort of 288 patients who met the inclusion criteria to assess the TSBRTC. Thyroid lesions were observed in various presentations within this cohort. Notably, a substantial gender discrepancy was observed, with 234 (81.3%) female cases and 54 (18.8%) male cases, resulting in a female-to-male ratio of 13:3. Despite the higher female prevalence, this was similar to the findings of other studies including the study of Renuka *et al.*[16] which reported a female-to-male ratio of 9:1. The age range among patients with thyroid nodules was wide, spanning from 18 to 91 years, with a mean age of 45.67 years. The SD of 15.02 underscores the variance in age distribution. This demographic detail is reflective of the geographical context of our study, conducted in Saudi Arabia.

Diagnostic categories based on TBSRTC

In terms of diagnostic categories based on TBSRTC, the most frequently encountered nodules were benign, constituting

Table 6: Comparison of literature findings with respect to the findings of our study

Classification	Yassa *et al.* (2007)	Nayar and ivanovic (2009)	Jo *et al.* 2010	Mufti *et al.* (2012)	Renuka *et al.* (2012)	Mondal *et al.* (2013)	Sameep Garg *et al.* (2015)	Our study
I. ND	181 (7%)	260 (5%)	573 (18.6%)	29 (11.6%)	96 (17%)	12 (1.2%)	6 (6%)	24 (8.3%)
II. Benign	1707 (66%)	3324 (64%)	1817 (59%)	194 (77.6%)	398 (70.6%)	893 (87.5%)	78 (78%)	89 (30.9%)
III. AUS/FLUS	104 (4%)	935 (18%)	105 (3.4%)	2 (0.8%)	11 (1.95)	10 (1%)	4 (4%)	35 (12.2%)
IV. FN/SFN	233 (9%)	311 (6%)	299 (9.7%)	10 (4%)	N/A	36 (3.6%)	4 (4%)	25 (8.7%)
V. FN/HCT	N/A	N/A	N/A	N/A	24 (4.2%)	07 (0.7%)	1 (1%)	9 (3.1%)
VI. Suspicious for malignancy	233 (9%)	104 (2%)	71 (2.3%)	06 (2.4%)	15 (2.6%)	14 (1.4%)	14 (1.4%)	28 (9.7%)
VII. Malignant	129 (5%)	260 (5%)	215 (7%)	09 (3.6%)	20 (3.5%)	48 (4.7%)	4 (4%)	78 (27.1%)
Total	2587	5194	3080	250	564	1020	100	288

30.9% of the cases. In contrast, higher percentages were reported among literature studies including 83.03% of benign nodules.[17] A contributor to the increasing detection of benign nodules is the amplified use of advanced imaging techniques, such as US, which has led to the detection of smaller thyroid nodules that may have gone unnoticed in the past.[18,19] Furthermore, malignancies accounted for 27.1% of the cases, indicating the presence of a significant number of thyroid malignancies. This was higher than recent reports that included 3.94% of malignant nodules.[17] A percentage of 2.6% of malignant nodules was also reported in the literature.[20] Cases categorized as AUS/FLUS represented 12.2% of the overall sample. Further analysis of demographic data within specific diagnostic categories revealed intriguing patterns. Notably, ND cases were exclusively presented among female patients, with a prevalence rate of 8.3%. The age range for ND cases spanned from 22 to 84 years. Despite ND being exclusively reported by females, it is common to observe a higher female prevalence across all diagnostic categories.[21]

The pattern and prevalence of thyroid lesions

Moreover, our study also delved into the specific types of thyroid lesions encountered. Papillary carcinoma emerged as the most prevalent lesion, representing 43.6% of cases, with an age range spanning from 22 to 82 years. Within this category, there was a substantial female-to-male prevalence of 89:30, echoing previous gender disparities.[22] One of the critical aspects of our study was the correlation between cytological diagnoses and subsequent histopathological findings. Notably, among the 24 cases categorized as ND based on cytopathology, histopathological examination revealed that nine of these cases were indeed malignant.

Sensitivity and specificity of TBSRTC

This highlights the challenges of accurately diagnosing thyroid nodules, especially when they fall into the indeterminate category.[23] Nonetheless, we reported an 80.92% sensitivity of the TBSRTC, a percentage lower than other studies including a sensitivity of 88.89%.[11] However, the specificity of the system was severely disparate from that reported by Garg *et al.*[11] Another literature comparison is illustrated in Table 6.[24-30] Finally, our results emphasize the need for ongoing research and the development of refined diagnostic criteria and methodologies to improve the sensitivity and specificity of fine needle aspiration cytology in detecting thyroid malignancy. To address the study limitation, studies with larger sample sizes and detailed demographic data are required.

Conclusion

Our study provides comprehensive insights into the demographic distribution of thyroid nodules, the variability in cytological diagnoses, and the diversity of thyroid lesions encountered. The findings underscore the importance of integrating clinical, radiological, and cytological data to enhance diagnostic accuracy, especially in cases with high clinical suspicion of malignancy. TBSRTC showed a good correlation with previous studies when categorizing benign, suspicious malignancy, and malignant thyroid nodules. However, the study had a higher percentage of AUS, which indicates a need to reduce the reporting of this category. Additionally, the percentage of ND results in the study was lower compared to other studies. Overall, the study supports the effectiveness of TBSRTC in reducing interobserver variability, improving communication, and providing clear guidelines for surgical management of thyroid nodules. Also, despite appropriate sensitivity levels, the specificity level reported in this study is recommended to undergo improvement.

Limitations of the study

This study presented limitations to some extent, which were related to the availability of data in the and how efficient and accurate the reported cases were. However, overall, the findings were consistent with the general knowledge of the condition, along with minor atypical findings. The research was conducted at an early stage with a preliminary understanding of the condition, which is subjected to further investigations that could provide new and novel data.

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Conflicts of interest

There are no conflicts of interest.

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