Abstract

Context: Fine needle aspiration (FNA) plays a crucial role in the evaluation of patients with thyroid lesions. The Bethesda system for reporting thyroid cytopathology (TBSRTC) was designed with a mission to standardize the process of diagnosis and management of thyroid lesions by FNA cytology (FNAC). Aim: We aim to see the benefits of adopting TBSRTC, seek the cytological pitfalls in the diagnosis of thyroid FNAC, and identify the spectrum of thyroid lesions in our setup. Settings and Design: This is a hospital-based cross-sectional study conducted from June 2009 to June 2014 of all thyroid FNACs with available histopathology reports. Cases were designated a specific diagnostic category according to TBSRTC. Materials and Methods: A total of 109 cases were included in the study. Sixty-eight cases had been reported without using TBSRTC and were reviewed and reclassified according to TBSRTC seeking the common reasons for interpretative errors. Statistical Analysis Used: Data were analyzed using SPSS ver. 11.5. Results: In both pre- and post-TBSRTC era, benign neoplasms constituted the major bulk. After the use of TBSRTC, there was increased ability to look for follicular neoplasms, improvement in making definitive diagnosis of the cases, decline in the suspicious category, and an improvement in diagnostic accuracy, and we were in line with the implied risk outlined by TBSRTC in most of the cases except the nondiagnostic or unsatisfactory category. Conclusion: Application of TBSRTC results in uniformity in reporting among pathologists and better interdisciplinary communication and patient management.

Keywords: Bethesda, diagnostic categories, thyroid

INTRODUCTION

Fine needle aspiration (FNA) plays a crucial role in the evaluation of thyroid nodules. However, studies have shown that up to 30% of thyroid FNA were diagnosed previously as “atypical,” “indeterminate,” and “susicious for malignancy.” Thus in October 2007, the Bethesda system for reporting thyroid cytopathology (TBSRTC) was designed to establish uniformity in diagnosing thyroid FNA cases and guiding the clinical management. In this study, a comparison was attempted between reports given 2.5 years before and after implementation of TBSRC in our institution. This study aims to identify pitfalls in the diagnosis of thyroid FNA cytology (FNAC) and identify the spectrum of thyroid lesions.

MATERIALS AND METHODS

This is a hospital-based cross-sectional study of 109 cases conducted in a tertiary care center from June 2009 to June 2014. Ethical clearance was obtained from Institutional Review Committee. (Code No. IRC/477/015). All thyroid FNACs performed during the study period were included in the study. Cases in which histopathology report was not available were excluded from the study.

All these cases were designated a specific diagnostic category according to TBSRTC as follows:

I. Nondiagnostic or unsatisfactory (ND/UNS)
II. Benign
III. Atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS)

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IV. Follicular neoplasm/“suspicious” for follicular neoplasm
V. Suspicious for malignancy
VI. Malignant.

Of the total 109 cases studied, in 68 cases, FNAC reports had not been provided according to TBSRTC. The remaining of 41 cases had been reported using TBSRTC. All cases (68) were reviewed independently (by PU and SD) and reclassified according to TBSRTC. Cases with mismatch between histopathological and cytological correlation were also reviewed by two investigators (PU and SD) independently and were recategorized into TBSRTC. The common reasons for morphologic interpretative errors in cytology were sought and are presented in subsequent tables. Data were entered into Microsoft Excel 2007 and converted into SPSS ver. 11.5 for statistical analysis.

RESULTS AND DISCUSSION

The category names used in this study to categorize reports before TBSRTC were as follows: inadequate, descriptive reports, benign, suspicious for malignancy, and malignancy. The spectrums of thyroid lesions categorized with and without using TBSRC are shown in Figures 1 and 2, respectively.

Comparison between the two eras revealed that there was a total absence of vague descriptive reports from 7.3% to 0% in the post-Bethesda era [Table 1]. We also observed that there was an ability to look out for follicular neoplasm from 0% to 11.9% once we confined ourselves to the diagnostic tier of TBSRTC. There was an improvement in making a definite diagnosis of malignancy from 14% to 19% and therefore a corresponding decrease on suspicious diagnoses from 13% to 4%.

After having categorized the FNAC reports into two types, the next step was to compare these diagnostic categories with biopsy reports. In the pre-Bethesda era, 60% of the indeterminate cases turned out to be follicular neoplasm on histopathology. However, after the implementation of TBSRTC, 83.3% of these cases were suspected as follicular neoplasm on FNAC. The fraction of cases that actually turned out to be malignant out of the category labeled as “suspicious” increased in the post-Bethesda era to 80% from that of 33% of the pre-Bethesda era. Therefore, the category “suspicious for follicular neoplasm” acted as a safety zone or as an emergency collection basket which could save from misdiagnosis of thyroid neoplasm into other benign categories. And the exact diagnosis could be sorted out later during histopathology.

The next step was to calculate the strength of the 68 FNAC reports given without using TBSRTC in predicting malignancy on histopathology. Sensitivity was 62.5%, specificity was 100%, positive predictive value (PPV) was 100%, negative predictive value (NPV) was 89.7%, and accuracy was 91.7%.

Similarly, the strength of the FNAC reports given using TBSRTC category in predicting malignancy was also calculated. Sensitivity was 75%, specificity was 100%, PPV was 100%, NPV was 92%, and accuracy was 93.57%.

There were a total of 109 FNAC reports which were reported implementing TBSRTC. This includes all the previous 68 cases reported in the pre-TBSRTC method, because all cases were screened and appropriately fitted into the TBSRTC. There was

![Figure 1: Diagrammatic representation of cytological and histopathological correlation of pre-TBS](image1)

![Figure 2: Diagrammatic representation of cytological and histopathological correlation of post-TBS](image2)

Table 1: Frequency distribution of diagnostic categories of FNAC reports before and after implementation of TBSRTC

| Diagnostic category | Pre-TBS (n=68) | Post-TBS (n=109) |
|---------------------|----------------|-----------------|
| Inadequate          | 1 (1.47%)      | -               |
| Nondiagnostic       | -              | 3 (2.8%)        |
| Benign              | 43 (63.23%)    | 67 (61.5%)      |
| Descriptive         | 5 (7.3%)       | -               |
| AUS                 | -              | -               |
| SFN                 | -              | 13 (11.9%)      |
| Suspicious for malignancy | 9 (13.23%) | 5 (4.6%)        |
| Malignancy          | 10 (14.70%)    | 21 (19.3%)      |

FNAC: Fine needle aspiration cytology; TBSRTC: The Bethesda system for reporting thyroid cytopathology; TBS: The Bethesda system; AUS: Atypia of undetermined significance; SFN: Suspicious for follicular neoplasm
an improvement in the diagnostic accuracy and sensitivity where sensitivity increased from 62.5% to 75% and the diagnostic accuracy increased from 91.17% to 93.57%.

We in our study have also tried to analyze the common cytologic features that hamper accurate diagnosis. Histopathology was considered as the gold standard for final diagnosis in all cases.

Two common scenarios were identified: overdiagnosis of malignancy and underdiagnosis of follicular neoplasm or malignancy. In the first scenario, hyperplastic changes in nodular goiter and Hashimoto’s thyroiditis were misdiagnosed as papillary thyroid carcinoma (PTC). In nodular goiter, increased cellularity, large sheets of follicular cells with round nucleus, pale chromatin, and occasional nuclear grooving were the cytological features misleading to diagnosis of PTC. The sheets of follicular cells entangled within the blood clots also gave impression of pale clear chromatin. The cases of Hashimoto’s thyroiditis with focal pale powdery chromatin, occasional nuclear inclusion, and intranuclear grooving were the culprit for the diagnosis of PTC.

Overdiagnosing PTC on the basis of few cytological features in the focal areas should be interpreted with caution. The following nuclear features should be carefully looked for: enlarged oval or irregularly shaped nuclei with longitudinal nuclear grooves and intranuclear cytoplasmic pseudo-inclusions, pale powdery chromatin, and solitary or multiple marginally placed nuclei.

In the other scenario, cases with limited cellularity, presence of more number of large follicles over microfollicles, and failure to pick up these microfollicles lead to underdiagnosis of follicular neoplasm as benign nodules. Awareness about microfollicles thus becomes important. There was failure to pick up atypical histiocyteid cells on cytological slides. Scattered groups and sheets of follicular cells with pale nuclei with occasional nuclear grooving and absence of intranuclear inclusion were considered as a part of cystic degeneration in colloid goiter and not as PTC, thereby leading to an underdiagnosis.

The beauty of TBSRTC is that the diagnosis is accompanied by an implied cancer risk for that particular category and it comes with recommendation [Table 2].[2] In most of the categories, we were in line with the implied risk outlined by TBSRTC except the nondiagnostic category where we exceeded the cut-off value outlined by TBSRTC [Table 3]. Classification of thyroid lesions according to TBSRTC standardized nomenclature yielded almost similar overall distribution between categories in different studies [Table 4].[3,4]

Comparison between the two eras revealed that there was a total absence of indeterminate cases (7.3% to 0%), an increase in ability to look out for follicular neoplasm (0% to 11.9%), improvement in making a definite diagnosis of malignancy (14% to 19%), and minimizing suspicious cases (13% to 4%).

Our study has shown a total absence of indeterminate cases after implementation of TBSRTC similar to that of Theoharis et al. which showed a dramatic reduction in percentage of thyroid FNA with indeterminate diagnosis after the use of TBSRTC.[1] Although the cytologic features of follicular neoplasm have been well-described in text books, these were mostly categorized as indeterminate in the pre-Bethesda era, hence were missed/miscommunicated. With the implementation of TBSRTC, most of the follicular neoplasms were picked up on FNA itself (0% to 11%). We would like to stress that a reporting cytopathologist should pay attention to the amount of colloid and architectural arrangement of follicular cells for the diagnosis of follicular neoplasm on FNAC. It is also said that when attention to the above scenarios/pitfalls are paid, it would definitely be easier to classify the indeterminate cases. Some studies (Gerhard et al. and Guo et al.) have also highlighted an important role of second opinion in categorizing thyroid FNA under a specific category.[5,6]

In our study, there was an increase in the fraction of cases diagnosed as suspicious for PTC that were ultimately malignant after resection (60% to 80%) and this finding is similar to that of Olson et al. Similarly, there was a decrease in the suspicious category from 13.23% to 4.6% and 4.5% to 2.4%, respectively, in ours and theirs.[7] Therefore, it was noticed that the decrease in suspicious category complemented the increase in definite malignant category. However, with the increase in the diagnosis of malignancy on FNA, the authors also noticed an increase in the rate of AUS.[7] TBSRTC recommends judicious use of AUS category stating that it preferably be limited to 7%.[1] The increase in the rate of AUS over this limit was also observed by Wu et al. and Sullivan et al. from 3% to 7%.[8] This finding is contrary to our study where the indeterminate cases dropped from 7.3% to 0%, and Crowe et al. have also experienced a similar drop in the rate of indeterminate reports from 3.7% to 0.5% after the implementation of TBSRTC similar to our study.[10] Mondal et al., Mahajan et al., and Dawish et al. have also derived the

**Table 2: The Bethesda system for reporting thyroid cytopathology: Implied risk of malignancy and recommended clinical management**

| Diagnostic category                                      | Risk of malignancy (%) | Usual management                      |
|----------------------------------------------------------|------------------------|---------------------------------------|
| Nondiagnostic or unsatisfactory                          | 1-4                    | Repeat FNA with ultrasound guidance   |
| Benign                                                   | 0-3                    | Clinical follow-up                    |
| Atypia of undetermined significance or follicular lesion of undetermined significance | 5-15 | Repeat FNA                           |
| Follicular neoplasm or suspicious for a follicular neoplasm | 15-30                 | Surgical lobectomy                    |
| Suspicious for malignancy                               | 60-75                  | Near-total thyroidectomy or surgical lobectomy |
| Malignant                                                | 97-99                  | Near-total thyroidectomy              |

FNA: Fine needle aspiration
Table 3: Implied cancer risk in each category after TBS implementation

| Diagnostic category | No. of cases diagnosed as malignancy | Cancer risk in our study (%) | Risk of malignancy according to TBSRC (%) |
|---------------------|---------------------------------------|-----------------------------|------------------------------------------|
| Nondiagnostic       | 1                                     | 33.3                        | 1-4                                      |
| Benign              | 1                                     | 1.49                        | 0-3                                      |
| AUS                 | -                                     | -                           | 5-15                                     |
| Suspicious of FN    | 1                                     | 7.60                        | 15-30                                    |
| Suspicious of malignancy | 4                          | 80.00                    | 60-75                                    |
| Malignant           | 20                                    | 95.23                       | 97-99                                    |

TBS: The Bethesda system; TBSRTC: The Bethesda system for reporting thyroid cytopathology; AUS: Atypia of undetermined significance; FN: Follicular neoplasm

Table 4: Comparison of overall distribution of TBSRTC categories in this study to other studies

| TBSRTC category | This study (2012) (%) | Mufti and Molah (2012) (%) | Mondal et al. (2013) (%) |
|-----------------|-----------------------|-----------------------------|--------------------------|
| ND/UNS          | 2.8                   | 11.6                        | 1.2                      |
| Benign          | 61.5                  | 77.6                        | 87.5                     |
| AUS/FLUS        | 0                     | 0.8%                        | 1                        |
| SFN             | 11.9%                 | 4.0                         | 4.2                      |
| SM              | 4.6%                  | 2.0                         | 1.4                      |
| Malignant       | 19.3%                 | 3.6                         | 4.7                      |

Conclusions from their study that application of TBSRTC has aided in minimizing indeterminate reports and thus helped in providing specific diagnosis, thereby helping in proper management of each cases. The common pitfalls for false-negative diagnosis in ND/UNS category are suboptimal material and underdiagnosis of PTC due to cystic changes – “geographical miss.” Fibrosis and calcification are also other causes of sampling error along with excessive blood in the sample. However, it is important to stress that a “ND/UNS specimen does not mean a negative specimen.”

Wong and Baloch in their review have also analyzed that the implied cancer risk of the ND/UNS category has shown marked variability in literature, most of them moving beyond the 1%–4% as outlined by TBSRTC. Similarly, Jo et al. have also reported the implied cancer risk of ND/UNS category as 8.9% which definitely exceeds the upper limit of 4% of TBSRTC.

Similarly, category III (AUS/FLUS) lesions were also seen to have a much higher risk of malignancy (26.6%–37.8%) than that outlined by TBSRTC (5%–15%) in a study by Ho et al. and the authors concluded that TBSRTC may warrant reconsideration of current recommendation for AFLUS category. Tepeoglu et al. also concluded that the classification and management recommendations of TBSRTC are applicable to practical setting, except the AFLUS category.

In our study, after the application of TBSRTC, sensitivity increased from 62.5% to 75% and diagnostic accuracy from 91.17% to 93.57%. This finding is similar to that of other studies except for Srbova et al. who did not notice any improvement in the diagnostic category between the two eras. They recommend that when in uncertainty, both cytopathologist’s recommendation and clinical decision including ultrasonography evaluation should be taken into consideration. Nevertheless, the authors accept that TBSRTC may be a better scheme to guide the clinical management of patients with thyroid nodules as evidenced by...
its high sensitivity and high NPV. They also stated that there was a growing trend across institutions to adopt TBSRTC because of its clear and comprehensible reports.\textsuperscript{[19]}

We conclude that application of TBSRTC results in reduction in percentage of indeterminate (noncommittal descriptive reports) cases, uniformity in reporting among pathologists in categorization of thyroid lesion, improvement in our capability to diagnose follicular neoplasm, improvement in our capacity to diagnose thyroid carcinoma, end of descriptive reports, and an adoption of more consistent and uniform reporting with better interdisciplinary communication and patient management.

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**Conflicts of interest**
There are no conflicts of interest.

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