Original Research Article

Indian Journal of Pathology: Research and Practice
Volume 6 Number 3, July - September 2017 (Part-II)
DOI: http://dx.doi.org/10.21088/ijprp.2278.148X.6317.42

Diagnostic Utility of Bethesda System in Cytological Smears of Thyroid Lesions

Nandam Mohan Rao*, Vissa Shanthi, Vangala Chidananda Reddy***, Grandhi Bhavana****, Byna Syam Sundara Rao*, Divya Sai G.*******

*Associate Professor **Professor and Head ****Assistant Professor *****Final year MBBS Student, Department of Pathology, Narayan Medical College, Nellore, Andhra Pradesh 524003, India. ***Assistant Professor, Pathology, Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research, Melmaruvathur, Tamil Nadu 603319, India.

Abstract

Background: Bethesda system of thyroid lesion is the six-tired diagnostic classification based on a probabilistic approach in increasing the specificity and sensitivity of FNAC thyroid lesions. Its capacity to facilitate better cytologic -histologic correlation and role of each diagnostic category to conveys specific risks of malignancy. *Methods:* The present retrospective study of Bethesda system of cytopathology of thyroid lesion was carried in 100 cases in the department of Pathology, Narayana Medical College & Hospital, Nellore, Andhra Pradesh, India, during the period of January 2016 to December 2016. Cytological smears was fixed in ethylalcohol and then stained with Haematoxylin and Eosin staining technique. *Results:* In our study the lesion wise distribution after The Bethesda System of Reporting Thyroid Cytopathology (TBSRTC) was benign 77.5%, Atypia of undetermined significance 3.5%, with Follicular Neoplasm at 6%, suspicious for malignancy at 2% and malignant at 11%. The sensitivity and specificity after TBSRTC were 88.13% and 100% respectively with a diagnostic accuracy of 98.55%. On estimation of risk for malignancy in each category it showed 1.95% for benign lesions, 33.33% for Follicular Neoplasm category, suspicious for malignancy had 50% risk and 100% risk for malignancy category. *Conclusion:* The malignancy potential of each category of Bethesda system gives clinician a clear idea regarding its treatment strategy and TBSRTC has a histopathological correlation as good as any system of reporting.

Keywords: Thyroid Cytopathology; Bethesda System.

Introduction

Since its inception in 2009 The Bethesda system for reporting thyroid cytopathology (TBSRTC) is being used widely across the globe by various organizations and institutions with mixed response over its utility in day to day cytopathology practice and overall as a reporting methodology in thyroid cytopathology. Its real contribution towards improving the study of thyroid cytology through fine needle aspiration is widely debated.

Thyroid nodular lesions are common clinical problem 4-7% of the adult population have a palpable thyroid nodule. The incidence of thyroid cancer in a clinical nodule either in solitary or multiple nodule is equal and is about 5% in non endemic areas [1]. Benign thyroid lesions are common where as malignant lesions are rare. Thyroid malignancies account for only about 1-2% of all cancers in most populations throughout the world.

Thyroid nodules constitute the main indication for FNAC, and the goal of this diagnostic procedure is to detect thyroid neoplasm for surgical resection and identify non neoplastic lesions that may be managed conservatively [2]. Over years thyroid FNAC is established as standard procedure for clinical triage of thyroid nodule and considered as safe, reliable and effective method for differentiating benign from malignant nodule. Also it has been claimed that FNAC has substantial cost saving effect on thyroid practice [3]. This method of clinical investigation has reduced the number of diagnostic thyroid surgeries for thyroid

Corresponding Author: N. Mohan Rao, Associate Professor, Department of Pathology, Narayan Medical College, Nellore, Andhra Pradesh 524003, India..
E-mail: nmr2020kmc@gmail.com

(Received on 29.05.2017, **Accepted on** 05.06.2017)

nodules by 60-85% [4]. More over it has been confirmed that the diagnostic value of clinical data alone is inferior to FNAC alone [5].

Whereas the role of fine needle aspiration cytology in thyroid lesions undeniable, TBSRTC and its contribution to existing FNAC status is yet to be proven. In conventional thyroid cytopathology the sensitivity ranging from 65% to 98% and specificity ranging from 55% to 100% has been reported in different settings [6].

We at department of pathology Narayana medical college, Nellore have decided to test the utility of TBSRTC by using the time tested method of Galen and gambino to estimate the efficacy by first testing the sensitivity and specificity of conventional cytopathology and use TBSRTC on same cases to see what effect it has on sensitivity and specificity of the test and compare both, to arrive at utility of Bethesda system on thyroid cytopathology.

Material and Methods

The present study deals with applying the TBSRTC classification systems on previously diagnosed cytopathology slides of thyroid FNA which were diagnosed by conventional reporting methodology. A retrospective study in undertaken at department of pathology Narayana Medical College, Nellore, Andhra Pradesh,India.A total of 100 cases were studied whose cytological diagnosis was established by conventional cytopathology reporting method. All the cases have diagnosis established by histopathology.

Inclusion/ Exclusion Criteria

1. All cases chosen were reported by a single cytopathologist by conventional reporting method.
2. All cases have a established histopathological diagnosis.
3. Cases whose slides are well preserved and fit for re-examination only were used
4. The experience of the reporting cytopathologists both in conventional reporting and applying TBSRTC was around 7-8 yrs.
5. No ancillary studies were applied for either of the reporting systems.

The chosen cases were first taken and analysed for sensitivity, specificity and diagnostic accuracy by Galen and Gambino method before applying TBSRTC, and later same principle was applied to calculate the sensitivity and specificity after applying TBSRTC .

All the cases were estimated for the malignancy risk by comparing each category with histopathogical diagnosis. The application of TBSRTC was done by two cytopathologists with similar experience in reporting (which is same as the cytopathologist who reported FNA by conventional cytopathology), and first two were compared to see the inter observer variability in applying TBSRTC to assess its reproducibility. All the cytopathology slides had staining done by standard Haematoxylin and Eosin staining technique. Histopathological examinations of these cases were already done. All the specimens were fixed in 10% formalin. Detailed gross examination was done and 3-10 tissue bits were selected from representative areas for routine paraffin sections, which were stained by Haematoxylin and Eosin.

Statistical Evaluation

The statistical evaluation to establish sensitivity, specificity, positive predictive value and negative predictive value will be done by Galen and Gambino method.

TP = True positive FP = False positive

TN = True negative FN = False negative

$$\text{Sensitivity} = \frac{TP}{TP + FN} \times 100$$

$$\text{Specificity} = \frac{TN}{TN + FP} \times 100$$

$$\text{Positive predictive value} = \frac{TP}{TP + FP} \times 100$$

$$\text{Negative predictive value} = \frac{TN}{TN + FN} \times 100$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \times 100$$

Result

The present study deals with the fine needle aspiration cytology of thyroid lesions and determination of diagnostic accuracy of aspiration cytology, especially focusing on change in diagnostic accuracy after implementation of The Bethesda system for reporting thyroid cytopathology. A total number of 100 cases which were reported according to conventional reporting pattern presently followed at our institute were taken and reclassified by two cytopathologists according to TBSRTC. All 100 cases have hitopathological diagnosis established.

Age and Sex Distribution

Age of the patients ranged from 14 years to 70 years with a mean age of 39 years. Majority of the patients referred for FNAC thyroid were females and male to female ratio of 1:9.

Thecytological diagnostic categories before TBSRTC were, benign 83 cases(83%), malignant 11 cases (11%), six cases were cellular follicular lesions with 3 cases(3%) being adenomatous nodule/ favouring hyperplastic nodule, and 3 cases (3%) being follicular neoplasm.

The histopathological correlation of the these lesions reported on FNAC before applying TBSRTC all 11 cases (100%) reported as malignant lesions were indeed malignant. Among 83(100%) cases reported as benign, there were 81 cases (97.59%) benign and 2 cases (2.41%) were malignancy. Among 3 cases (100%) reported as follicular neoplasms, these were 2 cases (66.67%) follicular adenoma and one case was follicular carcinoma (33.33%).

With results histopathological correlation for malignancy, using Galen and Gambino method we have estimated and found out that the pre Bethesda FNAC had True positive cases 11, True negative cases 89, False positive cases zero, False negative cases 2, a sensitivity of 84.61% and a specificity of 100% with positive predictive value of 100%, and negative predictive value of 97.80%. Diagnostic accuracy is estimated at 98.03. For diagnostic category follicular neoplasm on cytology is taken as positive histopathological correlation of follicular carcinoma and follicular adenomas.

After implementing TBSRTC on same group of cases by two equally experienced cytopatholgists we have found Benign category 78% by cytopathologist-1 (CYP-1), and 77% by cytopathologist-2, malignancy category-11% by CYP-1 and 11% by CYP-2 also. Atypia unknown significance category was reported at follicular neoplasm/ suspicious for follicular neoplasm was reported at 6% by both the cytopathologist. The category of Atypia of unknown significance/follicular lesion of undetermined significance was reported at 3% by CYP-1 and 4% by CYP-2. Suspicious for malignancy was reported at 2% by both cytopathologists. Non diagnostic category is not applicable as the study was retrospective with histopathology correlation already made we could not use the non diagnostic cases in our study (Table 1).

The hitopathological correlation of thyroid diagnostic categories show no significant difference between TBSRTC and conventional method, with only a marginal improvement in benign category at 0.24% and remains same in malignant category at 100% (Table 2 & 3).

The implementation of TBSRTC on FNAC of thyroid seems to have a minimal but positive effect on sensitivity and diagnostic accuracy (Table 4).

Comparison of sensitivity, specificity and diagnostic accuracy before and after TBSRTC, sensitivity is 84.61% before TBSRTC and is 88.13% after TBSRTC, specificity is 100% before TBSRC and after TBSRTC and diagnostic accuracy is 98.03% before TBSRTC and is 98.55% after TBSRTC.

Among benign category 100% agreement between two cytopathologists, among AUS/FLUS category 99% agreement between two cytopathology and 1% disagreement between two cytopathologists. FA/SFA category 100% agreement between two cytopathologists. Among suspicious of malignancy category 99% agreement between two cytopathologists and 1% disagreement between two cytopathologists. Among

Table 1: Lesions on FNAC after implementing TBSRTC, by two different cytopathologist

Lesion on FNAC	Cytopathologist-1		Cytopathologist -2	
	Number	Percentage	Number	Percentage
Non Diagnostic	-	-	-	-
Benign	78	78%	77	77%
AUS/FLUS	3	3%	4	4%
FN/SFN	6	6%	6	6%
Suspiciousfor Malignancy	2	2%	2	2%
Malignancy	11	11%	11	11%

Table 2: Histopathological correlation for the cases reported on FNAC after applying TBSRTC. For Cytopathologist -1

Diagnosis on FNAC (No)	Histopathological Diagnosis (No)	Correlation
Benign(81)	Benign (79)	97.53%
AUS/FLUS(3)	Benign (3)	-
FN/FSN(3)	Follicular adenoma(2)/ carcinoma(1)	100%
Suspicious for malignancy(2)	Benign (1), Malignant(1)	50%
Malignancy(11)	Malignancy (11)	100%

Table 3: Histopathological correlation for the cases reported on FNAC after applying TBSRTC. For Cytopathologist-2

Diagnosis on FNAC (No)	Histopathological Diagnosis (No)	Correlation
Benign(81)	Benign (80)	98.76%
AUS/FLUS(3)	Benign (4)	-
FN/FSN(3)	Follicular adenoma(2)/ carcinoma(1)	100%
Suspicious for malignancy(2)	Benign (1), Malignant(1)	50%
Malignancy(11)	Malignancy (11)	100%

Table 4: Sensitivity, Specificity and Diagnostic accuracy (by Galen and Gambino method.) for Cytopathologist-1 & 2 after implementation of TBSRTC.

	Cytopathologist-1	Cytopathologist-2
True positive	11	11
True negative	89	89
False positive	0	0
False negative	2	1
Sensitivity	84.61%	91.66%
Specificity	100%	100%
Positive predictive value	100%	100%
Negative predictive value	97.80%	98.88%
Diagnostic accuracy	98.03%	99.00%

Table 5: Malignancy risk for each category in TBSRTC

Category	Malignancy risk
Non diagnostic	-
Benign	1.93%
AUS/FLUS	-
FN/SFN	33.33%
Suspicious	50%
Malignancy	100%

malignant category 100% agreement between two cytopathologists. Our study has shown good reproducibility of TBSRTC.

The inter observer variability in implementing TBSRTC was minimal in our case as we had overall 98% agreement and only 2% disagreement between two cytopathologists.

In implementing TBSRTC the important aspect was calculating the risk of malignancy for each category due to small size of the sample and not having the Non diagnostic category of cases we were able to calculate this for the categories of Benign at a rate of 1.93% and for FN/SFN at 50% and for malignancy at 100% (Table 5).

Discussion

The current study attempted to evaluate the utility of the newly proposed six-tier diagnostic classification system in reporting thyroid FNA results. Diagnostic value of FNAC of thyroid is assessed by calculating sensitivity and specificity of the test in detecting a malignant lesion of thyroid. Our primary objective being what is the role of this six tired TBSRTC in making the FNAC thyroid a better investigative procedure? Will it improve the diagnostic accuracy? Based on a cohort of 100 thyroid FNAs we had calculated sensitivity and specificity and diagnostic accuracy of the cases before applying TBSRTC, which stood at

par with similar studies conducted before using the TBSRTC.

We have found the sensitivity and specificity and diagnostic accuracy is at par with many studies that were done before the introduction of TBSRTC in 2009. Comparison of diagnostic value for malignant lesion before TBSRTC. According to Hamiderza Bazrafshan et al 2008 [7] study sensitivity is 73.68%, specificity is 100% positive predictive value is 100%, negative predictive value is 89.36% and diagnostic accuracy is 91.07%. According to Haggi Mazen et al 2009 [8] study, sensitivity is 83% specificity is 98.5%, positive predictive value is 87.7%, negative predictive value is 78.70% and diagnostic accuracy is 84.70%. In our study 2016, sensitivity is 100% positive predictive value is 100%, negative predictive value is 97.80% and diagnostic accuracy is 98.03%.

The role of FNAC thyroid in detecting malignancy was undeniable, and had enjoyed high rate of diagnostic accuracy without following any classification systems. Comparison of diagnostic value for malignant lesion, after TBSRTC is implemented. According to Ozlucky et al 2011[9] study, sensitivity is 85%, specificity is 94% and diagnostic accuracy is 90%. According to I.V. Renuka et al 2012 [10] study sensitivity is 80.76%, specificity is 96.56% and diagnostic accuracy is 92.98%. In our study 2016 sensitivity is 88.13%, specificity is 100% and diagnostic accuracy is 98.55%. The implementation of tired classification system does not seem to add anything extra as for as the diagnostic accuracy is concerned there was a minimal increase in our study had revealed only a 0.52% increase in diagnostic accuracy. Our sensitivity and specificity after using TBSRTC is also comparable with many studies that were conducted by implementing TBSRTC. It is evident that implementation of TBSRTC has no specific effect on improving the diagnostic accuracy it remained same as any other diagnostic terminology methods which varied from place to place.

Comparison of diagnostic value using the same cases by both implementing conventional and TBSRTC have also shown minimal improvement as our study. According to Ozlucky et al 2011[9] study, sensitivity is 85% before TBSRTC and after TBSRTC, specificity is 87% before TBSRTC and is 94% after TBSRTC, diagnostic accuracy is 86% before TBSRTC and is 90% after TBSRTC. In the present study 2016 sensitivity is 86.16% before TBSRTC and is 88.13% after TBSRTC diagnostic accuracy is 98.03% before TBSRTC and is 98.55% after TBSRTC.

In our endeavour to assess the utility of TBSRTC our second objective was to see ease of implementation, this we set out to prove by implementing TBSRTC on our set of cases by two different cytopthologists. According to I.V. Renuka et al 2012[10] study non diagnostic/unsatisfactory is 17%, benign is 70.56%, AUS/FLUS is 1.95%, FN/SFN is 4.2%, suspicious of malignancy is 2.6% and malignancy is 3.5%. In our study 2016, benign is 77.5%, AUS/FLUS is 3.5%, FN/SFN is 6%, suspicious of malignancy is 2% and malignancy is 11%. We had 77.5% of cases reported as benign, and 3.5% as AUS/FLUS, 6% of cases in FN/SFN category and suspicious for malignancy is reported at a rate of 2% and malignancy is reported at 11% which are well within the limits when compared with other studies, indicating that TBSRTC is a simple 6 tier classification to be used by all to in reporting thyroid FNAC. Our classification is well correlated with similar studies done by different researches.

In our study we could not use the category Non diagnostic/ unsatisfactory as ours is a retrospective study using only those cases whose histopathological diagnosis was already proven, as few cases undergo thyroidectomy with a cytological diagnosis of non diagnostic smears we had no cases in that category. However we have a institutional rate of non diagnostic smear at rate of 7%. Also due to the same selection bias of taking only operated cases in study our malignancy rate is also seemed little higher than other studies.

Other way of proving the applicability of TBSRTC was by seeing the inter observer variability in implementing this classification on FNAC. According to Tejinder Singh et al 2013[11] study (Two experts used) agreement is 82.5% and disagreement is 17.5%. In our study 2016 (Two experts used), agreement is 98% and disagreement is 2%. Our study proved that there was a no significant inter observer variability in implementation of TBSRTC which is well correlated with other studies made by Tejinder singh et al in both the study only minimal difference was observed that too only in AUS/FLUS category.

The histopathological correlation of FNAC is a by product of its diagnostic accuracy it has not changed much in our study both before and after implementing the TBSRTC with marginal 0.24% increase for benign lesions and same for malignant lesion.

The risk of malignancy for each category in our study was estimated only for benign, suspicious for malignancy and malignancy categories as our study sample was small and require large size for each category to get enough histopathological correlations, however our estimation of risk of malignancy too is at par with TBSRTC proposed levels which is also same in other studies. According to TBSRTC

recommendation, risk of malignancy in non diagnostic category is 1-4% in Benign category is 0-3%, in AUS/FLUS is 5-15% in FN/SFN is 15-30%, in suspicious o malignancy category is 60-75% and in malignant category is 97-99%. According to I. V. Renuka et al 2011[10] study, risk of malignancy is 62.5% and in malignancy category is 98%. In the present study 2016, risk of malignancy in Benign category is 1.93%, in FN/SFN is 33.33%, in suspicious of malignancy is 50% and in malignant category is 100%.

Conclusion

The Bethesda system for reporting thyroid cytopathology was started offering a classification system which is closely related to clinical data. The aim was to ensure adequate terminology without risk of errors in understanding, to advise clinicians concerning therapeutic options in relationship to cytological diagnoses as well as to facilitate the comparison of cytology data at national and international levels.

In our study, the lesion wise distribution before TBSRTC was, benign 83%, malignant 11% and follicular neoplasm 3% with additional hyper plastic nodule/adenomatous nodule at 3%. The lesion wise distribution after TBSRTC was benign 77.5%, AUS/FLUS 3.5% with FN/SFN at 6% and suspicious for malignancy at 2%. Malignancy at 11%.The sensitivity and specificity was at 86.61% and 100 respectively with a diagnostic accuracy of 98.03%, before TBSRTC. The sensitivity and specificity after TBSRTC were 88.13% and 100% respectively with a diagnostic accuracy of 98.55%. The increase in diagnostic accuracy after implementing TBSRTC was 0.52%. The histopathological correlation before TBSRTC for benign lesions was at 97.58 and 100% for malignant lesions. The histopathological correlation after implementing TBSRTC was 98.13% for benign lesions and100% for malignant lesions. The histopathological correlation had shown a marginal improvement of 0.24% for benign lesions after implementation of TBSRTC. The reproducibility of TBSRTC has shown minimum inter observer variability with 98% agreement and 2% disagreement in implementing the six tiered categories.

On estimation of risk for malignancy in each category it showed 1.95% for benign lesions and 33.33% for FN/SFN category. Suspicious for malignancy had 50% risk with 100% for malignancy category. We could not estimate risk for malignancy for Non diagnostic and AUS/FLUS categories due to small size of our sample.

We, after the present study arrive at conclusion that there is great utility of TBSRTC in thyroid cytopathology. It definitely is better than having personalised reporting formats that are mostly followed in India, and shows great promise and potential to be very useful in future, with more and more information getting published on improving the present format.

Acknowledgement

The authors are thankful to the Miss. D. PADMAJA B.tech and all the faculty of department of pathology, Narayana Medical College and Hospital, Nellore.

References

1. Hossein Gharib, John R. Goellener. Fine-Needle Aspiration Biopsy of the Thyroid: An Appraisal. Annals of Internal Medicine. 1993;118:282-89.
2. Lester J. Layfeild, Edmund S. Cibas, Hossein Ghrib, Susan J. Mandel. Thyroid Aspiration Cytology: Current Status. CA Cancer J Clin 2009;59:99-110.
3. Isabella Borget, Philippe Veilh, Sophie Leboullex, Mark Allyn, sylviane Iacobelli, Martin Schlumberger, Gerard de Pouvourville. Assessment of the cost of Fine- Needle Aspiration Cytology as a Diagnostic Tool in Patients with Thyroid nodules. Am J Clin Pathol 2008;129:763-71.
4. Hadi M, Gharib H, Goellner JR, Heerden JA. Has Fine-needle aspiration biopsychanged thyroid practice?. Endocr Pract. 1997;3(1):9-13.
5. David L. Rimm, Janet F. Stastny, Eric B. Rimm, Sanjay Ayer, William J. Frable. Comparision of the Cost of Fine-Needle Aspiration and Open Surgical Biopsy as Method for Obtaining a Pathologic Diagnosis. CANCER (cancer cytopathology) 1997;81:51-6.
6. Gia-Khanh Nguyen, Mark W Lee, Jody Ginsberg, Tina Wragg and Dracy Bilodeau. Fine-needle aspiration of the thyroid: an overview. Cytojurnol 2005;2:12.
7. Hamidreza Bazrafshan, ramin Azarhoush, Ali Gholamrezanezhad.Fine needle aspiration of thyroid nodule in a general teaching hospital setting performing moderate number of biopsies: outcome of indeterminate cytologic results. PolishJournal of Endocrinology 2008;59(2):385-89.
8. Haggi Mazeh, Alexander Greenstein, Kristin Swedish, Shalini Arora, Hila Hermon, Ilana Ariel, Celia Divino, et al. From Mount Sinai to Mount Scopus: Differences in the Role and Value of Fine needle Aspiration for evaluating Thyroid Nodule. IMAJ 2009;11:291-96.
9. Ozluk Y, Pehlivan E, Gulluoglu MG, Poyanli A, Salmaslioglu A, Colak N, Kapran Y, Yilmazbayhan

D The use of the Bethesda terminology in thyroid fine-needle aspiration results in a lower rate of surgery for nonmalignant nodules: a report from a reference center in Turkey. J Surg Pathol. 2011 Dec;19(6):761-71.

10. I. V. Renuka, G. Saila Bala, C. Aparna, Ramana Kumari, K. Sumalatha The Bethesda System for Reporting Thyroid Cytopathology: Interpretation and Guidelines in Surgical Treatment Indian J Otolaryngol Head Neck Surg (October–December 2012) 64(4): 305–311.
11. Tejinder singh bhasin, Rahul mannan, Mridhu manjari, Monica mehra, amarinder.k gill sekhon, Manish chandey, Sonam Sharma, Parampreet kaur. Reproducibility of 'The Bethesda System for reporting Thyroid Cytopathology':A MultiCenter Study with Review of the Literature. Journal of Clinical and Diagnostic Research. 2013 June;7(6):1051-1054.