Original Article

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Pathology Section

Evaluation of the Italian Cytological Reporting System and Comparison with Histopathology with Respect to Indeterminate Thyroid Lesions

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ABSTRACT

Introduction: The British system (RCPath-Thy1-5), The Bethesda System for Reporting Thyroid Cyto-Pathology (BSRTC) and The Italian Society of Anatomic Pathology and Cytology (SIAPEC) classification are the most practised thyroid reporting systems with high discriminative factor in classifying thyroid lesions on Fine Needle Aspiration Cytology (FNAC). Surprisingly, none of these classification systems are reliable, when the question is about 'indeterminate for malignancy' category.

Aim: To find out a better cytological reporting system between Bethesda and Italian classification with respect to indeterminate lesions of thyroid.

Materials and Methods: A cross-sectional retrospective study was undertaken in department of Cyto pathology at SDM College of medical sciences and hospital, Dharwad from year January 2015 to January 2018. Thyroid FNAC cases were collected from departmental archives. Among these cases, all FNAC slides for which thyroid surgery were done were reviewed by two cytopathologists and reporting was done using SIAPEC reporting system and BSRTC system. Among those cases (N=33), only indeterminate lesions were selected for the study. Fourteen cases were reported under TIR-3A and 19 cases were reported under TIR-3B. Histological outcomes and cyto-histopathological comparision was done using Chi-Square test. Risk Of Malignancy (ROM), sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) were determined.

Results: ROM for TIR-3A lesions is 35.7% and for TIR-3B lesions is 58.89%. ROM for Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance (AUS/FLUS) lesions is 71.4% and Follicular Neoplasm (FN)/Suspicious for FN category (FN/SFN) lesions are 42.3%. The study revealed very high sensitivity and specificity under Italian system when compared to Bethesda system in identifying malignant outcomes. ROM in Italian sub-classification was more than the anticipated levels.

Conclusion: Current study concludes that SIAPEC reporting system is more satisfactory than BSRTC system while evaluating the indeterminate nodules for malignant outcomes. Our results indicate that cases classified solely on architectural atypia have almost 50% lower ROM when compared with cases with cytological atypia.

Keywords: Bethesda system, Cytology, Italian society of anatomic pathology and cytology, Thyroid indeterminate lesions

INTRODUCTION

Indeterminate lesions in thyroid FNAC are those lesions which fall in gray diagnostic area when there is uncertainty about whether a follicular nodule is neoplastic or non-neoplastic [1]. Fine Needle Aspiration (FNA) biopsy is a vital, well established method used worldwide in the diagnosis of patients with thyroid nodules [2,3]. Interpretation of thyroid FNA is challenging because there is comparatively little difference in the morphologic features of the many non-neoplastic and neoplastic conditions of the thyroid [4]. Due to subtle difference in the cytomorphology of non-neoplastic and neoplastic lesions of thyroid, interpretation is challenging on which clinical management is awaited. In order to promote effective communication between physicians and pathologists, different thyroid cytology reporting systems were designed to standardise thyroid cytopathology results by classifying them into six categories with respect to ROM [5].

The British system (RCPath-Thy1-5), The BSRTC and the SIAPEC classification are the most practised thyroid reporting systems with high discriminative factor in classifying thyroid lesions on FNAC [6-8]. Albeit, the applicability of a single system worldwide is still controversial. Surprisingly, none of these classification systems are reliable when the question is about 'indeterminate for malignancy' category with regard to diagnostic criteria, ROM, clinical impact of subclassification [9]. The British system (RCPath-Thy1-5), the BSRTC is similar in their subclassification. Thy-3a and Thy-3f classes of the British system are equivalent with AUS/FLUS and FN/SFN classes of the Bethesda system [10]. Instead, the Italian system differs from both Bethesda system and British system classes in the high-risk category, that is TIR-3B. Under the new Italian system (2014), TIR-3 was divided into TIR 3A (low-risk indeterminate lesion, LRIL) and TIR 3B (high-risk indeterminate lesion, HRIL) on the basis of architectural and cytological alterations and the background component. The SIAPEC recommended different ROM for both the categories. TIR 3A is characterised by increased cellularity with numerous microfollicular structures in a background of poor colloid amount. The overall proportion of microfollicles however, is not sufficient for the diagnosis of FN. Degenerative and regenerative changes may be present, as sometimes observed in non-neoplastic lesions [11,12]. Alternatively, sparsely cellular samples containing predominantly microfollicular groups, also with oxyphilic features ("Hurthle cells"), in a background of scant colloid, can fulfill the criteria for inclusion in the TIR 3A category [13]. This category also includes partially compromised specimens (because of preparation artifacts or blood contamination), with cytologic or architectural alterations that cannot be confidently classified as benign nor otherwise categorised. The SIAPEC system signifies using incidence of TIR 3A <10 % and ROM <10 %. TIR 3B is characterised by a high cellularity in a monotonous and repetitive microfollicular/trabecular arrangement, with scant or absent colloid, that is suggestive for a FN. This category also includes, sample constituting entirely of Hurthle cells (Hurthle cell neoplasm) [14,15].

Samples characterised by nuclear alterations suggestive of papillary carcinoma which do not permit to reliably exclude malignancy, but

too mild or focal to be included in the TIR 4 category, are added into category TIR3B [8,10,11]. It is recommended to maintain TIR 3B frequency under 10% and its cancer risk between 20 and 30%. Several studies shows that the subclassification of category TIR 3 into TIR 3A and TIR 3B is complementary to as AUS/FLUS-FN/SFN of BSRTC and to the Thy 3 "a" and "f" of BTA-RC Path, but differ in the ROM and different plan of action. The SIAPEC new Italian system included mild/focal nuclear atypia in category TIR 3B which is contrary to the other two systems. This new classification is compared with BRSTC and studied because several studies show very high rate of malignancy AUS/FLUS category. Evaluation of both reporting system helps in validating the reporting system and thus to apply in clinical practice [13-16].

Thus, objective of the study was to evaluate the ROM of thyroid lesions reported by SIAPEC and to compare the histopathological results of these indeterminate category lesions with that of cytology results obtained from Italian and Bethesda system.

MATERIALS AND METHODS

This was a cross-sectional retrospective study conducted at SDM collage of Medical Sciences and hospital, Dharwad, over a period of four years from January 2015 to January 2018. A total of 4,929 FNACs cases were collected from department archives. In that thyroid FNAC reporting was performed for 869 cases. Amongst these cases, FNAC slides for which thyroid surgery were done were included in the study and were reviewed and reported using Italian system and Bethesda system by two cytopathologists who were blinded. Thyroid FNACs for which there was no histopathological examination were excluded from the study. Out of 4929 FNAC cases, thyroid FNACs accounted for 869 cases. A total of 159 cases were obtained for which histopathological results. Reporting was done using both systems. FNA samples were reviewed, blinded to the histological diagnosis and clinical information (patient age, gender, nodule size, ultrasound records) by a team of cytopathologists with 5 to 10 years of experience. Among these, 33 cases were diagnosed as indeterminate lesions. ROM was calculated as mentioned. ROM=total number of histologically proven malignancy÷total number of cases diagnosed on TIR-3A and TIR-3B.

STATISTICAL ANALYSIS

Histological outcomes was noted and cyto-histopathological comparision was done. The sensitivity, specificity, PPV, NPV was determined using the software Statistical Package for the Social Sciences (SPSS) version 20.0.

RESULTS

Histological outcomes of indeterminate nodules by TIR-3A [Table/Fig-1]

Out of 33 cases, 14 cases (42.4%) were diagnosed as TIR 3A and remaining 19 cases (57.57%) were categorised into TIR3B. Under TIR-3A, 9 cases (64.3%) turned out to be benign lesions in which two were thyroiditis, four cases were nodular goitre, one was adenomatoid goitre, two case of follicular adenoma and one case of hurtle cell adenoma. Remaining 5 cases (35.75%) were diagnosed as follows: two case of follicular carcinoma, two cases of papillary carcinoma of thyroid and two case of follicular variant PCT papillary carcinoma of thyroid.

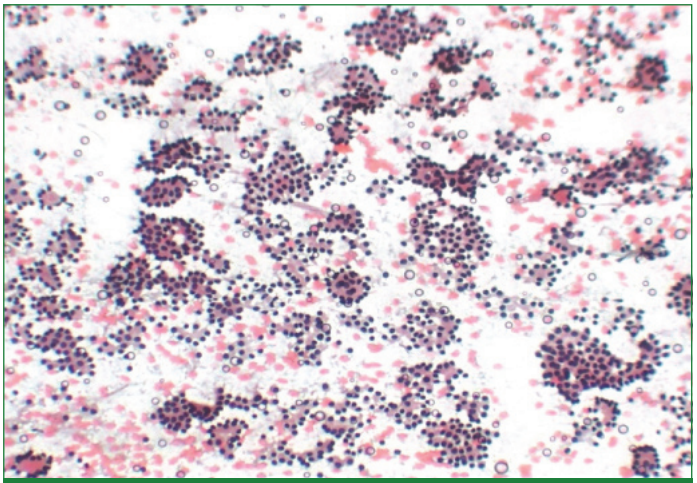
FNAC of TIR-3A showed architectural atypia with repetitive microfollicular pattern, abundant colloid, no cytological atypia [Table/Fig-2a]. Histopathological examination revealed multinodular goitre [Table/Fig-2b].

Histological outcomes of indeterminate nodules by TIR-3B [Table/Fig-1]

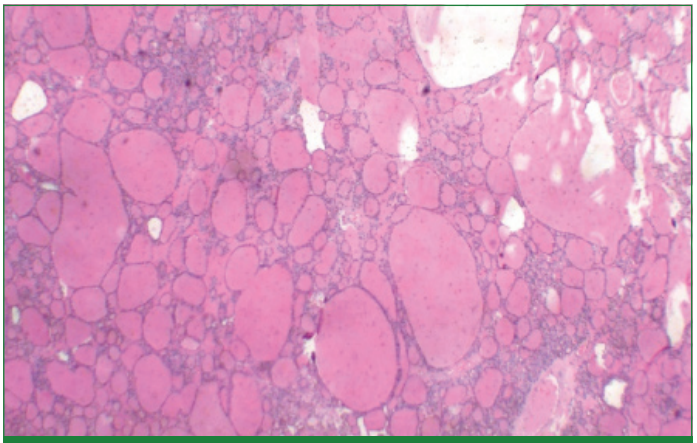
Out of 19 cases, eight cases (42.1%) were benign in which two cases were diagnosed as thyroiditis, three cases of nodular goiter, one case of follicular adenoma and three case of hurtle cell adenoma.

Histological diagnosis	Cytological diagnosis n (%) TIR-3A (n=14) (42.4%)	Cytological diagnosis n (%) TIR-3B (n=19) (57.57%)	Total (n)
Benign lesions	9 (64.3%)	8 (42.1%)	17
Thyroiditis	2	2	4
Nodular hyperplasia	-	-	-
Nodular goitre	4	3	7
Adenomaoid goitre	1	-	1
Follicular adenoma	1	1	2
Hurtle cell adenoma	1	2	3
Malignant lesions	5 (35.7%)	11 (58.89%)	16
Follicular carcinoma	1	6	7
Papillary carcinoma thyroid	2	3	5
FV-PCT	2	2	4
Total	14	19	33

[Table/Fig-1]: Histological outcomes of indeterminate nodules by TIR-3A and TIR-3B. FVPCT: Follicular variant papillary carcinoma of thyroid; n: Number



[Table/Fig-2a]: (Pap smear,10x)- Artichecturalatypia reported as TIR 3A.

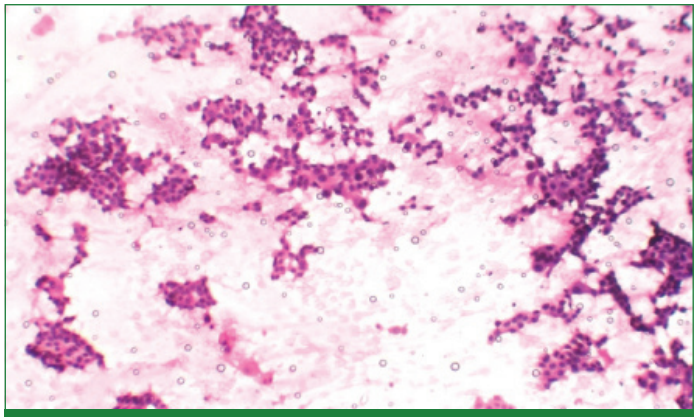


[Table/Fig-2b]: (H&E section, 10x): Multinodular goitre.

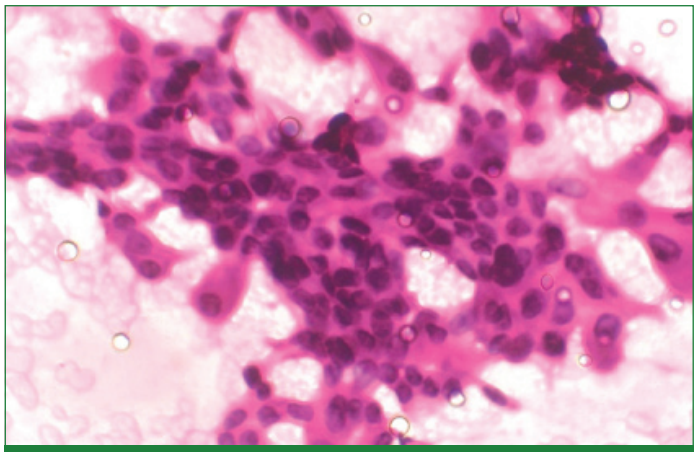
Remaining 11 cases (58.89%) were malignant in which follicular carcinoma were six cases, three cases of papillary carcinoma of thyroid and two cases of follicular variant PCT. FNAC smears of TIR3B showed repetitive microfollicular pattern, focal nuclear atypia [Table/Fig-3a,b]. Histopathological examination revealed papillary carcinoma of thyroid [Table/Fig-3c].

Histological outcomes of indeterminate nodules by Bethesda category III (AUS /FLUS) [Table/Fig-4]

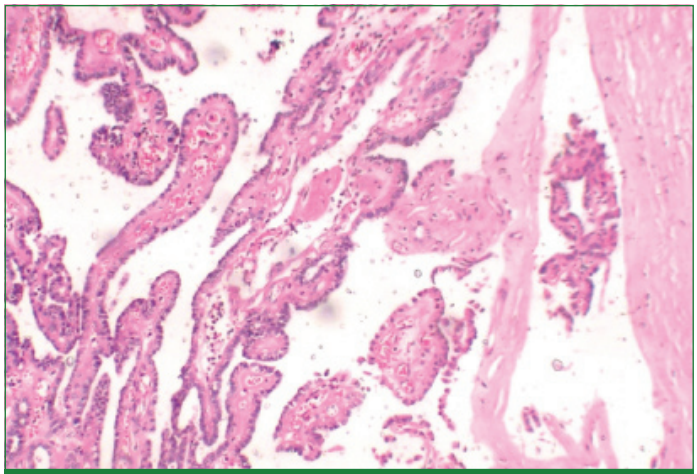
Out of 33 cases, seven cases (21.2%) were diagnosed as AUS/FLUS and remaining 26 cases (78.8%) were categorised into SFN/FN. Under AUS/FLUS, two cases (28.6%) turned out to be benign lesions in which one case was nodular goitre and other follicular adenoma.



[Table/Fig-3a]: (10x H&E)- Microfollicular pattern and, focal cytological atypia-TIR-3B.



[Table/Fig-3b]: (40x H&E)- Microfollicular pattern and, focal cytological atypia-TIR-3B.



[Table/Fig-3c]: (40X, H&E) -Papillary carcinoma of thyroid on biopsy.

Five out of seven cases (71.4%) were diagnosed as malignant in which two cases of follicular carcinoma, two cases of papillary carcinoma of thyroid and 1 case of follicular variant PCT.

Histological outcomes of indeterminate nodules by Bethesda category IV (SFN/FN) [Table/Fig-4]

Under SFN/FN, 15 cases out of 26 (57.7%) turned out to be benign lesions in which four were thyroiditis, six cases were nodular goitre, one was adenomatoid goitre, one case of follicular adenoma and three cases of hurtle cell adenoma.

Eleven out of 26 cases, 11 (42.3%) were diagnosed as malignant in which six cases of follicular carcinoma, three cases of papillary carcinoma of thyroid and two cases of follicular variant PCT.

ROM for Italian and Bethesda system [Table/Fig-5]

ROM under TIR 3A was higher than the recommended value that is 35.7%, but under AUS /FLUS the ROM was too high that is 71.4% ROM under TIR 3B and FN/SFN was 58.89% and 42.3%, respectively. Both are more than the recommended values. The sensitivity and specificity of Italian system was higher than Bethesda system with respect to malignant outcome [Table/Fig-6].

Histological diagnosis	Cytological diagnosis n (%)		Total
	AUS/FLUS (n=7) (21.2%)	FN/SFN (n=26) (78.8%)	
Benign lesions	2 (28.6%)	15 (57.7%)	17
Thyroiditis	-	4	4
Nodular hyperplasia	-	-	-
Nodular goitre	1	6	7
Adenomaoid goitre	-	1	1
Follicular adenoma	1	1	2
Hurtle cell adenoma	-	3	3
Malignant lesions	5 (71.4%)	11 (42.3%)	16
Follicular carcinoma	1	6	7
Papillary carcinoma thyroid	2	3	5
FV-PCT	2	2	4
Total	7	26	33

[Table/Fig-4]: Histological outcomes of indeterminate nodules by Bethesda category III and category IV.
*N: Number; AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN: Follicular neoplasm/Suspicious for follicular neoplasm; FV-PCT: Follicular variant papillary carcinoma thyroid

Italian system	Risk of Malignancy (%)
TIR-3A	35.71
TIR-3B	58.89
Bethesda system	**Risk of Malignancy (%)**
AUS/FLUS	71.4
FN/SFN	42.3

[Table/Fig-5]: Risk of Malignancy (ROM) (original).
AUS/FLUS: Atypia of undetermined significance/Follicular lesion of undetermined significance; FN/SFN: Follicular neoplasm/Suspicious for follicular neoplasm

With respect to malignant outcome		
Statistical value	**Italian system**	**Bethesda system**
Sensitivity	68.2	60.2
Specificity	52.3	10.2
Positive predictive value	57.2	43.3
Negative predictive value	64.2	14

[Table/Fig-6]: Statistical value with Respect to malignant outcome.

DISCUSSION

In 2007, a five tiered classification system was proposed by Italian Society for Anatomic Pathology and Cytology joint with the Italian Division of the International Academy of Pathology (SIAPEC-IAP) [17]. In 2012, an expert working panel decided to update the former Italian system as per the recommendations of the 2009 European Federation of Cytology Societies (EFCS) symposium [17,18]. Calculating ROM for indeterminate category is a reasonably better approach which will limit unnecessary surgery for benign nodules of thyroid [19]. ROM of TIR 3A in present study was 35.71%. The recommended value of ROM for TIR 3A is <10%. Rullo E et al., showed that ROM as 10.2% and Medas F et al., showed a higher value of 21% [10,20]. ROM in Bethesda category III (AUS/FLUS) in the present study was 71.1%. The expected ROM for this category is 5 to 15% for AUS/FLUS. The present value is much higher than the expected value. Studies done by Kim SK et al., reported that the ROM for this category as 36.2% [21]. Few studies found a ROM value around 46.5% [22]. Bohacek I et al., calculated a lower ROM of 12.5% in their study [23].

There are several reasons for high ROM. It is not possible to arrive at the exact ROM in the community because only cases with surgical removal of thyroid are available as cohort. Many non-neoplastic

lesions show hurtle cell change with mild nuclear atypia leading to over diagnosis of non-neoplastic lesions. Clinical risk factors like age (>40 y), sex, nodule size >2 cm in diameter and USG features inclining towards malignancy like hypo echogenicity, irregular margin, micro calcification, nodule size, increased vascularity in Doppler ultrasound play a vital role in the diagnosis of FNAC slides. Most of the cases do not go for repeat FNAC as per the protocol, otherwise they require surgical excision. Several studies show that repeat FNAC have proven to reduce the ROM in category III and TIR 3A. Since present study is a tertiary care hospital many cases which are suspicious of malignancy are encountered. This may lead to referral bias. Studies show that many pathologists have tendency to go for over diagnosis on seeing few atypical cells on cytology. High ROM can be avoided by reclassifing Noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) as nonmalignant under Bethesda system [24]. Studies show decrease in ROM when Stratification of category III was followed while reporting. ROM of TIR-3B in present study was 58.89% and the recommended value is 15.3%. ROM for TIR 3B by Rullo E et al., was 43.2% [10]. Study done by Medas F et al., observed a ROM of 57.8% almost similar to present study [20]. ROM for Bethesda category IV (FN/SFN) was 42.3% and expected value is 15-30%. Deniwar A et al., calculated a similar ROM in his study (50%) [25]. Few studies observed a ROM of 34.3% while Jo VY et al., found a ROM of 25.4% [26,27]. Rullo E et al., accounted for 44.1%(128) cases under TIR 3 A in which most of them were Benign (115 cases) and few were malignant (13 cases) [10]. But, in the present study 42.4%(14 cases) were under TIR 3A in which 64.3% (nine cases) were benign and 35.7%(5 cases) were malignant. Under TIR 3B Rullo E et al., observed 55.9% cases. In this, majority were (91 cases) benign and 71 cases were malignant [10]. But current study showed 57.57% cases in TIR 3B in which 58.89% (11 cases) were malignant and (42.1%) 8 cases were benign. Under AUS/FLUS, present study confounded 71.4% cases as malignant and 28.6% as benign. So ROM was tremendously high. Theoharis CG et al., showed that out of 27 cases, AUS 14 cases (52%) were benign and 13 cases (48%) were malignant which lead to higher ROM [26].

Researchers studied 53 cases of AUS with histopathological correlation, among them 85% of cases were benign and 17% cases were malignant which was dissimilar to present results [27]. The present study observed a high ROM difference (35.4%) in TIR-3A and nearly half value of ROM in TIR 3 B (57.3%). Similarly in AUS of Bethesda system, more diagnostic qualifiers should be identified and different ROM should be calculated for AUS with different patterns. This helps to cut down the ROM in AUS category. On assessing the ROM, Sensitivity (Italian- 68.2%, Bethesda- 60.2%), Specificity (Italian-52.3%, Bethesda-10.2%) PPV (Italian- 57.2%, Bethesda- 43.3%) and NPV (Italian- 64.2%, Bethesda- 14%) of both reporting systems, the present study warrants that it is high time for BSRTC to reclassify the AUS category with regards to incomplete nuclear/cytological features of papillary carcinoma and also clinician should upgrade their management algorithm for cases falling into AUS category. Study conducted by Shi Y et al., has observed that inter and intra observer review of cytology cases helps to increase the sensitivity in AUS category [28]. Periodic intra and interobserver review of slide is recommended to avoid high false positives and false negatives. Idiosyncrasy of ROM may be due to diversity in the algorithm/protocol for solving a case of AUS/FLUS in different institution worldwide. Diversities may be at the grass root level like preparing an slide (direct smear versus Liquid Based Cytology) and type of staining used, guided FNAC, number of FNAC passes and on site adequacy assessment.

Limitation(s)

The foremost limitation of the study is low numerical sample size. More number of cases from large population is to be assessed. Nevertheless, results of present study coincides with above mentioned recent studies. Since present study was a retrospective studies, complete follow-up of the cases is not feasible.

CONCLUSION(S)

Based on present study findings, it can be concluded that cases classified solely on architectural atypia have almost 50% lower ROM when compared with cases with cytological atypia. Regular validation of currently used thyroid cytology reporting system with other international reporting systems is necessary for practicing cytopathologists and surgeons should always be aware of the malignancy rates in thyroid reporting. Present study with the future scope recommends for Genetic analysis, BRAF-V600 mutation detection, Immunocytochemistry for definitive diagnosis.

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