

Classifying the Thyroid Lesions on FNAC According to TBSRTC with Cytohistopathological Correlation

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Abstract: *The objective of this prospective study was to analyze the thyroid cytology smears by The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), to analyze cytological features, and to correlate the cytopathology with its histopathology. Stastical analysis was done. Possible reasons for false positive and false negative results were discussed. Out of 103 fine needle aspirations (FNA) of thyroid nodules, 11.7% nondiagnostic/unsatisfactory (ND/UNS), 20.3% benign, 10.7% atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), 9.7%, follicular neoplasm/suspicious of a follicular neoplasm(FN/SFN), 11.7% suspicious for malignancy (SFM), and 35.9% malignant. So, it was concluded that TBSRTC is not only useful method for standardization the reporting of thyroid cytopathology but also provides clear management guidelines to clinicians whether to go for follow-up FNA or to do surgery. Thus, unnecessary surgery will be avoided.*

Short running title: Thyroid lesions according to TBSRTC

Keywords: TBSRTC, histology, FNAC, thyroid

1. Introduction

After diabetes mellitus, the thyroid gland is the most common organ to cause endocrine disorders.¹ Thyroid carcinoma closely resembles its benign counterpart. A solitary thyroid nodule is more concern because of high probability of malignancy ranges from 5-35%.² Therefore, the surgical excision of the nodule and its histological examination is the only way to differentiate between benign and malignant nodules. In spite of great advances in the understanding of thyroid malignancies various types and their aggressiveness continue to complicate both diagnosis and management. In India, there are 216,000 new cases of thyroid malignancies per year³ and hence the role of properly evaluating thyroid lesions is significant. Fine Needle Aspiration Cytology (FNAC) has proven to be a first line tool to evaluate the thyroid lesions because of its cost effectiveness and high patient acceptance and is highly successful in triaging patients with thyroid nodules into operative and non-operative groups. Thus, enables surgeons to take an early decision regarding mode of treatment to be applied. Though, thyroid FNAC is highly sensitive technique, there has been wide variation and subjectivity in the interpretation and reporting of uncertain categories by different institutions which led to inconsistent practices among pathologists and clinicians.⁴ Until recently, there were no uniform criteria established for the various diagnostic categories and specimen adequacy. Various terminologies like "atypical," "indeterminate," and "suspicious for malignancy," were used. In an attempt to establish a standardized diagnostic terminology classification system and morphologic criteria for reporting thyroid FNAs, the National Cancer Institute (NCI) hosted "The NCI Thyroid Fine Needle Aspiration State of the Science Conference" at Bethesda, Maryland. There were six committees which dealt with different areas regarding

thyroid cytology. Committee IV dealt with diagnostic terminology and morphologic criteria for cytological diagnosis of thyroid lesions. Its recommendations were widely published.⁵ Subsequently a monograph "The Bethesda System for Reporting Thyroid Cytopathology" (TBSRTC) which includes definitions, diagnostic/morphologic criteria, explanatory notes, and a brief management plan for each diagnostic category was published.⁶ TBSRTC has well- defined and rational management algorithms with implied risk of malignancy in each of the six diagnostic categories.^{4,7,8} Each category has an implied cancer risk, which ranges from 0% to 3% for the "benign" category to virtually 100% for the "malignant" category.

The aim of the present prospective study, was to start reporting the thyroid cytology smears by TBSRTC into various diagnostic categories and to assess its efficacy, to analyse cytological features and correlate them with histology of surgical specimens received.

2. Material & Methods

This is a prospective study of thyroid FNACs accrued over a period of 2 years, from 2014 to 2016. These smears were collected from patients with signs and symptoms of various thyroid lesions, who presented to the M.P.Shah Cancer Hospital, Gujarat, India. Related clinical history including physical examination, radiological findings and laboratory investigations were noted. Patients with past history of thyroid malignancy and/or FNAC cases which were not followed surgically were excluded from study.

Fine needle aspiration cytology was performed in the Cytology section of Pathology Department, G.C.R.I, Ahmedabad after taking verbal consent. FNA was done with

needle (22 or 24 gauge) by non-aspiration technique. In cystic swelling, fluid was aspirated as much as possible. Repeat FNA was done from firm area if necessary. Five or six smears were prepared. One smear was air dried and stained by May-Grunwald Giemsa stain. Remaining smears were quickly fixed with 100% methanol and stained with Modified Papanicolaou stain. All the smears were thoroughly examined and diagnosis was done on the basis of the newly proposed Bethesda System of Reporting Thyroid Cytopathology (TBSRTC).⁶(Table:1) The thyroid specimen were fixed in 10% formalin. Representative tissue bits were taken. Histopathological specimens were processed as per standard methods. Blocks were stained with routine Hematoxylin and Eosin (HE) stain. The final diagnoses were determined by the reports of surgical pathology. Cytologic-histologic correlation were done. Histology reports were considered as gold standard for final diagnosis and also for future management. Approval was sought from the institute's ethics committee which approved the current study.

Statistical analysis: Diagnostic yield, diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were calculated using histopathology diagnosis as gold standard. For calculating statistical parameters ND/UNS and AUS/FLUS cases were excluded. Categories "SFM" and "malignant" were considered as malignant and put together. The concordance and discordance rates were also calculated.

3. Observation & Results

Fine needle aspiration cytology was performed on total 401 patients with various thyroid lesions. Out of the 401 FNAs, 103 were operated in-house, thus were included in the study. Age ranged from 8 to 75 years. Mean age was 42.68 years. Female to Male ratio was 2.96:1. Out of 103 cases, 12(11.7%) were in diagnostic category I(ND/UNS), 21(20.4%) were diagnostic category II(Benign), 11(10.7%) were in diagnostic category III(AUS/FLUS), 10(9.7%) were in diagnostic category IV (FN/SFN), 12(11.7%) were in diagnostic category V(SFM) and 37(35.9%) were in diagnostic category VI(Malignant). Out of 103 cases, 24 cases had hemi-thyroidectomies, 3 had subtotal thyroidectomies and remaining 76 had total thyroidectomies. Histology - cytology correlation was shown in Table:2. Of the 12 cases of ND/UNS, smears of 3 cases had low cell content, in 6 cases had cyst fluid with or without histiocytes, while remaining 3 cases revealed presence of blood obscuring the thyroid follicular cells. Out of 21 cases of benign lesion, 19 cases were sub categorized as Benign Follicular Nodules and 2 cases given as Hashimoto's thyroiditis. In AUS/FLUS category, 4 cases showed predominant population of Hürthle cells, 5 cases showed focal nuclear features suggestive of papillary carcinoma, one case showed microfollicular pattern in an otherwise predominantly benign appearing samples and last single case showed follicular cell nuclear atypia hindered by air drying artifact. FN/SFN included 10 cases out of which only single case showed hurthle cell morphology. Out of 12 cases of SFM 10 cases showed features suggestive of SFM for papillary carcinoma and remaining two cases showed SFM features suggestive of medullary carcinoma. In

malignant category, 30 cases showed features of papillary carcinoma, 3 of medullary carcinoma, 2 of anaplastic carcinoma and one case each of primary Lymphoma and primary thyroid carcinoma-NOS type in total of 37 cases.

4. Discussion

Thyroid nodules are common clinical findings and have a reported prevalence of 4 -7 % of the adult population, however fewer than 5 percent of adult thyroid nodules are malignant.⁹ Fine needle aspiration biopsy is extremely helpful in the diagnosis of various thyroid lesions including goiter, thyroiditis and neoplasms. This extremely useful cost-effective, minimally invasive worldwide technique helps to avoid unnecessary thyroid surgery. The recently introduced and much anticipated Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has standardized cytomorphological criteria for diagnosis and adequacy of specimen. It has well-defined and rational management algorithms with implicit risk of malignancy in each of the 6 diagnostic categories. A uniform reporting system for thyroid FNA will facilitate effective communication among clinician and cytopathologist, and also allow easy and reliable sharing of data from different laboratories for national and international collaborative studies. Since the publication of TBSRTC, it has been widely used and articles implementing TBSRTC have started appearing in the literature.^{6,9,10,11,12,13}

In the present study we also share our experience in reporting FNA of thyroid by TBSRTC with its correlation with histology in an Indian academic institution. The diagnostic yield of FNA cytological results according to TBSRTC from our Institute was 88.3% overall, the sensitivity was 95% and specificity was 90% to diagnose malignancy on routine cytology. These results were comparable to the other studies.¹⁴⁻²² We had 11.7% cases in ND/UNS group and 20.3% in benign group. Other studies had a range of 1.2% to 18.6% cases in first group and 34% to 87.5% in "benign" category. An AUS/FLUS group of thyroid has been reported in the range of 1-29% and FN/SFN group had a range of 2.2-16.1%. We had 10.7% in AUS/FLUS group and 9.7% in FN/SFN. SFM category varies from 1.3 to 10% and malignant group had a range of 2.9% to 11%. We had 11.7% for SFM and 35.9% in malignant group. These results are comparable to the previously published studies.^{4,7,8,23,24} Risk of malignancy in our study was 41.7% for ND/UNS, 14.3% for benign, 54.5% for AUS, 60% for FN/SFN, 91.7% suspicious for malignancy and 97.3% for malignant lesion. As compare to the published data we had more percentages of risk of malignancy.^{4,7,8,23,24} Our hospital is the regional cancer centre. Many benign thyroid conditions filtered out at lower centres, so we had mainly the specimen of malignant cases. Out of 401 FNAs only 103 cases were operated in house.

In the literature^{15,16,18,21} accuracy rate ranged from 86.1% to 98%. In the present series, we obtained 93.75% by routine cytological reporting. The false positive rate ranged from 0.2 to 11.1% and the false negative rates ranged from 1.4% to 44.7% in the series of various workers.¹⁵⁻²¹ In our study, the false positive rate was 2.5% and false negative rate was 3.75%. Possible reasons were: a) Cellular atypia due to

hyperplastic reaction in adenoma, b) sampling inadequacy leads to the misdiagnosis in sclerosed/fibrous areas of tumors like anaplastic carcinoma and papillary carcinoma, c) untrained pathologists performing the sampling procedure, d) cellular material with 3-D clusters e) microfollicular pattern with focal nuclear features of PTC were the major reasons for our discrepancy. Repeat FNAC after 3 months interval was suggested in category I cases, but because of clinical indications surgery was done. Suen KC and Quenville NF³³ concluded that the common false positives were a) Cellular colloid goitre mistaken for neoplasm, b) Thyroiditis mistaken for lymphoma and c) Cellular atypia due to hyperplastic reaction in adenoma. False negatives are due to misdiagnosis of papillary and follicular carcinomas as goiters' lesion.¹⁷The difficulty in distinguishing follicular carcinoma from its benign counterpart was experienced even in histological sections since capsular and vascular invasion are essential for the diagnosis of malignancy, which cannot be demonstrated on cytology. Committee V of the NCI Thyroid Fine Needle Aspiration State of the Science Conference has provided guidelines for indications of ancillary studies, specific ancillary studies to be performed, and sample preparation for each study. Following immunohistochemistry panels have been suggested for suspicious malignancies. Calcitonin, thyroglobulin, CEA, and chromogranin for medullary carcinoma, pan-cytokeratin for anaplastic carcinoma, and TTF-1 for metastatic carcinoma. These are to be done on cell block from FNA, preferably including at least one dedicated pass for the study. For suspicious of lymphoma, flow cytometric

immunophenotyping is suggested. Dedicated passes are also needed for studies to detect genetic alterations such as BRAF mutation or RET/PTC chromosomal rearrangements, which are very promising for the diagnosis of papillary carcinoma. Immunocytochemistry on cytospin, direct smear, or prefixed monolayer may also be utilized, but protocols should be carefully validated.³⁴

This study inferred that TBSRTC using the Bethesda monograph is a very useful method for standardization the reporting of thyroid cytopathology. The monograph is succinctly written in an easy-to-read format and has useful colour images which help in making the diagnosis and to reduce inter-observer variability. TBSRTC also mentioned implied risk of malignancy to specific diagnostic categories and recommends the clinical management and thus, improving the communication between clinicians and cytopathologists for more consistent management approaches.

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Table 1: The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories.

I. Nondiagnostic 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, Colloidnodule, etc.)
Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
Consistent with granulomatous (subacute) thyroiditis

III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm

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 lymphoma
 Other

Table 2: Cytological-Histological Correlation of total 103 cases

Diagnosis	Goiter	Hash. Thy.	Adenoma	FC/HC	PC	MC	AC	NHL	PDC-Nos	Total
ND/UNS	5		2		4	1				12
Begin	17	1		1	1		1			21
AUS/FLUS	3		2		6					11
FN/SFN			4	4	1				1	10
SFM-PC	1				9					10
SFM-MC						2				2
PC	1				29					30
MC					1	2				3
AC							2			2
NHL								1		1
PDC						1				1
Total	27	1	8	5	51	6	3	1	1	103

(Hashi. Thy – Hashimotos Thyroiditis, FC/HC- Follicular carcinoma/Hurthle cell carcinoma , PC- Papillary carcinoma ,MC- Medullary carcinoma ,AC- Anaplastic carcinoma, NHL- Nonhodgkins lymphoma, PDC- Poorly differentiated carcinoma , Nos- Not otherwise specified type)

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