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A study of histologic follow-up of thyroid fine needle aspirates reported in The Bethesda system of reporting thyroid cytopathology: A two year experience in a teaching hospital

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Abstract

Purpose of study: To evaluate the application of The Bethesda System of Reporting of Thyroid Cytopathology (TBSRTC) in a non-referral setting of a teaching hospital.

Materials and Method: We included consecutive thyroid FNAs performed in our institute for a period of two years. The FNAs were classified into six general diagnostic categories (DCs) as per TBSRTC. Analysis was done by calculating the sensitivity, specificity, negative and positive predictive values, likelihood ratios and the incidence of malignancy in each of the categories with respect to the histopathologic diagnosis obtained after surgical resection.

Results: A total of 1270 FNAs were categorized as per TBSRTC. DC I constituted 15.6 % of cases, DC II-74.3%, DC III-3.8%, DC IV- 2.4%, DC V-1.% and DC VI-3.1% of cases. Histopathological follow up was available for 253 cases(19.9%)The incidence of malignancy was 0%in DC I, 2.6% in DC II, 33.3% in DC III, 46.15% in DC IV, 77.8% in DC V and 100% in DC VI.The positive predictive value for DC IV,V and VI was 79%and negative predictive value for DC II lesions was 97.2% . A repeat FNA without sonological guidance could re-categorize 22 of the 38 DC I patients into DC II.

Conclusion: The TBRTC is a valid method of reporting thyroid FNAs in a non-referral setting as evidenced by the increasing incidence of malignancy obtained with higher DCs.

Keywords: The Bethesda System, Thyroid Cytopathology, Histopathologic evaluation, Diagnostic category, Malignancy

Introduction

Fine Needle Aspiration (FNA) is a reliable technique for evaluation of thyroid nodule. To avoid ambiguity in reporting terminology the National Cancer Institute(NCI) hosted the NCI Thyroid FNA State of the Science Conference and proposed the Bethesda System of reporting of Thyroid Cytopathology (TBSRTC) in 2007.[(1)]The TBSRTC categorises the thyroid FNAs into six categories- Diagnostic category I(DC I)- includes aspirates which are unsatisfactory due to obscuring factors like blood or are non- diagnostic due to the exclusive presence of cyst fluid with no representative cellular elements from the lesion proper. DC II comprises lesions that are unequivocally benign e.g. nodular colloid goitre/ Hashimoto's thyroiditis. DC III includes those aspirates which show a degree of atypia neither innocuous enough to be a benign lesion nor ominous enough to be categorised into suspicious for malignancy or into malignant categories. It also encompasses follicular lesions which cannot be categorised into DC IV or in DC II. Diagnostic category IV lesions are those which conform to the follicular neoplastic category or are suspicious thereof. DC V lesions have features that are highly suspicious for malignancy and DC VI are frankly malignant lesions.[(1)]

The primary purpose of introducing TBSRTC was to ensure clarity of communication between the physicians from multiple disciples involved in management of patients with thyroid lesions. It-aimed at uniformity of reporting and at better communication between laboratories in collaborative studies. The system also gave an implied risk of malignancy in each category so as to convey to the clinicians an idea of the nature of the lesion to enable them to decide on the line of treatment- whether medical or surgical, to decide on the type of surgery and to triage the patients accordingly.[(1)]

We attempted to evaluate its applicability in a setting where most of the patients were not referrals and hence represented a cross-section of the general population derived from a region where endemic as well as sporadic goitre of the non-neoplastic variety is relatively common.[(2)]

Materials and Method

Consecutive FNAs of the thyroid in the period between January 2014 to December 2015 were included. The lesions were categorized into six Diagnostic Categories (DC). Majority of the FNAs were performed without radiological guidance by cytopathologists varying in experience from one to twenty years. For purpose of calculating the risk of malignancy only those cases which had surgical follow up were included as histopathological diagnosis was considered as decisive. The cytological and histopathological specimens were evaluated by different pathologists to avoid bias.

The surgical specimens consisted of lobectomy, near total and total thyroidectomies.

The data was analysed by calculating the sensitivity and specificity for individual categories. The positive

predictive value and negative predictive value for malignancy in different categories and combination of categories was determined.

For calculation purposes DC I was excluded, category II lesions were deemed negative. Category III, V and VI were considered as a positive. Cases in DC II with carcinomas including papillary microcarcinomas on histopathological examination were considered as false-negative. Patients with positive cytological examination and diagnosed as nodular goiter or thyroiditis on histopathological examination were considered as false positives.

Results

A total for 1270 thyroid FNAs were performed during the study period. The age of the patients ranged from 12 years to 89 years with a mean age of 44.3 years. Females constituted 81.4% of the patients.

Of the 1270 cases 210 cases were non diagnostic on initial aspirate. Of these 38 patients underwent repeat FNAs within 1 week of the first attempt. On repeat aspiration 13 were non-diagnostic 22 were re-categorized into category II and 3 in category III. The final categorization of these patients into different DCs was based on the second FNA result.

Surgical resection was performed for 253 patients constituting 19.9% of cases.(Table 1)

Table 1: Distribution of cases evaluated in individual diagnostic categories with number of cases with surgical follow-up in each DC.*only includes cases managed in institute. Average of 19.9%

Category	No of cases (n=1270)	No of cases managed surgically (n)	*Cases managed surgically(%)	Average Percentage
I. Non-diagnostic or Unsatisfactory	195	8	3.07%	3.07%
II. Benign				17.75%
- Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.)	731	158	22.7%	
- Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context	195	28	12.8%	
- Consistent with granulomatous (subacute) thyroiditis Other	18	0	0%	
III. Atypia of Undetermined Significance(AUS) or	39	10	28.2%	
Follicular Lesion of Undetermined Significance(FLUS)	9	5	55.5%	41.8%
IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm	27	10	37.03%	68.5%
Hürthle cell (oncocytic) type	4	4	100%	
V. Suspicious for Malignancy				52.25%
- Suspicious for papillary carcinoma	11	7	54.5%	
- Suspicious for medullary carcinoma	2	2	50%	
VI. Malignant				42.5%
- Papillary thyroid carcinoma	34	20	61.7%	
- Medullarycarcinoma	3	1	33.35	
- Undifferentiated (anaplastic) carcinoma	2	0	0	
Number of cases(n)	1270	253		

Histopathological outcomes for cytologically categorized cases is presented in Table 2.

Table 2: Histopathologic result in patients of each diagnostic categories

General Category Assigned	Final FNA Diagnosis	No of patients	Histopathologic diagnosis	Number of patients
DC I	Nondiagnostic or Unsatisfactory	8	Nodular goiter	8
DC II	Hashimoto thyroiditis and Nodular goiter	186	Hashimoto thyroiditis	21
			Multinodular goiter	159
			Follicular adenoma	1
			Papillary microcarcinoma	2
			Papillary carcinoma	2
			Well differentiated tumor of uncertain malignant potential	1
DC III	Lesions of undetermined significance (AUS/FLUS)	15	MNG	7
			Follicular adenoma	3
			Follicular carcinoma	2
			Papillary microcarcinoma	1
			Papillary carcinoma	2
DC IV	Follicular Neoplasm (Category IV)	13	MNG	2
			Follicular adenoma (one with microcarcinoma)	5
			Follicular carcinoma	2
			Papillary carcinoma-FV	3
			Well differentiated tumor of uncertain malignant potential	1
DC V	Suspicious for malignancy (Category V)	9	MNG with adenomatous hyperplasia	1
			Hurthle cell adenoma	1
			Papillary carcinoma	5
			Medullary carcinoma	2
DC VI	Papillary carcinoma	20	Papillary carcinoma	20
	Medullary carcinoma	1	Medullary carcinoma	1

Commonest pathology was multinodular Goiter seen in 66.7%. Incidence of neoplasm was found to be 21.3%. Incidence of malignancy was 16.9%.(Table 3)

Table 3: Incidence of malignancy in each diagnostic category based on the histopathologic outcome. DC-Diagnostic category

DC	%of cases N- 1270	N-253	Incidence of malignancy
I	15.35	2.4	0.0
II	74.33	73.5	2.6
III	3.78	5.9	33.3
IV	2.44	5.5	46.15
V	1.02	3.6	77.8
VI	3.07	8.3	100.0

Commonest neoplasm was Papillary thyroid carcinoma(PTC) seen in 81.3% of cases followed by follicular carcinoma(9.2%), medullary carcinoma (6.7%) and tumors of uncertain malignant potential(4.7%).

Positive predictive value for DC IV, DC V and DC VI excluding DC III was 79%(Table 4).

Table 4: Statistical parameters for malignancies in different combinations of categories. PPv- Positive predictive value. NPV- Negative Predictive Value. PLR- positive likelihood ratio. NLR- Negative likelihood ratio. DC- Diagnostic categories

	Excluding category I lesions		
Parameters	**Considering DC IV as malignant**	**Considering DC IV as benign**	**Excluding DC IV in addition to DC I**
Sensitivity	88.64	75	86.9
Specificity	90.50	94	93.78
PPV	67.24	73.33	73.3
NPV	97.31	94.42	97.3
PLR	9.33	12.5	13.9
NLR	0.13	0.27	0.14
Concordance	90.1%	87%	92.6%

Discussion

In our study DCI constituted nearly 15% of the cases. When compared to similar studies it is on the higher side. However of the 195 cases, 61 cases showed only macrophages and if these are excluded then the DC falls 10.5%which is minimally above that recommended by TBSRTC.[1](Table 5)(Fig. 1)

Table 5: Distribution of cases different DCs in the current study in comparison with similar other studies. DC- DC- Diagnostic categories

	DC I	**DC II**	**DC III**	**DC IV**	**DC V**	**DC VI**
Mondal *et al*[3]	1.25	87.5%	1%	4.2%	1.4%	4.7%
Lee *et al*[4]	10%	67.7	3.1	1.1	5.1	13%
Mehra et al[5]	7.2%	80%	4.9%	2.2%	2.2	3.6
Mufti et al[6]	11.6%	77.6%	0.8%	4%	2.4%	3.6%
Jo et al[7]	18.6%	59%	3.4%	10%	2.3%	7%
Yassa et al[8]	7	66	4	9	9	5
Yang et al[9]	10.4	64.6	3.2	11.6	2.6	7.6
Renshaw[10]	23.6	54	7.7	8.6	1.9	4.2
Nayar et al[11]	5.3	64.2	17.8	5.9	1.9	4.9
Theoharis et al[12]	11.1	73.8	3	5.5	1.4	5.2
Kim et al[13]	1.8	58.3	16.3	1.2	6.2	16.2
Her Juing Wu *et al*[14]	20.1	39	27.2	8.4	2.6	2.7
Bongiovanni *et al*[15]	2	54.7	6.3	25.3	6.3	5.4
Bohacek *et al*[16]	16	66.4	11.2	2.4	2	2
Present study	15.4	74.3	3.8	2.4	1.02	3.07

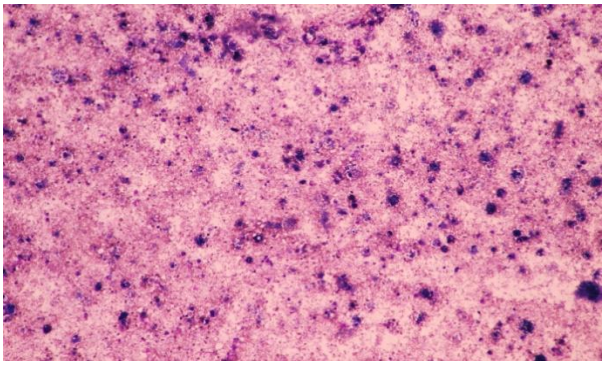

Fig.1: Aspirate from a nodule exhibiting a population composed exclusively of cyst macrophages in a background of cyst fluid and blood- Categorized into DC I. MGG. Original magnification 40x

The incidence of malignancy was 0 as opposed to an expected value of 1-4%. Histopathological follow-up in DC I was available for only 3% of the patients who underwent a surgical resection. The dis-proportionately small number of patients may have impacted the rate of malignancy in this category and hence may not be representative of the actual risk.

Eighteen percent of the initially diagnosed DC I category patients underwent repeat FNA within 1 week of the first FNA. Of the repeat FNAs only one was performed under radiological guidance. A benign diagnosis was obtained in more than half of the cases(22/38) implying that the DC I was more likely due to technical issues than due to the inherent nature of the lesion.

Though not conclusive, the negative predictive value of 97.3% for DC II lesions can be reliably predict a benign diagnosis in most of the cases.

Renshaw et al found a negative correlation between the non diagnostic category and malignant category implying that a benign nodule is more likely to give rise to a non diagnostic aspirate as opposed to a malignant nodule.[17]

Since a repeat study could successfully re-categorise more than half of the DC I into a definite group of DC II a blind FNA could be considered as a reliable alternative to a sonologically guided FNA where resources are be limited and the percentage of cases in DC I is high.

Category II comprised 73.5% of the cases. Including all the patients who underwent surgical resection (all DCs) nodular goiter was seen in 66.7% of the cases. The DC II ranged from 39% to 87.5% in recent studies.(Fig. 2)

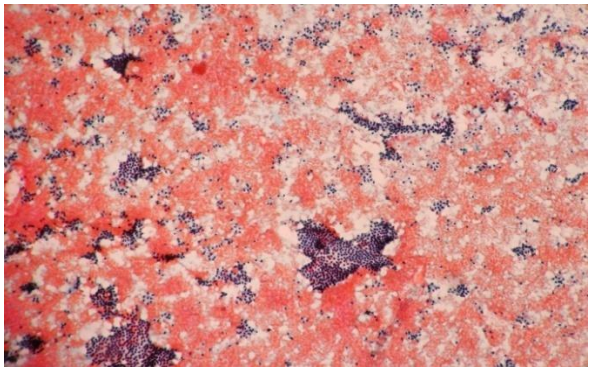

Fig. 2: Aspirates composed of small and large monolayered sheets of thyroid follicular cells which on higher magnification had bland chromatin pattern. Papanicoloau stain. Original magnification 40x

The higher percentage of nodular goiters seen in our study probably reflects the distribution of lesions in the general population as opposed to the lower percentages seen in the study done in referral centers.

The risk of malignancy in DC II was 2.6% and was well within the limits described by TBSRTC. On exclusion of papillary microcarcinomas the risk of malignancy was even lower (1.6%).[1]

DC III constituted 3.8 % of the cases. TBSRTC recommends limiting the cases to 7%of the FNAs. This is the most controversial of all categories and was included on the strength of recommendation of the clinicians who voted in favour of including this category.[1]

As per TBSRTC the risk of malignancy in DC III is about 5-15%. Similar studies based on TBSRTC have obtained a value between 6% to 48%(Table 6)(Fig. 3)

Table 6: Incidence/ rate of malignancy in current study in comparison with similar other studies

	Jo et al	Mondal et al	Renshawet al	Nayar et al	Theoharris et al	Marchevsky[18] et al	Current study
DC I	8.9%	0	20	9	32	7.5	0.0
DC II	1.1%	4.5	2	26	9.8	32.2	2.6
DC III	17%	20	25	6	48	37.9	33.3
DC IV	25.4	30.6	28	14	34	27.3	46.15
DC V	70	75	97	53	87	100	77.8
DC VI	98.1	97.8	100	97	100	100	100.0

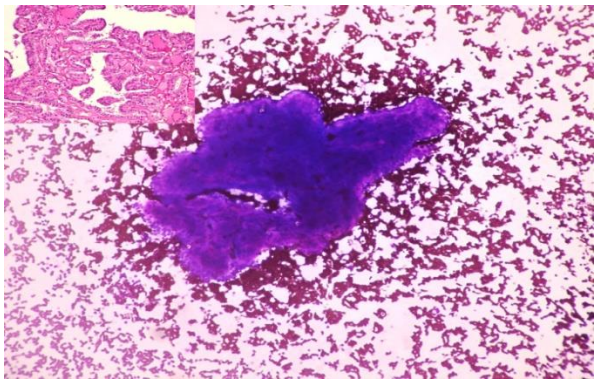

Fig. 3: A hypo-cellular aspirates composed exclusively of fragments of tissue in papillaroid configuration. The individual cells appeared bland. MGG. Original magnification 40x.Histopathology revealed papillary hyperplasia(inset)

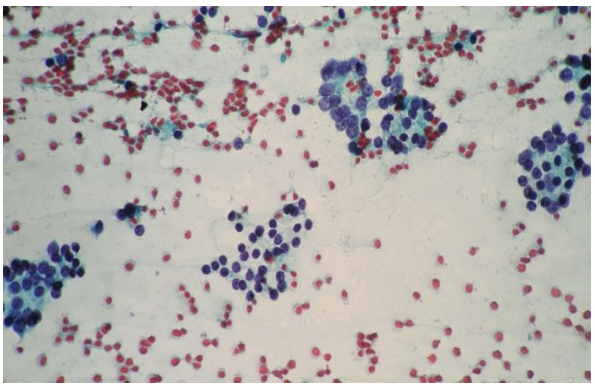

Fig. 4: Lesion categorized as FLUS. Smears showed cells arranged in follicles. Some of the follicles showed overlapping of cells with pale nuclear chromatin. These were admixed with benign follicles.(arrow head)

The pattern of distribution of cases in DC I and DC III in our series similar to that observed by Vander Laan et al who in their review suggest of there being an inverse relationship between DC I and DC III. They proposed the existence of a subset of lesions which when evaluated with even the best of techniques still remain categorized into either DC I or DC III.[19]

They also suggest that it is a malignant lesion more likely to give rise to the AUS/ FLUS category result than a benign lesion as supported by our observation of 33.3% incidence of malignancy in DC III as opposed to 0%in DC I.[19]

Krane et al recommend maintaining a AUS/FLUS: malignant ratio between 1 and 3 as performance measure for DC III akin to the ASCUS: HSIL ratio of Papanicolouo smears as the malignancy rate in DC VI in all the case series is constant and approaches 100%.The AUS: malignancy ratio in our study is just over 1(n-1270) and among patients who underwent surgery less than one suggesting underutilization of this category in our institution.[20]

TBSRTC recommends repeat FNA study in DC III after an interval of 3 months. In our study nearly 42%of the patients underwent thyroidectomy. The rate of surgical resection was nearly twice more for FLUS(55.5) as compared to AUS(28.2) and is nearly same as for DC V.[1]

The high rate of surgical resections give an insight into the treating clinicians perception of DC III as being nearly same as DC V and lends weight to those researchers urging to eliminate DC III entirely. However it must be noted that the PPV for malignancy is significantly less when DC III is considered in the malignant group as opposed to when DC III is excluded.(67.2 vs. 79) and hence may result in a higher number of surgeries than warranted if the above recommendation is accepted.

The purpose of DC IV was to identify those lesions which could be follicular carcinomas and the plan of management in these cases is surgical lobectomy.(Fig. 4)The implied risk of malignancy is between 15-30%. The incidence of malignancy in the current study is among the highest of all the recent studies the false negative result on follicular variant of papillary carcinoma in three of the cases being the main reason. In two of the cases it was the result of sampling error with the needle tract being identified just adjacent to the lesion. The nuclear features in the third case were subtle and was overlooked by the reporting pathologist.[1]

Since the benign diagnosis constitutes more than half of the cases in DC IV the overall positive predictive value for malignant lesions is slightly lesser when we include DC IV in the malignant diagnosis category than the benign category.

DC V includes those cases which are highly suspicious but not definite enough to confirm malignancy. In our study all but two of the cases had malignancy on histopathology. In both the cases there was extensive hurthle cell change with marked anisonucleosis frequent nuclear grooving and the case of Hashimotos thyroiditis showed a single intra nuclear cytoplasmic pseudo-inclusions. Additionally both of these cases showed minimal colloid prompting a suspicion for papillary thyroid carcinoma (PTC).

Cases of PTC diagnosed as DC V had varying combinations cellularity and in some cases incomplete nuclear changes. In one case suspected to be medullary carcinoma the smears had low cellularity and in the other the cells looked more like Hurthle cells with some cells showing the characteristic stippled chromatin. Both cases had no amyloid in the smears. The serum calcitonin done subsequent to the FNA diagnosis showed raised levels-Cases in DC VI were relatively easy to diagnose as they had adequate cellularity and the characteristic features described for each of the malignancies. No microcarcinomas were diagnosed on FNA in this category. Majority of the patients presented with solitary nodules in an otherwise clinically normal thyroid.

Conclusion

TBSRTC is a reliable modality of reporting thyroid lesions even in a non-referral settings as evidenced by the increasing risk of malignancy in higher categories which is in accordance with the initial assessment by the proposers. The subsequent management of the lesions not suspicious or frankly malignant may however depend on the perception of risk by the clinician rather than on the modalities recommended by TBSRTC

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