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TO EVALUATE EFFICACY OF PREOPERATIVE DIAGNOSTIC MODALITIES IN ASSESSING 200 SOLITARY THYROID NODULES-A STUDY AT TERTIARY CANCER CENTER

Oncopathology

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ABSTRACT

Background: Thyroid nodule is defined as a single palpable or radiologically identifiable lesion standing out distinctly from the surrounding thyroid parenchyma. Solitary nodules of thyroid are about four times more common in women than in men. STNs are more likely to be malignant than the multiple nodules. Because of this reason, STNs have to be investigated with high degree of suspicion and treatment planned in a systematic manner. **Material and methods:** We conducted one-year retrospective study from April 2021-April 2022 at department of pathology, BMCHRC on 200 consecutive cases of solitary thyroid nodule reported from department between 2015 TO 2018. **Results:** Biochemical parameters were available in 162 cases (81%), radiological findings were retrieved in 176 cases (88%), FNAC were available in 154 cases (77%). 85 patients (42.5%) underwent an intraoperative frozen section. IHC was done in 19 cases with inconclusive histological diagnosis. Patients presenting with solitary thyroid nodule fell in age group between 12 to 76 years, with the most common age group affected was 5th decade. Mean age of 44 years was noted irrespective of the nature of the lesion with female preponderance and male: female ratio of 1:3.54. Most patients presented with swelling neck which on examination moved with deglutination. Right lobe was more commonly affected then left lobe of thyroid. Most common type of surgery being done was total thyroidectomy (42.5%).Majority (71%) of cases were euthyroid. On final histopathology report ,out of 200 cases 49 were non neoplastic,21 were benign neoplasm and 130 were malignant. Overall histopathology-radiology concordance was 68.75 % in 176 patients with available radiological findings. Overall cyto-histopathology concordance achieved in our study was 58.44%. 85 cases underwent intraoperative frozen section with 83.54% cases concordant with final histological diagnosis. Immunohistochemistry was performed on 19 cases with inconclusive diagnosis with a concordance rate of 78.94%. **Conclusion:-** We concluded that intraoperative frozen section offer higher concordance in diagnosing solitary thyroid nodule.

KEYWORDS

Thyroid, FNAC, Frozen Section, IHC

INTRODUCTION

Thyroid nodule is defined as a single palpable or radiologically identifiable lesion standing out distinctly from the surrounding thyroid parenchyma. Solitary nodules of thyroid are about four times more common in women than in men. STNs are more likely to be malignant than the multiple nodules, therefore have to be investigated with high degree of suspicion and treatment planned in a systematic manner.[1]

In India, the prevalence of a palpable solitary thyroid nodule is about 12.2% and 10% to 30% of STNs are of malignant aetiology. However, the overall incidence of thyroid cancer is relatively rare, with an incidence rate of 8.7 per 100,000 population per year.[1]

At beginning evaluation of any person suspected of having thyroid disease includes a clinical history, physical examination, and a variable number of laboratory investigations.[2] Historically, the thyroid nodules with restricted mobility and a hard consistency are considered as markers of invasive thyroid cancer. Compressive symptoms such as dysphagia, dyspnea, and a foreign body sensation in the throat are present in both benign and malignant thyroid swellings.[3]

Initial screening test for all patients with a thyroid nodule is serum TSH level to know if the patient is euthyroid, hypothyroid or hyperthyroid. Most of the patients with a thyroid nodule are euthyroid and if they are not euthyroid, then the underlying pathology is likely to be benign and functional.[4]

Evaluation of the thyroid gland can be performed using various imaging techniques these modalities include plain radiography, radionuclide imaging, ultrasonography, CT, and MR imaging. High resolution ultrasonography (USG) is the first line investigations in clinically detected thyroid nodules that are biochemically euthyroid.[2]

Fine Needle Aspiration Cytology (FNAC) of the thyroid gland is now well-established diagnostic test for the evaluation of diffuse thyroid lesions as well as of thyroid nodules with the main purpose of confirming benign lesions and thereby, reducing unnecessary surgery. It is easy to perform, has a low complication rates and high diagnostic value and is a cost-effective test used in the diagnosis of thyroid nodules.[5]

Radioactive iodine scanning is used in the hyperthyroid patient to differentiate between a toxic nodule > 1 cm in diameter and the diffuse pattern in Grave's disease. The ability of isotope scanning to detect metastatic disease is its most important diagnostic utility.[4]

Frozen section is a quick intraoperative micro-and/or macroscopic examination involving freezing of a surgical tissue fragment, and is classically the prime guide to surgical extension. It thus first serves to confirm diagnosis and its efficacy can be assessed in terms of the elimination of false positives so as to avoid "over-treatment" (unnecessarily extensive surgery) and of false negatives, to limit the risk of "under-treatment" (failure to perform neck dissection, or 2-step thyroidectomy).[6]

The main diagnostic gold standard is pathologic evaluation with routine hematoxylin and eosin (H and E).[7] However, for those tumors that are poorly differentiated or undifferentiated, not follicular derived, and exhibit equivocal histomorphologic features, the application of immunohistochemical biomarkers may play an active or complementary role in their accurate classification.[8]

The combination of HBME-1, GAL-3, and CK19 was by far the most common panel evaluated by investigators, and their diffuse expression has not been reported in benign lesions.[8]

AIMS & OBJECTIVES

- To evaluate efficacy of various preoperative diagnostic modalities.
- To correlate pre and post-operative diagnostic modalities and requirement of IHC in evaluation of solitary thyroid nodules.

Research Questions: -

- What is the correlation and efficacy of preoperative diagnostic modalities of solitary thyroid nodule with final histopathology report?
- How is IHC helpful in making the final diagnosis?

MATERIAL AND METHODS

This retrospective study was conducted at Department of Pathology, BMCHRC, Jaipur on 200 consecutive cases of solitary thyroid nodule operated at the institute during the study period & who fits the study criteria, after obtaining approval from scientific & research committee and institutional Ethical Committee.

Inclusion criteria:-

1. All Hemithyroidectomy / Subtotal Thyroidectomy /Near Total Thyroidectomy /Total Thyroidectomy/Frozen section specimens received at the Pathology department, BMCHRC during study period 2. All age group and both genders are included.3. Cases given consent to be a part of the study.4. All thyroid lesions including benign as well as malignant.

Exclusion criteria: -

1. Incisional biopsies of thyroid lesions.2. Outside operated cases (where no details are available).

All clinicopathological and radiological details of cases were retrieved from medical records and studied.

Statistical methods:-

Continuous variables summarized as Mean & Standard deviation, whereas Nominal/categorical variables expressed as Proportions (%). Unpaired T test, One-way Anova test & Pearson correlation test used for analysis of continuous variables while Chi-square test & Fischer exact test used for analysis of nominal/categorical variables. P value <0.05% taken as significant. Medcalc 16.4 version software will be used for all statistical calculations.

OBSERVATIONS AND RESULTS

This one-year retrospective study from April 2021-April 2022 was conducted at department of pathology, BMCHRC on 200 consecutive cases of solitary thyroid nodule from 2015 TO 2018.

Biochemical parameters were available in 162 cases (81%), radiological findings were retrieved in 176 cases (88%), FNAC were available in 154 cases (77%). 85 patients (42.5%) underwent an intraoperative frozen section. IHC was done in 19 cases with inconclusive histological diagnosis.

Table 1: Age And Gender Wise Distribution Of Subjects:

AGE GROUP	FEMALES	MALES	Total
Less than 20	9	0	9
21-40	66	15	81
41-60	57	21	78
61-80	24	8	32
TOTAL	156	44	200

- Age ranges from 12 years to 76 years
- Mean age:44.55+15.46 (Mean +Standard deviation)
- Female:- 44.42+15.48
- Male:- 44.47+15.47
- Male : Female ratio:-1:3.54

Table 2: Distribution Of Cases According To Type Of Surgery:

TYPE OF SURGERY DONE	N	%
Total thyroidectomy	85	42.5
Subtotal thyroidectomy	8	4
Completion thyroidectomy	43	21.5
Near total thyroidectomy	1	0.5
HEMITHYROIDECTOMY (right)	38	19
HEMITHYROIDECTOMY (left)	15	7.5
Thyroid nodule excision	4	2
Lobectomy	3	1.5
Parathyroidectomy	3	1.5
Total	200	100

Table 3: Biochemical Status Of Patients Presenting With Solitary Thyroid Nodule

Thyroid status	N	Percentage
EUTHYROID	142	71
HYPOTHYROID	11	5.5
HYPERTHYROID	9	4.5
STATUS UNKNOWN	38	19
	200	100
TOTAL		

Table 4. Distribution Of Cases As Per Histology

	NON NEOPLASTIC	NEOPLASTIC	
		BENIGN	MALIGNANT
NO.OF CASES	49	21	130
PERCENTAGE	24%	11%	65%

65% cases of solitary thyroid nodule turned out to be malignant on final histopathology.

Table 5: Distribution Of Benign Neoplasm:

S.no	BENIGN LESION	NO OF CASES	Percentage
1	FOLLICULAR ADENOMA	12	57.15
2	ONCOCYTOMA	1	4.76
3	PARATHYROID ADENOMA	3	14.29
4	TRABECULAR ADENOMA	2	9.52
5	HYALINIZING TRABECULAR ADENOMA	1	4.76
6	MICROFOLLICULAR ADENOMA	2	9.52
	Total	21	100

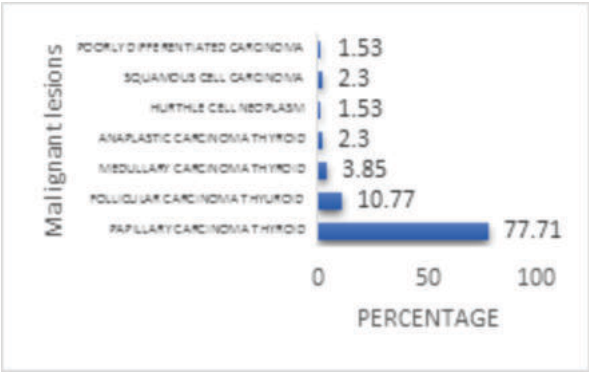

Figure-1: Distribution Of Malignant Neoplasm:

Majority of malignant neoplasm (77.71%) were papillary carcinoma thyroid

Table 6: Distribution Of Non Neoplastic Cases

S.no	BENIGN LESION	NO OF CASES	Percentage
1	ADENOMATOUS GOITRE	12	24.49
2	COLLOID GOITRE	2	4.08
3	GOITROUS PATHOLOGY	11	22.45
4	HASHIMOTO'S THYROIDITIS	8	16.32
5	NODULAR GOITRE	13	26.54
6	HYPERPLASTIC NODULE	1	2.04
7	SUBACUTE THYROIDITIS	1	2.04
8	THYROID CYST	1	2.04
	Total	49	100

Table 7: Association Between Radiological Categorisation Of Solitary Thyroid Lesions And Final Diagnosis

RADIOLOGY CATEGORISATION	NO OF CASES CONCORADANT ON HISTOLOGY (n-121)	NO OF CASES NON CONCORADANT ON HISTOLOGY (n-55)	NO. OF CASES
BENIGN	19	22	41
PROBABLY BENIGN	21	15	36
SUSPICIOUS FOR MALIGNANCY	41	14	55
MALIGNANT	28	4	32
COLD NODULE	12	0	12
N/A	0	0	24
Total	121	55	200

P value: <0.05 (statistically significant) Degree of freedom: 4 x2 value: 22.95

48.05% cases with benign /probably benign lesion on radiology showed non concordance on histology as in some of the cases only a microscopic focus of papillary carcinoma was found which could be missed on radiology. Some of the lesions with papillary carcinoma had cystic degenerative lesions which appeared benign on radiology.

Reason for more no. of non-concordance specially in lower grade

Bethesda lesions (34%) on cytology could be due to smaller size of lesion being not sampled properly on FNAC or benign neoplastic lesions associated with inflammatory/goitrous condition which is sampled on FNAC.

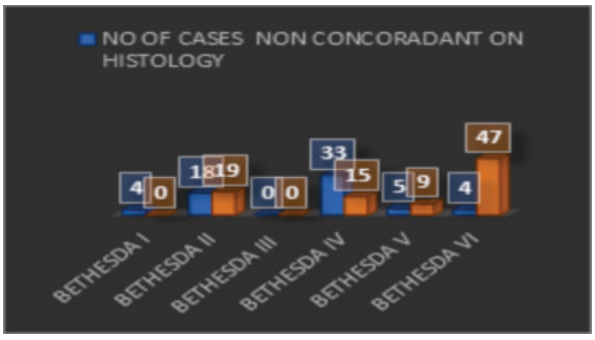

Figure 2: Cytology Diagnosis (according To Bethesda Classification) Distribution Of Cases And Correlation With Histopathology

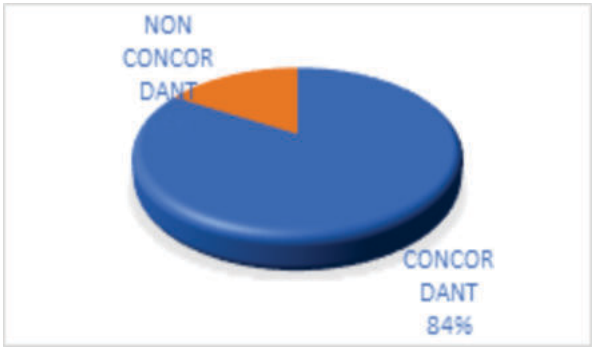

Figure 3: Distribution Of Frozen Section On The Basis Of Final Histology Diagnosis

Table 8: List Enlisting The Reason For Non Concordance Of Frozen Section With Final Diagnosis

S.NO	FROZEN SECTION DIAGNOSIS	FINAL HISTOLOGY DIAGNOSIS	POSSIBLE REASONS FOR NON CONCORDANCE
1	Poorly differentiated epithelial neoplasm	Adenomatous goitre with degenerative changes	Due to degenerative changes, morphology was not clear on frozen section
2	Metastatic carcinoma in a k/c/o Ca Breast	Papillary carcinoma thyroid	Second primary
3	Anaplastic carcinoma	Squamous cell carcinoma	Frozen section didn't show squamous differentiation;features of anaplastic carcinoma were seen
4	Oncocytoma	Minimally invasive follicular thyroid carcinoma	Capsular invasion was not seen on frozen section
5	Nodular goitre	Hashimoto's thyroiditis with goitre	Changes of hashimoto's thyroiditis were not seen in the sections studied on frozen section
6	Follicular carcinoma	Papillary carcinoma thyroid follicular variant	Nuclear features and papillary architecture was not apparent on frozen section.
7	Lymphocytic thyroiditis	Follicular variant of papillary carcinoma thyroid with lymphocytic thyroditis	A small microscopic foci of neoplasm was seen on final histopathology.relevant section were not processed on frozen section.
8	Goitrous pathology	Hashimoto's thyroiditis	Changes of hashimoto's thyroiditis were not seen in the sections studied on frozen section
9	Goitrous pathology	Papillary carcinoma thyroid	A small microscopic foci of neoplasm was seen on final histopathology.
10	Follicular lesion	Papillary carcinoma thyroid follicular variant	Nuclear features and papillary architecture was not apparent on frozen section.
11	Follicular adenoma	Papillary carcinoma thyroid follicular variant	Nuclear features and papillary architecture was not apparent on frozen section.
12	Few follicles and pseudopapillary aggregates of thyroid follicles devoid of any papillary nuclear features ?papillary carcinoma	Papillary carcinoma thyroid	Frozen section findings were confirmed on routine histopathology.
13	Infiltration of round cells? lymphoid with few epithelial cell clusters	Hashimoto's thyroiditis	Features were suspicious of hashimoto's thyroiditis which were confirmed on routine histopathology.
14	Hashimoto's thyroiditis	Adenomatous goitre with hashimoto's thyroiditis	Goitrous changes were seen on routine histopathology.

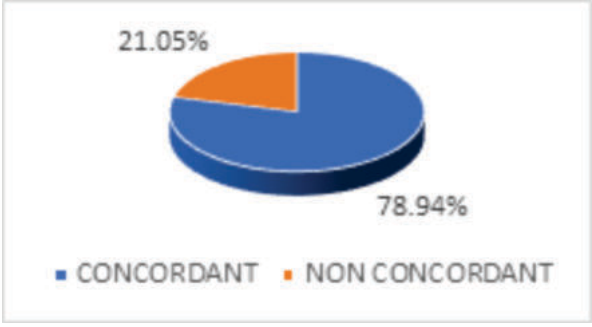

Figure 4: Correlation Of Histogical Diagnosis With Final Diagnosis After Applying Ihc

DISCUSSION

Thyroid nodule is a lesion within the thyroid gland which is distinct from its surrounding parenchyma. It may be clinically palpable or incidentally detected on imaging.

We evaluated the efficacy of prediagnostic modalities which included clinical features, biochemical markers, radiological findings on USG, CT/MRI, Thyroid Scan, Fine needle aspiration cytology findings, intraoperative frozen section findings in solitary thyroid nodule with final diagnosis obtained by histopathological examination postoperatively followed by immunohistochemistry in inconclusive cases.

Clinical And Demographic Data

In our study, patients presenting with solitary thyroid nodule fell in age group between 12 to 76 years, with the most common age group affected was 5th decade. Mean age of 44 years was noted irrespective of the nature of the lesion. **Singh P et al,** in 2000, reported a mean age incidence of solitary nodules as 47 years in their study conducted on 108 cases which fell in the age range of 12-80 years. **Rangaswamy M et al.**, studied 585 cases of solitary nodules of thyroid and age range noted was 11-70 years and mean age was 40.57 years. The mean age of incidence of SNTs in our study was in close proximity to that of the other studies.[9,10]We observed female preponderance in our cases with male: female ratio of 1:3.54. Our findings were similar to the study

conducted by **Gupta et al,** in which out of 100 patients, females (77 cases) outnumbered the males (23 cases) with male-female ratio of 1:3.4. This female preponderance is uniform in many studies as similar results were observed in other studies e.g **Singh P et al** (1:3.13),**Sangal G et al** (1:4.21), **Mandal S, et al** (1:5), **Kilpatrick et al** (1:4) and **Fahim, et al**(1:5.6). This female preponderance is due to the fact that females are more prone to thyroid disorder owing to the presence of oestrogen receptors in the thyroid tissue.[10-13]

Patients mostly presented with chief complaints of swelling neck which on examination moved with deglutination with right lobe more commonly affected than left lobe of thyroid. These findings were also noted by study conducted by **Shashikala et al**[14] was that the right lobe of thyroid (58.63%) more commonly involved than left lobe (41.37%). Similar observations were also noted in the studies of **Khadilkar et al** and **Manoj Gupta et al.**[9,11]

Patients underwent surgery at BMCHRC with most common type of surgery being total thyroidectomy (42.5%) which were comparable with results by **N.Siddhartha Chakravrathy et al**[3].

Biochemical Parameters

In our study, majority (71%) cases were euthyroid. Similar findings were noted by studies conducted by Bhamanikar et al and Handa U et al were euthyroid cases ranged from 56 to 66% .[15,16]

Radiological Findings

The use of high-resolution ultrasound is commonly preferred method for the evaluation of thyroid size and morphology.[17]

Kwak et al. reported the following US features to be significantly associated with malignancy: solid component, hypoechogenicity, marked hypoechogenicity, microlobulated or irregular margins, microcalcification, and taller-than-wide shape.[18]

In our study, the overall histopathology-radiology concordance was 68.75 % in 176 patients with available radiological findings. This value was statistically significant (p value:<0.05).

Cytology Findings

FNA has become a primary diagnostic tool for evaluating thyroid nodules and a correct cytologic diagnosis obviates unnecessary thyroid surgeries. Therefore, incidence of benign cytological lesions subjected for surgical excision are less over the period of time due to efficacy of cytology.

The overall cyto-histopathology concordance achieved in our study was 58.44%. According to **Kotasthane et al**[5] and other Indian studies, it ranged from 50% to 95% Majority of thyroid lesions on cytology were malignant accounting for 65 % and most common malignant lesion found was papillary carcinoma thyroid.

These findings were non concordant with other studies as ours is a tertiary cancer care institute, therefore our results were skewed towards malignancy. Other studies showed more prevalence of benign lesions with colloid goitre being the most common presentation and frequency of malignancy ranging from 1 to 16 %.

We have categorized cytological results according to BETHESDA system into 6 categories. This division is very helpful to clinicians in the management of patients, with specific reference to the need of thyroid surgery.

On statistical analysis, sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value were found to be 79.77%, 31.14%, 60%, 62.85% and 51.35% respectively.

The advent of ultrasound (US)-guided FNA has improved sample acquisition from patients with small thyroid nodules, which are difficult or impossible to detect on physical examination. **Borget et al.** did an assessment of the cost of FNAC as a diagnostic tool in patients with thyroid nodules and concluded that in future, routine ultrasound guidance and on-site assessment of cytopathological adequacy would help reduce costs.[19]

Pitfalls in FNAC of the thyroid as mentioned by S**haha (2000)**[20] are: Adequacy of specimens (quantitative and qualitative), Accuracy of specimens (nonhomogeneity of needle placement), accuracy of cytopathological interpretation, Cysts (difficulties with degenerative nodules), Follicular lesions (benign vs. malignant), Hurthle cell lesions (benign vs. malignant), and Lymphocytic lesions (Lymphocytic thyroiditis vs. Lymphoma)

Intraoperative Frozen Section Findings

In the present study, 85 cases underwent intraoperative frozen section.83.54% cases diagnosis on frozen was concordant with final histological diagnosis which was comparable with study conducted by **N. Guevara et al**[6].

P.carcai et al[21] study also concluded that frozen section results had good sensitivity (80%) and a high specificity (99%) It remains, however, a difficult and operator-dependent examination. However slight its contribution, FS complements FNAC in intraoperative diagnosis, optimizing individual management by enabling 1-step surgery.

Histopathological Findings

Out of 200 cases 49 were non neoplastic, 21 were benign neoplasm and 130 were malignant on final histology.Most common malignant lesion was papillary carcinoma thyroid and most common benign presentation was nodular goitre.

In this study we have encountered relatively more cases of malignancies in comparison to benign lesions which is in contradiction to the studies of **Manoj Gupta et al**[9], **Rabia Basharat et al**[22] in which benign lesions outnumbered the malignant ones.But in the studies of **Amitabh Jena et al**[23]**and Khadilkar et al**[11] malignant lesions were reported to be higher when compared to that of the benign ones.

The relatively higher incidence of malignant lesions in our study can be because of the fact that this is an oncology referral centre.

Immunohistochemical Findings

Several IHC markers have been proposed for the differentiation of benign from malignant nodules: KI-67, CK 19, GAL-3, p 53, HBME-1, etc. Immunohistochemistry was performed on 19 cases with inconclusive diagnosis. 78.94% concordance was noted between histology diagnosis and final diagnosis made after IHC.

Ize Fridrihsone et al[24] concluded that HBME-1, TROP-2, CITED1 and CK19 can be helpful in diagnostics of papillary carcinoma, while galectin-3 might serve as second-line marker. Expression of CD20 in PC has been recently reported. Distinction between FA and FC is difficult; HBME-1, p27 and galectin evaluation has been recommended. MC holds neuroendocrine differentiation.

Ioana Zosin et al[25] concluded that from the used panel of IHC markers, CK 19 showed the best value in malignant vs benign lesions. Its positivity was remarked in all variants of PTC, being able to differentiate FVPTC from FTC and PTC from papillary nodular hyperplasia. We too found similar results using Ck19.

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