

Original Article

A Study on Galectin 3 Expression in Solitary Thyroid Nodule

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Abstract

The incidence of solitary thyroid lesions are more common now a days. There is a chance of increase in malignancy rate especially in solitary nodules. Always there will be diagnostic dilemma in differentiating benign and malignant lesions. Our study mainly focused to find the expression of galectin 3 in differential diagnosis of solitary thyroid lesions in a tertiary care hospital for a period of 2 years.

Keywords: Gal 3, SNT, Thyroid lesions..

Introduction

Thyroid lesions clinically present as nodule. These nodules are solitary or multiple comprises of both Non Neoplastic and Neoplastic lesions.

A discrete swelling in an otherwise impalpable gland is termed as Solitary thyroid nodule. Solitary nodule occurs in 4-7% of adult population. It presents in 5% of population at an average age of 60 years. It is more common in females (6.4%) as compared to males (1.5%). The prevalence of malignancy in solitary cold nodule is more common, ranges from 10% to 44.7%.¹ The incidence of thyroid malignancy in SNT varies from 4.7%-18.3%.²

Solitary nodule thyroid are common in 3rd and 5th decades, the youngest patient being 15 years old and older age being 65 years. SNT is found more

common in right lobe (74%) than left lobe (26%).³

The first investigation of choice to differentiate benign and malignant is fine needle aspiration. Fine needle aspiration technique helps to prevent unwanted surgeries and therapeutic protocol.

Thyroid tumors are the most common endocrine neoplasms, originate mainly from follicular epithelial cells. The most common malignant neoplasm of thyroid is papillary carcinoma. The gold standard method of diagnosing thyroid nodules is histopathology. Diagnostic difficulties still persist in differentiating papillary hyperplasia vs encapsulated papillary carcinoma, follicular carcinoma vs follicular variant of papillary thyroid carcinoma, minimally invasive follicular carcinoma vs follicular adenoma. IHC markers may aid in accurate diagnosis of thyroid neoplasms. My study aimed to evaluate the expression of Galectin 3 in the solitary lesions of thyroid.

Galectin3 is a 30 kDa protein, encoded by LGAL S3 gene in humans, carbohydrate recognition-binding domain. Galectin 3 is a beta-galactosidase binding peptide on the cell surface glycoproteins and has been identified in nuclear and cytoplasmic compartment. Galectin 3 has been implicated in the regulation of normal cellular proliferation, apoptosis and promote angiogenesis. It helps in

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differential diagnosis of solitary encapsulated follicular lesions, especially minimally invasive follicular carcinoma.

Galectin 3 is a member of lectin family of 31 kDa molecular weight. It plays an important role in biological and pathological processes. It is a regulating component of cell cycle, cell-cell and cell matrix interaction, adhesion and migration.⁵ Galectin3 is expressed in various tissues and cell types in which it is localized in the nucleus and or cytoplasm.⁶

Aim and Objective

1. To study the Incidence and prevalence of solitary thyroid lesions
2. To study the expression of immunohistochemical marker Galectin 3 in solitary nodular lesions of thyroid
3. Assess the value of IHC markers in differential diagnosis of solitary thyroid nodules.

Materials and Methods

This is a retrospective study, includes 50 specimens surgically removed solitary thyroid lesion. The clinical details, investigations, type of surgery were collected from the medical records between the period of 2 years in a tertiary care centre. Corresponding histopathological slides were made from formalin fixed, paraffin embedded tissue of resected thyroid specimens. H&E staining was done. Histological diagnosis of each was reviewed to confirm the diagnosis. The tumors were classified according to the WHO classification and grading of the thyroid tumors. Galectin 3 IHC marker was done.

Antigen	Vendor	Species	Dilution	Positive Control
Galectin 3	Path In Situ	Mouse IgG1	Ready To Use	Papillary Thyroid Carcinoma

Scoring: galectin 3

Depends on the Intensity of staining and percentage of positive cells.

0 - <10%	Negative
>10- 25%	Weak (1+)
26 - 50%	Moderate (2+)
>50%	Strong (3+)

Statistical Analysis

Statistical analysis was performed using SPSS program version 20. Comparison of qualitative variables was done using the Chi-square test. The sensitivity and the specificity for each marker and their combination in the diagnosis were calculated.

Results

In 643 surgically resected thyroid specimens were sent for histopathological examination during the study period from June 2014-May 2016. Among the 643 thyroid specimens, 171 cases were clinically, radiologically diagnosed as solitary thyroid lesions. The incidence of solitary thyroid lesions was 13.29%

Table:1 Distribution of Thyroid Lesions

MNG			SNT		
Non Neoplastic	Neoplastic		Non Neoplastic	Neoplastic	
	Benign	Malignant		Benign	Malignant
395	20	57	127	12	32
83.69%	4.24%	12.07%	74.27%	7.01%	18.72%

Non Neoplastic Lesions

Out of 127 cases of Non Neoplastic lesions, 62 (49%) cases were Nodular colloid goiter, Adenomatous goitre / Nodular colloid goiter with adenomatous hyperplasia were 59 cases (46%), nodular colloid goiter with papillary hyperplasia were 4 cases (3%), Hashimoto's thyroiditis were 2 cases (2%)

The non neoplastic lesions were common in 3rd to 6th decade, and in females than males.

Neoplasm

Benign Neoplasm

Out of 12 benign neoplasms of SNT, Follicular adenoma were 8 cases (67%), Hurthle cell adenoma were 4 cases (33%). The peak age incidence was 20-50 years for follicular adenoma and 6th decade for Hurthle cell adenoma. Adenoma was found to common in males. Male to female ratio was 2.5:1.

Malignant Neoplasm

Out of 32 malignant neoplasms, there were 27 cases of papillary carcinoma (85%), 1 case of anaplastic carcinoma (3%), 3 cases of medullary carcinoma (9%), 1 case of insular carcinoma (3%). Papillary carcinoma constitutes about 67.5% of all thyroid neoplasms. The malignant neoplasms were

common in 3rd to 5th decade and in males.

Out of 27 cases of Papillary carcinoma of thyroid, 21 cases were conventional, 5 cases Follicular variant of papillary carcinoma, 1 case of warthin variant of papillary carcinoma. Maximum age incidence of papillary carcinoma of thyroid, during 3rd and 4th decade of life, the females are more affected. Male:female ratio was 1:8.

Medullary Carcinoma

Among the malignant neoplasm, there were 3 cases of medullary carcinoma. Male to female ratio of 2:1(2 cases were male of 17 years and 44 years. 1 case was 25 year female.)

Anaplastic Carcinoma

Only one case of anaplastic carcinoma was reported, female with age of 70 years.

Poorly Differentiated Carcinoma

Only one case of insular carcinoma was reported, female with age of 68 years.

IHC

Immunohistochemistry was done for 50 cases, of which 26 cases of papillary carcinoma, 2 cases of medullary carcinoma, 1 case of anaplastic carcinoma, 1 case of insular carcinoma, 8 cases of follicular adenoma, 4 cases of hurthle cell adenoma, 6 cases of adenomatous goiter, 1 case of adenomatous goitre with papillary hyperplasia, 1 case of adenomatous goiter with hyperplasia. Among 26 cases of papillary carcinoma, 20 cases of conventional type, 5 cases of follicular variant of papillary carcinoma, 1 case of warthin variant of papillary carcinoma

Result

Galectin 3 Expression In Papillary Carcinoma

Among the 20 cases of papillary carcinoma, conventional type 12 cases showed 3+, strong positivity (Fig. 1 & 2) and 8 cases showed moderate positivity. In follicular variant of papillary carcinoma (5 cases), galectin 3 showed strong positivity in 1 case and moderate positivity in 4 cases (fig. 3 & 4). Warthin variant was found to be negative for galectin 3 expression.

Galectin 3 was found to be positive in 86% of papillary carcinoma which is statistically significant with $P < 0.001$. (table 2)

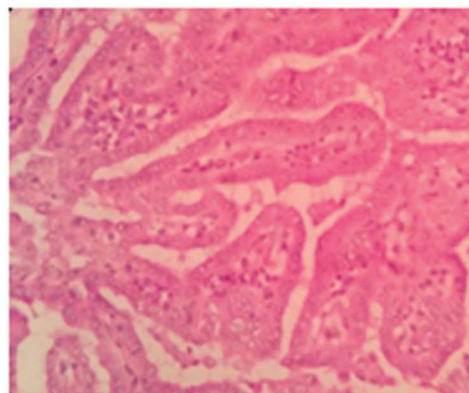


Fig. 1: Conventional type of PTC with arborizing papillary process (H & E, 100x)

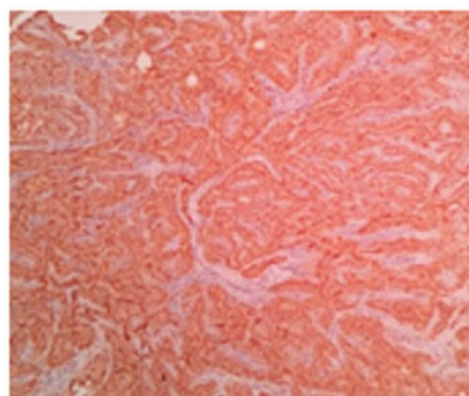


Fig. 2: Galectin3 strong immunoreactivity in conventional type of PTC (40x)

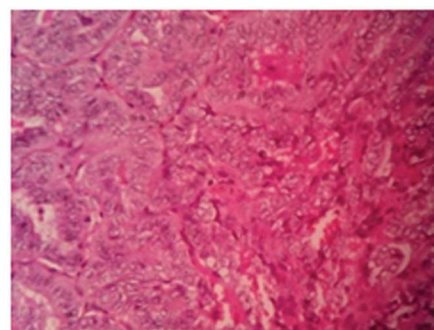


Fig. 3: Microscopy showing predominantly follicular pattern (H & E, 100X)

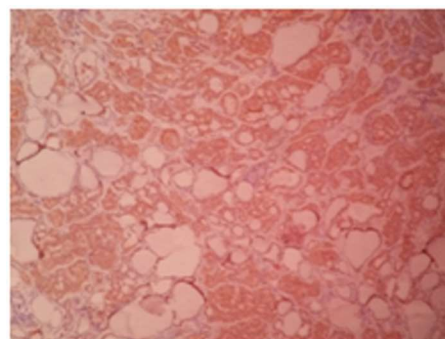
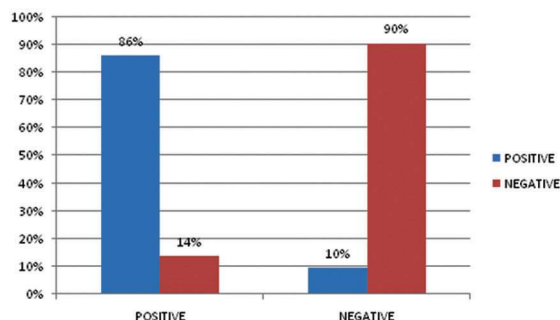


Fig. 4: Galectin 3 Moderate Positivity In Follicular Variant of Ptpc(40X)

Table: 2 Galectin 3 expression in papillary carcinoma

Papillary Carcinoma	Positive	Negative	Total	Chi Square =28.333 P<0.001
Positive	25	2	27	
Negative	4	19	23	
Total	29	21	50	



For a diagnosis of papillary carcinoma, Galectin 3 has a sensitivity of 86.21%, specificity of 90.48%. the positive predictive value of 92.5%, negative predictive value of 82.61%. The diagnostic accuracy was 88%.

Table 3: Galectin 3 in the diagnosis of papillary carcinoma.

Parameter	Percentage
Sensitivity	86.21%
Specificity	90.48%
Postive Predictive Value	92.59%
Negative Predictive Value	82.61%
Disease Prevalence	58.00%
Diagnostic Accuracy	88%
False Positivity Rate	9.52%
False Negativity Rate	13.79%

Medullary Carcinoma

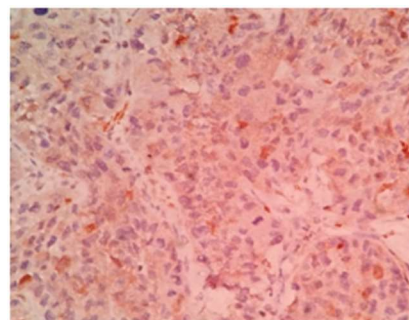
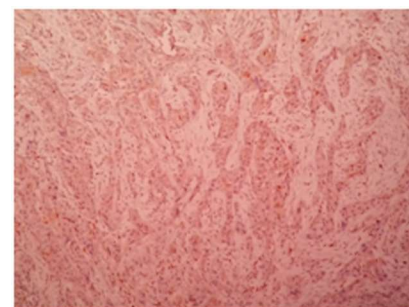
Galectin 3 expression was found to be moderate positivity in one case and weak positivity in other among the 2 cases of Medullary carcinoma, (fig. 5).

Anaplastic Carcinoma

Galectin 3 expression found to be moderate positive intensity, (fig. 6).

Insular Carcinoma

Galectin 3 was found to be negative

**Fig. 5:** Galectin 3 Moderate Immunoreactivity In Medullary Carcinoma (100X)**Fig. 6:** Galectin 3 moderate immunoreactivity in Anaplastic carcinoma(40x)

Benign Neoplasm

Follicular Adenoma

Galectin 3 expression was found in 1 of 8 cases of follicular adenoma. One case showed only weak staining, other 7 cases were negative.

Hurthle Cell Adenoma

Galectin3 was found to be weak staining 1 of 4 cases of hurthle cell adenoma. All the other 3 cases were negative for galectin 3 expression

Nonneoplastic Lesion

8 cases of non neoplastic lesions were subjected to galectin 3 expression.

Out of 8 cases, 6 cases were adenomatous goiter, 1 case of adenomatous goiter with papillary hyperplasia And 1 case of nodular colloid goiter with adenomatous hyperplasia.

Galectin 3 was negative in all the 6 cases of adenomatous goiter. In 1 case of papillary hyperplasia (fig. 7 & 8) and 1 case of adenomatous hyperplasia (fig. 9 & 10) showed moderate positivity.

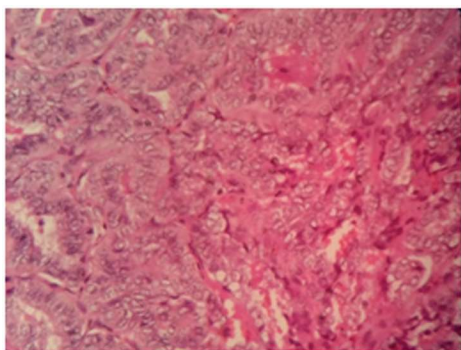


Fig. 7: Microscopic Appearance of papillary hyperplasia (H & E, 100X)

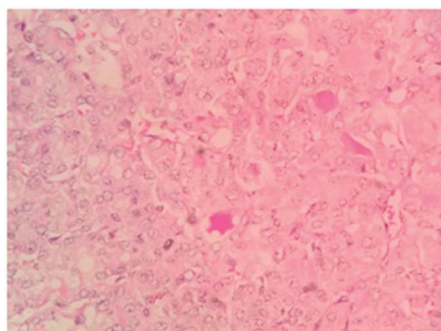


Fig.9: Microscopic appearance of adenomatous hyperplasia (H & E, 100X)

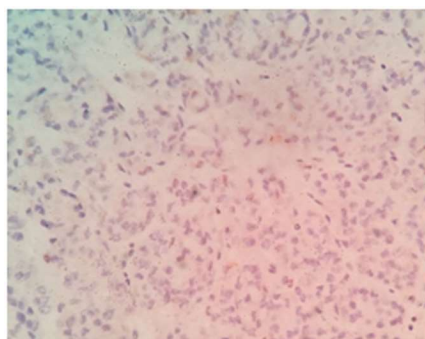


Fig. 8: Galectin 3 negativity in papillary hyperplasia (100x)

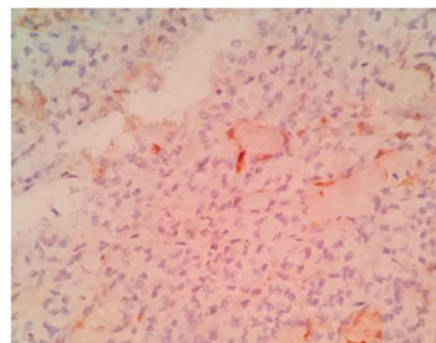


Fig. 10: Galectin 3 negativity in adenomatous hyperplasia (40x)

Table 4: Galectin 3 Expression In SNT

	Cases	%s	0	1+	2+	3+
PTC	20	40	-	-	8(40%)	12(60%)
FVPTC	5	10	-	-	4(80%)	1(20%)
Warthin	1	2	1(100%)	-	-	-
Medullary	2	4	-	1(50%)	1(50%)	-
Anaplastic	1	2	-	-	1(100%)	-
Insular	1	2	1(100%)	-	-	-
FA	8	16	7(88%)	1(12%)	-	-
HA	4	8	3(75%)	1(25%)	-	-
AG	6	12	6(100%)	-	-	-
AG+PH	1	2	1(100%)	-	-	-
NCG+AH	1	2%	1(100%)	-	-	-

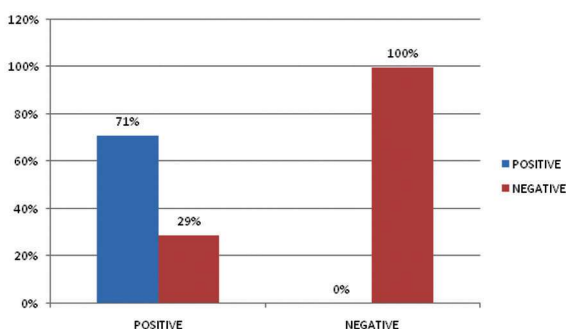
Table 5: Galectin 3 expression in all the cases of present study.

		Disease		Total	
		positive	negative		
Gal ³	positive	Count	30	0	30
		% within disease	71.40%	0.00%	60.00%
	negative	Count	12	8	20
		% within disease	28.60%	100.00%	40.00%
	Total	Count	42	8	50
		% within disease	100.00%	100.00%	100.00%

chi square =14.286*
p<0.001

Galectin 3 expression was negative in normal thyroid follicles.

Galectin 3 expression in all the cases of present study has been tabulated below. (table 5)



Sensitivity	71.43%
Specificity	100.00
Positive Predictive Value	100.00
Negative Predictive Value	40.00
Disease Prevalence	84.00
Diagnostic Accuracy	76.00
False Positivity Rate	0.00
False Negativity Rate	28.57

Discussion

The incidence of solitary thyroid nodule is common among the 4-7% of adult population. Solitary nodule were more common in females. The malignancy incidence is more common in males. The ultimate aim in evaluation of the solitary nodule is to differentiate benign hyperplasia from the true malignancy.

Currently available modalities to evaluate the solitary lesions FNAC, diagnostic imaging, serology, histopathology technique and immunohistochemistry.

Out of 643 resected thyroid specimens, 171 cases were solitary nodular lesions. In 171 cases, 127 were non neoplastic and 44 cases were neoplastic (benign-12, malignant-32). Among the 171 solitary thyroid lesions, 50 thyroid lesions were evaluated with Galectin3 to assess the potential in the diagnosis. 26 cases of papillary carcinoma, 1 case of anaplastic carcinoma, 2 cases of medullary carcinoma, 1 case of insular carcinoma, 8 cases of follicular adenoma, 3 cases of hurthle cell.

Out of 32 malignant cases, 10 cases lies between the age group of 21-30 years. Female outnumbered the males with a ratio of 7.5:1.

The percentage of benign and malignant cases in

	Psarras et al ⁷	Nagori et al ⁸	Ananthakrishnan et al ⁹	Khadhikar et al ¹⁰	Tsegaye et al ¹⁵	Chetan et al ³	Ravi kamalkumar et al ⁵	Present study
Benign	88.30%	89%	84.70%	79%	91.80%	83.50%	85.70%	81.28%
Malignant	11.70%	11%	15.30%	21%	8.20%	16.50%	14.29%	18.72%

our study is benign (81.28%) and malignant-18.72%. The present study results are similar to that of Chetan et al³ study. The other studies has been tabulated below. (Table. 6)

Malignant Neoplasm

Papillary Carcinoma

Papillary carcinoma is the common malignant neoplasm of thyroid. The incidence of papillary carcinoma was 31.25% of all malignant thyroid neoplasm. Among the SNT the incidence was 84.5%. In our study the peak age incidence of PTC in the 3rd to 5th decade (22 /32 cases)

Out of 26 cases of papillary carcinoma, 20 cases were conventional, 5 cases were follicular variant of papillary thyroid carcinoma, 1 case of warthin variant.

Galectin 3 showed strong positivity in 12 cases and 8 cases showed moderate positivity in 4 cases, strong positivity in 1 case. Warthin variant was negative .

As compared to the other studies, the present study was near to the El katebet al¹² study.

In all the literatures reviewed Galectin³ expression showed moderate to strong intensity in all the cases of papillary carcinoma. Galectin³ expression is slightly more when compared with the literature.

In present study there was a weak staining in normal thyroid. But according to Beesley¹³ study, neither CK 19 nor Galectin 3 were expressed in normal thyroid

Fonseca et al²⁰ identified that there was a weakly staining in normal thyroid.

Dockhorn – Dworniczak²¹ found,that there was a focal staining in normal thyroid.

Table 7: Comparative study of Galectin 3 expression in papillary carcinoma

	Cases	0	1+	2+	3+
Beesley ¹³	26	4	3	1	18
Gong et al ⁶	38	1	1	22	14
El kateb et al ¹²	15	0	1	1	12
Theresa et al ¹¹	78			73	
Qingbin et al ¹⁴	441	14		427	
Dunderovic et al ¹⁵	87			80	
Rita et al ¹⁶	20			1	19
Marie et al ¹⁷	12				10
Saleh et al ¹⁸	46			1	18
Hanen ¹⁹	22		1	3	18
Present study	26			12	13

Medullary Carcinoma

Anandhakrishnan et al⁹, Taegaye et al¹¹, Khadikar et al¹⁰, found that the incidence of medullary carcinoma was 5.2%, 1.5%, 2.94% respectively. Present study shows the incidence of 6.81%.

In present study Male to female ratio is 2:1. Kishore et al²² study showed the male to female ratio of 1:2.(table-8)

Table 8: Comparative study of Galectin³ expression in Medullary Carcinoma

	Cases	0	1+	2+	3+
Beesley ¹³	2	1			1
Elkateb et al ¹²	6	2		2	2
Rita et al ¹⁶	5	1		1	3
Cvejic et al ²³	20	4	7	7	2
Present study	2		1	1	

Galectin 3 expression is slightly higher than reviewed in the literature.

Anaplastic Carcinoma

Anaplastic carcinoma constitute about 5-10% of all thyroid malignancies. Anandhakrishnan et al⁹ and kishore et al²² noticed about 3.9% and 3.27% respectively.

Galectin 3 expression in present study was strongly positive staining in anaplastic carcinoma.

It was similar to the studies conducted by Cvejic et al²³ (10/10 cases), Gasbarri et al²⁴ (5/5), Inhora et al²⁵ (3/4) showed strong positivity for Galectin 3 expression.

Table 9: Galectin 3 expression in anaplastic carcinoma

	Cases	0	1+	2+	3+
Beesley ¹³	1	1	-	-	-
El kateb et al ¹²	2	-	-	2	-
Fernandez et al ²⁶	5	-	-	-	5
Prasad et al ²⁷	4	-	-	4	-
Bartolazzi et al ²⁸	20	-	-	18	-
Our study	1	-	-	1	-

Insular Carcinoma

Pilotti et al²⁹ and Volante et al³⁰ found the incidence of 4% and 6.3% respectively, mean age of 53 years and 57 years in Insular carcinoma. In our study the age was 68 year, female.

Galectin 3 was found to be negative in present

study.

Benign neoplasm

Out of 12 cases, 8 cases were follicular adenoma, 4 cases were Hurthle cell adenoma.

Incidence of benign neoplasm is less in present study when compared with the literature.

Table 10: Comparative study of Galectin 3 expression in insular carcinoma

	Cases	0	1+	2+	3+
El kateb et al ¹²	2			2	
Fernandez et al ²⁶	3			2	
Bartolazzi et al ²⁸	20			13	
Our study	1	1			

Follicular adenoma

Out of 8 cases Galectin 3 expression was found in 1/8 cases. Weak positivity in that case.

Beesley M F, K M M c Laren¹³ study showed Galectin 3 expression was found in 2/20 cases. One case showed strong positivity, it was confined to the neoplasm, but it was distributed focally.

Hurthle cell adenoma

Out of 4 cases, 2 cases showed moderate positivity, 1 case showed weak staining and the other one case was negative

Dunderovic et al¹⁵ study found that, out of 10 cases of Hurthle cell adenoma, Galectin 3 expression in 5 cases (50%).

	Cases	0	1+	2+	3+
Beesley ¹³	20	15	1	2	2
Theresa et al ¹¹	49			7	
Qingbin et al ¹⁴	54	41	13		
Dunderovic et al ¹⁵	27			6	
Carol et al ³¹	35			6	1
Saleh et al ¹⁸	46			23	
Hanan ²¹	7	3	1	3	
Our study	8	5		2	

Table-11. Galectin 3 expression in Follicular adenoma

	Cases	0	1+	2+	3+
Beesley ¹³	20	18	1		1
El kateb et al ¹²	10	6			
Theresa et al ¹¹	49		9		

Qingbin et al ¹⁴	54	28	26	
Dunderovic et al ¹⁵	27		11	
Rita et al ¹⁶	19	15	4	0
Marie et al ¹⁷	12		4	
Bose et al ³²	8	2	6	
Present study	8	7	1	

Papillary Hyperplasia

In present study of 2 cases showed negative in Galectin 3 expression

Gong et al⁶ study found that, Galectin 3 expression was weak in 1/12 cases of papillary hyperplasia. Positive rate of 16.7%

Kovacs et al³³ study on 3 cases of papillary hyperplasia, all were negative for galectin 3 expression

HBME-1 may be the useful marker in distinguishing papillary hyperplasia from papillary carcinoma³⁴.

Galectin 3 positive rate in papillary carcinoma was 16.7%.⁴¹

Table 12: Specificity and sensitivity of Galectin 3 in Neoplasm

		Sensitivity	Specificity
Wu et al ³⁵	Galectin3	81.90%	92.30%
Dunderovic et al ¹⁵	Galectin 3	88.52%	65%
Saussez et al ³⁶	Galectin 3	11%	100%
Zu x et al ³⁷	Galectin 3	86%	66%
Barut F ³⁸	Galectin 3	94%	96%
Beesley ¹³	Galectin3	85%	82%
Rossi ED et al ³⁹	Galectin3	88%	100%
Present study	Galectin3	71%	100%

Adenomatous Goitre

In present study 6 cases of adenomatous goiter were found to be negative for Galectin 3 expression

Marie et al¹⁷ study 12 cases of adenomatous goitre expressed galectin 3 in less than 75% of cells

In the Present study, Galectin3 has a sensitivity of 71.43%, specificity of 100%, PPV-100%, NPV-40%. The diagnostic accuracy was 76%. Statistically significant P < 0.001

Galectin3 staining in papillary carcinoma shows sensitivity of 86.21%, specificity of 90.48%, PPV-92.59%, NPV-82.61%, diagnostic accuracy of 88%. Both are statistically significant P value of < 0.001.

Summary and Conclusion

A total of 643 thyroid specimens, 171 cases were solitary nodule thyroid during the study period from June 2014 to May 2016 were subjected to histopathology and were classified according to the WHO classification

The incidence of solitary thyroid was 13.29% with an age incidence of 3rd to 5th decade. Females are more commonly affected, but male has the higher incidence for malignancy. Right lobe is more commonly affected

Among the solitary thyroid lesions, benign neoplasm constitutes about 81.28%, malignant lesions were 18.72%. The commonest malignant neoplasm was papillary carcinoma constitute about 84.5%.

Immunohistochemical analysis of galectin 3 was done in 50 cases of SNT. The following cases were selected for IHC. 20 cases of papillary carcinoma, variants of PTC were 5 cases, 2 cases of medullary carcinoma, 1 case of anaplastic carcinoma, 1 case of insular carcinoma. Benign cases were 8 cases of follicular adenoma, 4 cases of Hurthle cell adenoma, 6 cases of adenomatous goiter, 1 case of papillary hyperplasia and 1 case of adenomatous hyperplasia

Galectin 3 expression was also found to show moderate to strong positivity in papillary carcinoma. It was found to be negative in all the benign conditions. Galectin 3 helps in differentiating benign and malignant lesions

Galectin 3 has a sensitivity of 71.43%, specificity of 100%, ppv-100%, npv-40%. The diagnostic accuracy was 76%. Statistically significant $p < 0.001$

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