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Original Research Article

EXPRESSION OF GALECTIN-3 IN THYROID NEOPLASM

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ABSTRACT

BACKGROUND
Thyroid cancer is the most common malignant endocrine cancer worldwide. The diagnosis and distinction between benign and malignant thyroid neoplasm, especially in follicular patterned thyroid lesions is still difficult. Of the various immuno histochemical markers, Galectin-3 was most reliable in diagnosis of thyroid carcinoma.

AIM
To study diagnostic utility of Galectin-3 in thyroid neoplasm.

METHODS
This was laboratory based diagnostic study, where 92 cases of thyroid neoplasm (48-malignant and 44 benign) were analyzed for Galectin -3 expression. The Galectin- 3 staining was quantitatively evaluated as percentage of positive tumor cells and qualitatively for intensity of staining. When membrane ± cytoplasmic immunoreactivity of Galectin -3 was present in more than 10% of tumor cells was considered as positive staining.

RESULTS
Galectin 3 expression was significantly higher in thyroid cancer as compared to benign thyroid neoplasm ($p<0.001$). 33/35 cases of PTC were positive for Galectin -3 expression. Galectin -3 expression was significantly higher in FTC as compared to FA ($p <0.01$). Galectin -3 was also useful to differentiate between FVPTC and FTC ($p<0.01$) and FVPTC from other benign neoplasm (<0.01).The sensitivity, specificity, positive predictive value and negative predictive value in differentiating benign and malignant thyroid neoplasm were 83.33%, 100%,100%, 84.62% respectively.

CONCLUSION
Galectin-3 is a potential marker in differentiating benign and malignant thyroid neoplasm. It can used as sole marker for differentiating PTC and benign thyroid neoplasm and also useful to differentiate between FVPTC and FTC.

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CATEGORIES
Pathology, Oncology.
KEYWORDS: FNA, MTC, ATC, FTC, FVPTC, Galectin-3, Thyroid, Endocrine, Thyroid Neoplasm, Immunostaining.

INTRODUCTION

Thyroid cancer is the most common malignant endocrine neoplasm experienced all over the world. It is the 7th most common cancer in female and 14th in the male with estimated prevalence of 1%-5% in female and 2% of all malignancies in male respectively.[1] In India over a decade, the age standardized incidence rate of thyroid cancer has increased from 2.5 to 3.5/100,000 in women and 1.0 to 1.3/100,000 in men.[2]

The various diagnostic modalities are employed for pre surgical diagnosis of the thyroid lesions of which the FNA biopsy is the most important. Though it depicts great diagnostic accuracy, false negative results are not uncommon.[3] Also, preoperative evaluation of solitary thyroid nodule by FNA is challenging.[4] Due to such shortcomings of the diagnostic modalities; the patients with indeterminant thyroid nodule are taken up for diagnostic lobectomy, of which less than 25% patients are diagnosed as malignant.[5]

Even on histopathology the diagnosis and distinction between benign and malignant thyroid neoplasm can be difficult, especially in follicular patterned thyroid lesions.[4] The detection of focal minimal capsular invasion requires extensive sampling and examination of several deep sections. An adenomatoid nodule with extensive follicular pattern and disruption of capsule further add difficulties in the diagnosis.[4,5] Furthermore, high vascularity of thyroid gland, suboptimal fixation and tissue processing lead to altered staining of nuclei and focal clearing, adding confusion to the diagnosis.[5,6]

In the recent year several Immunohistochemistry markers including, cyclin D1, p63, Ki67, Galectin-3, Glypicans, CK19, HMWC, Ret oncoprotein have been evaluated to differentiate between benign and malignant neoplasm of thyroid.[6,7] However, there is need of cost effective single specific IHC marker rather than panel of IHC markers for diagnosis of malignant thyroid neoplasm. In the present study we evaluated expression Galectin-3 as a sole marker to differentiate benign and malignant thyroid neoplasm.

MATERIALS AND METHODS

This was a laboratory based diagnostic study conducted in histopathology section of the department of Pathology from August 2013 to July 2018. Ethical Committee Clearance was obtained (Ethics committee certificate no.: MGIMS/EC/PATH/103/2015). During this study a total of 4400 patients were diagnosed with malignancies of which 57 (1.3%) patients were diagnosed with thyroid cancer. A 103 specimens of thyroid neoplasm were received in histopathology section, of these 57 cases were malignant thyroid neoplasm and 44 were benign. Among those 57 malignant lesions, nine blocks were issued to patients as per their request. So, at the time of our study, we had total 92 cases of thyroid neoplasm (48 malignant and 44 benign tumors). Relevant clinical details were retrieved from Hospital information system and from patients records kept in Pathology department. Appropriate paraffin embedded tissue blocks of all these cases were retrieved from histopathology archives. Hematoxylin and Eosin-stained slides were carefully examined, their diagnosis was confirmed and representative sections were selected for immuno histochemical staining.

Immuno Histochemical Staining

Immuno histochemical staining was performed on 4 μ-thick, representative tissue sections. The primary antibody used was Anti -Galectin-3 protein (9C4)-Cell Marque. Galectin-3 staining was quantitatively evaluated as percentage of positive tumor cells and qualitatively

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for intensity of staining. The staining intensity was graded weak, intermediate or strong staining.[8] The percentage of tumor cell positive for staining, were graded as grade I, II, III, IV when 10-25%, 26 - 50%, 51-75% and 75- 100% of tumor cells show staining respectively. No staining or weak staining in less than 10% of the cells was scored as negative. When membrane ± cytoplasmic immunoreactivity of Galectin -3 present in more than 10% of tumor cells was considered as positive staining.[9]

Statistical Analysis

Statistical analysis was done using descriptive and inferential statistics using Chi-square test, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. The software used for the analysis was SPSS 22.0 and graph pad prism 6.0 version. P value less than 0.05 is considered as level of significance.

RESULTS

A total of 92 cases of thyroid neoplasm including 44 benign and 48 malignant neoplasms were study cases. The maximum number of cases was in the age group of 15-40 years both for benign (27/44) and malignant (23/48) tumors. 20/35 (57.14%) patients who were diagnosed with Papillary thyroid carcinoma (PTC) belonged to the age group of 15-40 years while 13 patients belonged to 41-60 years. In case of follicular thyroid carcinoma (FTC) 4/9 patients were above 60 years (Table -1).

Thyroid Neoplasm	**Number of Patients(Age in years)**			**Total Number of Patients**
	15-40	40-60	> 60 years	
	Benign thyroid neoplasm			
Follicular Adenoma	24(68.57%)	10(28.57%)	01(2.86%)	35
Hurthle cell adenoma	03(33.33%)	02(22.22%)	04(44.44%)	09
Total number of patients	27 (61.37%)	12 (27.27%)	05(11.36%)	44
Malignant thyroid neoplasm				
Follicular carcinoma of thyroid	02(22.22%)	03(33.33%)	04(44.44%)	09
Papillary carcinoma of thyroid	20(57.14%)	13(37.14%)	02(5.17%)	35
Medullary carcinoma of thyroid	01(50%)	01(50%)	-	02
Anaplastic carcinoma of thyroid		01(50%)	01(50%)	02
Total number of patients (%)	23(47.92%)	18(37.5%0	7(14.58%)	48

Table 1: Age wise distribution of thyroid neoplasm

Overall Incidence of thyroid neoplasm was higher in females (86%) with male to female ratio of 1:6. It was 1:4 for malignant thyroid neoplasm and 1: 10 for benign. Of the 35 cases of PTC, 27 patients were female. The rest of the 13 cases which included nine cases of FTC, two cases of medullary carcinoma (MTC) and one case of anaplastic carcinoma, were all female except one who diagnosed with anaplastic carcinoma (ATC). Among the 35 cases of follicular adenoma (FA) only 3 were male patients.

None of the benign tumors (0/44) were positive for Galectin-3 immunostaining (Figure -1). However, three cases of (3/35) FA showed focal (less than 10% of cells were positive for the stain) positivity.

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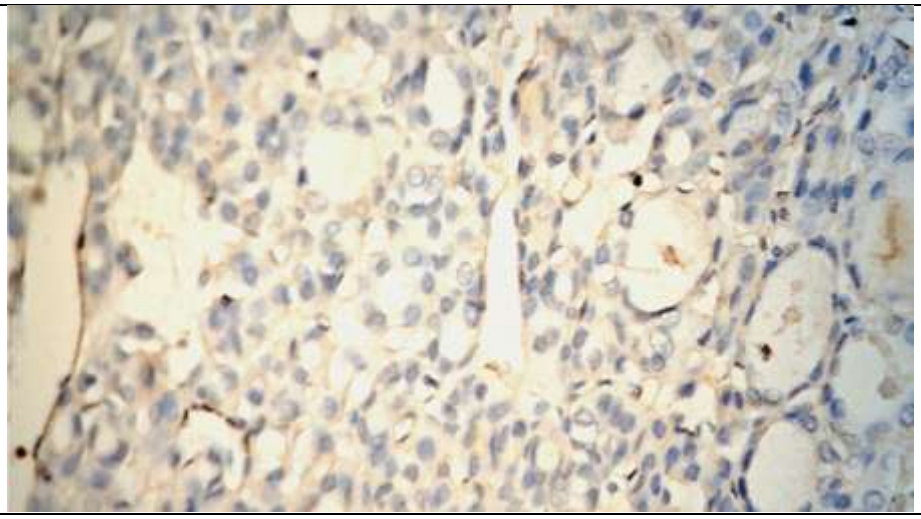

Figure 1: Photomicrograph of follicular adenoma showing no expression of Galectin-3 (100x)

In the malignant thyroid tumors, 33/ 35 cases of PTC and 7 / 9 cases of FTC showed positive expression for Galectin-3 (Figure -2). Out of the two cases of FTC that did not take up the stain, one was minimally invasive type. None of the Medullary and anaplastic thyroid carcinoma cases were positive for Galectin-3 (Table -2)

Sr. No	**Thyroid Neoplasm**	**Galectin -3 Expression**					**Total**
		Negative	Grade –(% of tumor cells positive)				
			I (11-25%)	II (26-50%)	III (51-75%)	IV (76-100%)	
1	Follicular Adenoma	35	-	-	-	-	35
2	Hurthle cell adenoma	09	-	-	-	-	9
3	Follicular carcinoma	2	-	4	3	-	9
4	Papillary carcinoma	02	2	5	8	18	35
	Classical variant of PTC	0	0	02	07	13	22
	Follicular variant of PTC	02	02	03	01	02	10
	Encapsulated variant of PTC	0	0	0	0	02	02
	Oncocytic variant of PTC	0	0	0	0	01	01
5	Medullary carcinoma	02	-	-	-	-	02
6	Anaplastic carcinoma	02	-	-	-	-	02
	Total	52	04	14	19	36	92

Table 2: Percentage of tumor cells positive for galectin-3 expression

Of the 33 cases PTC, 26 (78.79%) cases showed grade III / IV positivity (Figure -3). In five cases the stain was limited to 26-50% of the cells (grade II). While in two cases galectin-3 positivity was of grade I and these cases were diagnosed as follicular variant of papillary carcinoma (FVPTC) one being encapsulated variant. Among the seven FTC cases that were positive for galectin-3 expression, three cases showed grade IV positivity.

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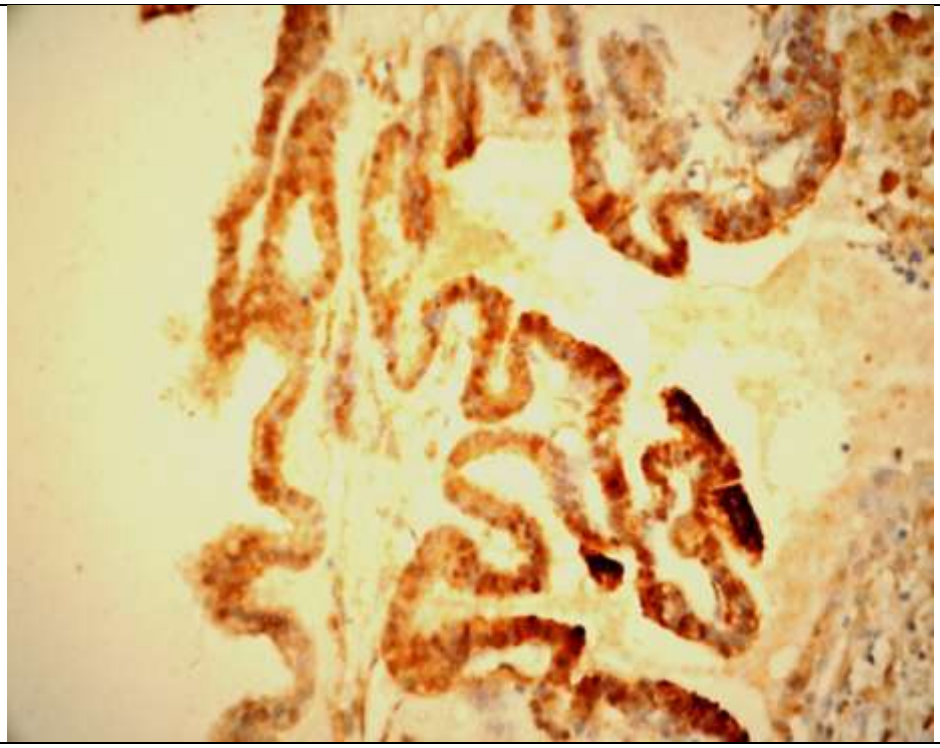

Figure 2: Photomicrograph of papillary carcinoma of thyroid (76 -100% of the tumor cells were positive for Galectin -3 expression, Grade – IV (strong intensity) (400x)

On evaluating the intensity of staining, 31/33(93.94%) cases of PTC showed moderate to strong positivity. Whereas all the seven cases of FTC showed moderate intensity of staining (Table -3). In subtypes of PTC, 20/22 classical subtypes and six of the eight cases of FVPTC showed grade II expression. While both the encapsulated and oncocytic variant showed grade IV positivity and strong intensity of staining of Galectin-3 (Figure -4).

Sr. No	**Thyroid Neoplasm**	**Galectin -3 expression**				**Total**
		Neg	**Positive (intensity of staining) Weak**	**Moderate**	**Strong**	
1	Follicular Adenoma	35	-	-	-	35
2	Hurthle cell adenoma	09	-	-	-	9
3	Follicular carcinoma	2	-	7	-	9
4	Papillary carcinoma	02	2	12	19	35
	Classical variant of PTC	0	1	07	14	22
	Follicular variant of PTC	02	01	05	02	10
	Encapsulated variant of PTC	0	0	0	02	02
	Oncocytic variant of PTC	0	0	0	01	01
5	Medullary carcinoma	02	-	-	-	02
6	Anaplastic carcinoma	02	-	-	-	02
	Total	92	04	14	19	92

Table 3: Intensity of Galectin -3 expression of thyroid tumors

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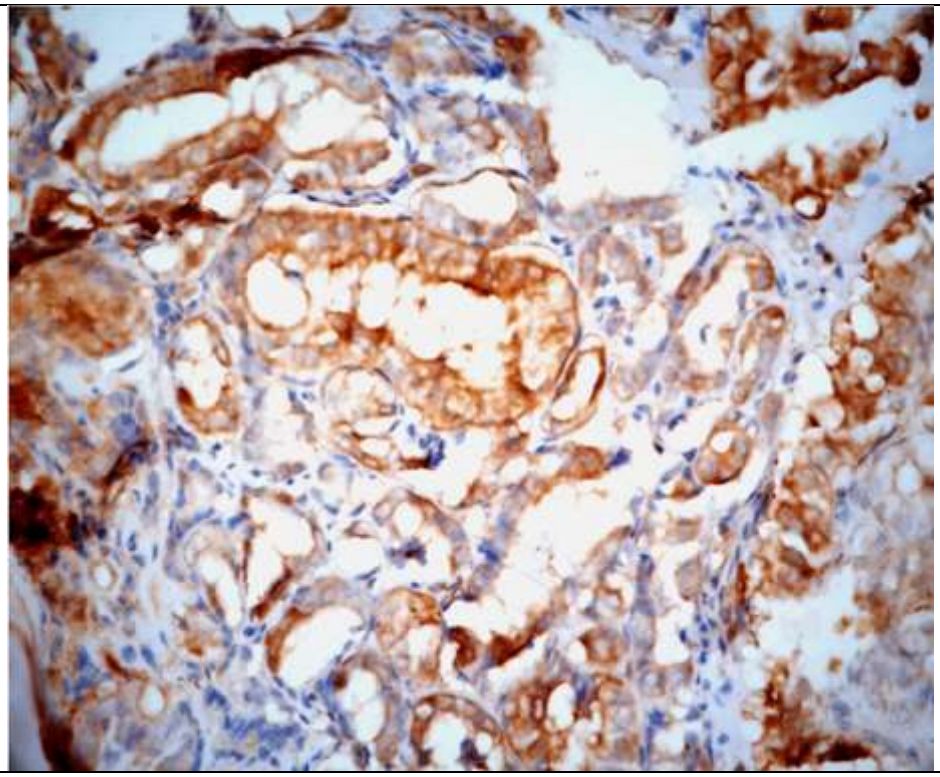

Figure 3: Photomicrograph of follicular variant of papillary carcinoma of thyroid showing Galectin -3 expression, Grade – IV (strong intensity) (400x)

The sensitivity and specificity of Galectin-3 in diagnosing malignant thyroid neoplasm were 83.33% and 100% respectively (p=0.0001). The positive predictive value (PPV) and negative predictive value (NPV) were 100% and 83.33% respectively. While the diagnostic accuracy was found to be 91.3%.

The expression of Galectin-3 in FTC compared to FA was found to be statistically significant (p=0.0001), with diagnostic accuracy of 95.59%. Also, Galectin- 3 immunostaining in differentiating FVPTC vs. follicular adenoma and FVPTC from other benign neoplasm of thyroid was statistically significant (p=0.0001).

DISCUSSION

The incidence of thyroid malignancy is rising worldwide over last three decades.[10] This is mainly because of widely available sensitive detection method like ultrasound guided FNA which can detect subclinical thyroid cancer.[11] At the same time thyroid cancer mortality rate has also increased by 50% worldwide with the highest mortality rate compared to other endocrine cancers.[1]

The differentiation between benign and malignant thyroid lesion is still difficult at all the level of radiology, cytology and histopathology.[12] On the contrary, over diagnosis of malignancy can lead to surgical intervention that can influence quality of life by its complications such as vocal cord paresis due to resection of recurrent laryngeal nerve, hyperparathyroidism and hypothyroidism as well as the psychological and potential financial impacts of a cancer diagnosis.[11,12]

Although in most of the thyroid lesion routine stains are sufficient for correct diagnosis and classification, ancillary methods like Immunohistochemistry are necessary in tumors with controversial morphology, doubtful invasion and questionable nuclear features.[13]

In thyroid neoplasm several antigen groups have been explored including membrane

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protein HMBE-1, CK- 19, TROP-2, glypicans, galectins etc.[12] Among the various markers studied Galectins belonging to the family of beta galactoside binding lectin appears as sole novel marker for thyroid neoplasm.[12] Galectins are located in cell nuclei, cytoplasm or extracellular space. The abnormal expression of galectin-3 blocks the apoptosis, allowing accumulation of DNA mutations and molecular alterations, which in turn promote the development of thyroid cancer.[14]

Further Galectin 3 has anti-apoptotic role due to structural homology to Bcl2 protein. However, this action is site dependent and cytoplasmic location favours the antiapoptotic action.[15] In Our study most of the neoplastic cells that were positive for Galectin-3 showed a pan cytoplasmic distribution which was similar to the findings of Sumana et al,[4] and Borkar et al.[6]

In the present study, during a study period (2012-2017), 436 patients were operated for thyroid lesion of which 57 (13.07%) cases turned out to be malignant neoplasm. However, Doddi, et al,[5] reported 25% of resected thyroid lesions as malignant.

In this study, none of the 44 benign thyroid tumors were positive for Galectin-3 expression. Booma K, et al[16] and Weinberger, et al[17] also found 100% negativity of Galectin-3 expression in FA. However, Sumana, et al[4] and Borkar, et al[6] observed that 3/20 cases and 3/10 of benign thyroid neoplasm were positive for Galectin-3 expression respectively.

We found three cases of FA that were focally positive (less than 10% of tumor cells) and localization of these cells was just beneath the capsule. This focal and subcapsular localization of Galectin-3 expression can be considered as potential FTC whose vascular and capsular invasion could not be demonstrated on routine histological section. Nevertheless, this FA with abnormal expression of galectin-3 should be reassessed and subjected to molecular studies for confirmation of malignant transformation at genetic levels.[18]

In contrast, Galectin-3 expression in thyroid cancer ranged from70-100% in different studies in the literature.[15] In our study it was 83% (40/48), similar to the results of Sumana et al,[4] (87%) and Borkar, et al[6] (91%). In PTC 33/35 (94.29%) cases were positive for Galectin-3 expression. In most of the variant of PTC galectin-3 expressions was 100% except for FVPTC in which it was 80% in the present study. Dunđerović D, et al[8] and Bartolazzi A, et al[14] reported Galectin-3 expression in 97% and 92% cases of PTC respectively.

In FVPTC, Galectin-3 expression ranged from 33% to 100%, with the majority of studies reporting positivity in more than 75% of cases.[15] In papillary micro carcinoma (PMC), Cvejic, et al[19] reportedGalectin-3 expression in 81% cases, suggesting that alteration of Gal-3 expression is an early event in PTC progression and thus involved in PTC tumorigenesis. However, in present study there was no case of papillary micro carcinoma.

The expression of Galectin-3 in FTC is comparatively low it was 77.7% (7/9) in present study. Bartolazzi, et al,[14] identified Galectin-3 expression in 95% (54/57) of FTC whereas it was just 50% (1/2) in Sumana, et al study.[4] We reported two cases of FTC negative for Galectin-3 expression. We could not find any acceptable explanation for this; however, Kovacs et al,[20] suggested that, when differentiation between FA and FTC is difficult, than cytokeratin 19 along with galectin-3 can be employed.

In our study none of the Medullary and Anaplastic carcinoma showed Galectin-3 expression. Most of the study showed variable expression of Galectin -3 in medullary carcinoma.[15] As the MTC derived from parafollicular C cells, expression of Galectin-3 is inconsistent and variable.[15] However, in ATC Galectin-3 expression was reported in the majority of cases (75% to 100%).[15] Increasing evidence suggests that differentiated thyroid cancer can undergo transformation into ATC, leading to up-regulation of Galectin -3 in ATC.[21]

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The moderate to strong staining intensity (Grade III/ IV) of galectin-3 was noted 94.45% cases of classical subtype of PTC and 87.5% of FVPTC. Both oncocytic and encapsulated variant of PTC showed strong expression of Galectin-3. Our findings of strong intensity of Galectin -3 expression in classical PTC was similar to Barut et al[9] who reported 93.75% of classical subtype of PTC showed moderate to strong intensity.

The overall sensitivity of Galectin-3 to differentiate between benign and malignant thyroid neoplasm was 83.33% in the present study. The sensitivity was 100%, while the positive predictive value and negative predictive value was 100% and 81% respectively. The diagnostic accuracy of this marker was 91.30% in our study. Our findings correlated well with Bartolazzi, et al[14] and Sumana, et al[4] who also noted sensitivity 86.67%, specificity 85% and diagnostic accuracy of 86%. While Rydlova, et al[22] reported low diagnostic accuracy of Galectin-3 as 69.4% (Table -4).

	Total no. of /% of positive cases	**Total no. of malignant neoplasm/ % of positive cases**	**Total no. of benign neoplasm /% of positive cases**	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**Diagnostic accuracy**
Bartolazzi et al[14]	618	331	132	92.75 %	97.56 %	97.77 %	92.11 %	94.98 %
	50.81%	92.75 %	3.79 %					
Kovacs et al[20]	91	72	19	88.89%	78.18%	72.73%	91.49%	82.42 %
	48.35%	88.89%	21.05%					
Rydlova et al[22]	36	24	12	70.83 %	66.67 %	80.95 %	53.33 %	69.44 %
	58.33%	70.83 %	33.55%					
Sumana et al[4]	50	30	20	86.67%	85 %	89.66 %	80.95 %	86 %
	58%	86.67 %	15 %					
Dunderrovic et al[8]	201	122	79	88.52 %	64.56%	79.41 %	78.46 %	79.5 %
	67.66%	88.52 %	35.45 %					
Present study	92	48	44	83.33 %	100 %	100%	79.5 %	91.3 %
	43.88%	83.33 %	0 %					

Table 4 -Comparing the diagnostic utility of Galectin-3 in thyroid neoplasm in various studies with the present study

We observed significant difference ($p<0.001$) in expression of Galectin-3 between benign and malignant thyroid neoplasm. Most of the studies showed similar findings (4, 6, 8).Similarly, differential Galectin-3 expression in benign thyroid neoplasm i.e., FA and FTC were significant ($p<0.001$). Galectin -3 was also useful to differentiate between FVPTC and FTC ($p<0.01$) and FVPTC from other benign neoplasm (<0.01). Dunderovic, et al[8] also reported significantly higher expression of Galectin-3 in FTC vs. FA (p value <0.05) and FVPTC vs. FA (p value < 0.01).

However, there are few limitations of our study first our sample size is small and distribution of cases was unequal. There were only two cases each of MC and ATC and only few variants of PTC were included. Thus, studies with large sample size pertaining to follicular patterned thyroid lesions are required.

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CONCLUSIONS

Galectin-3 is useful as potential marker in differentiating benign and malignant thyroid lesions. Though its overall expression is somewhat less in follicular patterned neoplastic lesions of thyroid (Follicular carcinoma and follicular variant of papillary carcinoma) as compared to papillary carcinoma and few cases of follicular carcinoma were negative also. However, it still serves as promising marker in differentiating benign and malignant thyroid neoplasm, particularly as sole marker in differentiating papillary carcinoma and benign thyroid neoplasm.

Additional Information

Disclosures

Human Subject

Human tissue was used and Institutional Ethical committee approval was taken prior to commencement of study.

Conflicts of interest

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info

All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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