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Original Research Article

# Diagnostic value of Galectin-3 expression in papillary thyroid carcinoma and its variants

**Chumila Thinely Bhutia[1], Ajay Kr Singh[2], Raj Mehrotra[3], Madhu Mati Goel[4], Malti Kumari[5]**
[1]Assistant Prof., Deptt of Pathology, Sikkim Manipal Institute of Medical sciences, Gangtok, Sikkim, India.
[2]Associate Prof., Deptt of Pathology, KGMU, Lucknow, UP, India
[3]Prof. (Retd.) Deptt of Pathology, KGMU, Lucknow, UP, India
[4]Professor, Deptt of Pathology, KGMU, Lucknow, UP, India
[5]Associate Prof., Deptt of Pathology, KGMU, Lucknow, UP, India

***Corresponding author**
Dr. Chumila Thinley Bhutia
Email: drchumila2012@gmail.com

**Abstract:** Galectin-3 is a member of beta-galectoside binding protein family and function as modulator of cell growth through galectoside-protein correlated with the occurance and diagnostic valu of papillary thyroid carcinoma (PTC). The study performed in 67 known histopathological cases of institution including neoplastic and non-neoplastic cases of thyroid. The immunohistochemistry perfomed and result showed that, cases of papillary thyroid carcinoma in spite of any variant give 2 to 3+ positive for majority of case. The other neoplastic and non-neoplastic cases which give negative or lesser positive for galectin-3 .The author conclude that galectin-3 could be a valuable antibody for diagnosis of papillary thyroid carcinoma and a potential immunomarker, in making a preoperative distinction between PTC and non-PTC patients. In addition galectin-3 may provide more significant contributions in distinguishing PTC with or without lymph node metastasis.
**Keywords:** Galectin-3, immunohistochemisty, papillary thyroid carcinoma

## INTRODUCTION

Thyroid nodules are extremely common in the general population and usually discovered during routine medical check-up. However, the widely used of new techniques like ultrasound and fine needle aspiration cytology has led the discovery of an infra-clinical reservoir of thyroid nodules in 20 to 76 % of population [1]. In which most of the thyroid nodule are benign, while thyroid cancer represents only 2-4%. Out of which papillary thyroid carcinoma is by far the most common type of thyroid malignancy (85%) and it's characterized by distinctive nuclear features [2]. The diagnosis of benign lesion, such as hyperplastic nodules, colloid nodules and auto-immune disease like thyroiditis, can be cytologically established [3]. However, to distinguish between malignant and benign lesion in some instance like papillary and microfollicular pattern lesion is challenging in cytology and even in histopathology. Exclusive follicular pattern in adenomatoid nodule and disruption of capsule in adenomas create difficulties in diagnosis by histopathology [4]. However papillary carcinomas are prone to diagnostic discrepancies among pathologists [5]. In this regard, the diagnostic approach to these tumours should include IHC (immunohistochemistry) markers that can aid the better assessment of morphologic details. There are several studies have shown that immunohistochemical may provide additional support in the evaluation of diagnosis of thyroid discripancies lesions. Many IHC markers including Galectin-3 have been evaluated in this regard. Galectin-3 is a beta-galactosyl-binding lectin that is normally expressed in macropahges, mast cells, langerhans cells and various malignant cells, including thyroid cells [6]. It has been suggested that galectin-3 could also play a role in the malignant transformation of thyroid cells and many studies have shown that PTC (papillary thyroid carcinoma) cases are characterized by strong, intense Gal-3 expression [7-10]. In this study we aimed to determine the diagnostic valu of galectin-3 in papillary thyroid carcinoma and its variants.

## MATERIALS AND METHODS

### Inclusion Criteria

Histopathologically diagnosed non-neoplastic and neoplastic (benign and malignant) cases of thyroid

lesions were taken. Positive tissue control (Carcinoma Prostate) and negative tissue control (Normal thyroid tissue) were taken.

**Exclusion Criteria:**
1.Inadequate biopsies.2.Tissue samples with inadequate material or with necrosis hemorrhage.

**Histopathology**

Histopathologically diagnosed non-neoplastic and neoplastic (benign and malignant) cases of thyroid lesions were taken from archives of department of pathology of King George,s Medical university, Lucknow. These surgical specimen were fixed in 10% formalin, routinely processed, paraffine-embedded and the sections were stained with hematoxylin and eosine stain. Study duration was two year ( retrospectiveand prospective). The histopathological evaluations were performed and final diagnosis of the tumour histotype and subtype was made in accordance with world health organization [11]. For statistical purpose the histopathologic diagnosis was considered the gold standard. The diagnosis of the neoplastic lesion were distributed as follows: 30 PTC (included 9 classical variant, 18 follicular, 02 solid variant, 01 micropapillary), 10 FTC, 14 benign neoplasm (including follicular adenoma and hurthle cell adenoma) and 13 non neoplastic (includes hyperplasia and inflammatory lesions) cases (**Table-1**).

**Table-1: Study Sample**

| Thyroid lesions | | No.of cases |
|---|---|---|
| Nonneoplastic | | |
| Inflammatory lesions | : Hashimoto's Thyroiditis | 2 |
| | Lymphocytic thyroiditis | 2 |
| Reidel's Thyroiditis | | 1 |
| Hyperplasia | : Colloid Nodule /goiter | 5 |
| Multinodular Goiter | | 2 |
| | Adenomatous Colloid Goiter | 1 |
| Neoplastic | | |
| Benign | : Follicular adenoma | 12 |
| | Hurthle cell adenoma | 2 |
| Malignant | : Papillary Thyroid Carcinoma | |
| | •Classical type | 9 |
| | •Follicular variant | 18 |
| | •Solid variant | 2 |
| | •Micropapillary Carcinoma | 1 |
| | Follicular Thyroid Carcinoma | 10 |
| | Total | 67 |

**Immunohistochemistry** [12] (Standard protocols were used)

Immunohistochemical evaluation using Streptavidin Biotin immunoperoxidase method was done. Staining and evaluation using specific monoclonal antibody to Gal-3 was done as per following protocol:

- Deparaffinization
- Unmasking of antigenic sites by microwave antigen retrieval method
- Peroxidase Treatment
- Primary Antibody (Novocastra™ Lyophilized Mouse Monoclonal Antibody Galectin-3, product code: NCL-GAL-3; 1:100 dilution)- Slides were wiped off excess buffer and incubated overnight with primary antibody (monoclonal antibody for Gal -3)
- Biotinylated link antibody
- Enzyme Conjugate- Enzyme conjugate (Streptavidin horse radish peroxidase) was applied for 30 minutes.

- Substrate Chromogen Solution- Concentrated diaminobenzidine solution (DAB) was diluted with substrate buffer (500 μL of substrate buffer + 2 drops of DAB). Diluted DAB solution was added to smears for 5-10 minutes followed by Tris buffer washing.
- Counterstain and Mounting- Presence of brown coloured end product at the site of target antigen was indicative of positive reactivity. Positive tissue control (Carcinoma Prostate) and negative tissue control (Normal thyroid tissue) were taken. For negative reagent control, % non-immune serum was used in place of primary antibody; the rest of steps are the same as for the positive control.

**Immunohistochemical scoring of Gal-3**

Staining pattern of Gal -3 protein detected in many tissues and cell types, localized in the cytoplasm and / the nucleus, on the cell surface, or in the extracellular environment.

**Interpretation of Gal-3 staining and corelation with histopathology features**

**I**nterpretation was done according to the criteria defined by Fabio Orlandi *et al*. in 1998 [13] and Katie B Weber *et al*.in 2004 [14] in a research paper titled (Gal-3 is a presurgical marker in Human Thyroid Carcinoma and The use of a combination of Gal-3 and Thyroid peroxidase for the diagnosis and prognosis of Thyroid Cancer respectively.

**Qualitative criteria**

| Score | Pattern |
|---|---|
| 0 | No staining |
| 1 | Light / weak staining |
| 2 | Moderate staining |
| 3 | Intense staining |

**Quantitative criteria**

| Score ∗ | Pattern |
|---|---|
| +++ | >60% of neoplastic cells in cytoplasm / nucleus/ both (cytoplasm and nucleus) /extracellular matrix |
| ++ | 30 - 60% of neoplastic cells in cytoplasm /nucleus/ both (cytoplasm and nucleus) /extracellular matrix |
| + | <30% of neoplastic cells in cytoplasm /nucleus/ both (cytoplasm and nucleus) /extracellular matrix |
| - | No reactivity |

∗In our study, only those cases have been taken who had scoring grade ++ and +++

**Statistical Tools Employed**

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) statistical Analysis Software. The values were represented in Number (%) and Mean±SD. The Statistical formulas were used ie. Chi square test and Interobserver differences (Kappa) used. P <0.05 was considered statistically Significant And κ=0.20-0.40 is considered as Fair agreement.

**RESULTS**

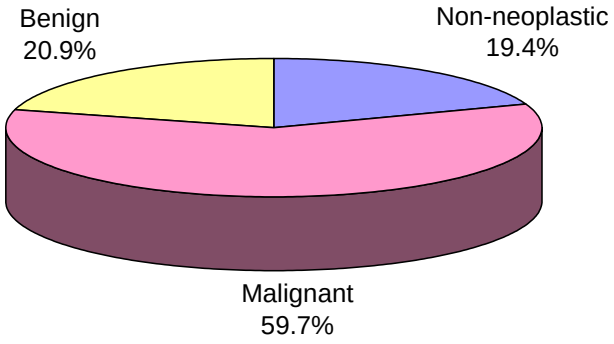
The present study was carried out at Department of Pathology, King George,s Medical University, Lucknow with an aim to evaluate Galectin-3 as ancillary test in diagnosis of thyroid Papillary carcinoma and correlation of Gal-3 with the histopathology of Thyroid neoplasia.

For this purpose a total of 67 histopathologically diagnosed neoplastic (benign and malignant) and non-neoplastic cases of thyroid lesions were evaluated.

Distribution of specimen according to the final diagnosis has been shown in Table 4 below

**Table-2: Distribution of Specimen according to the Final Diagnosis (n=67)**

| S.No. | Final Diagnosis | No. of cases | Percentage |
|---|---|---|---|
| 1. | Neoplastic | 54 | 80.6 |
| | Malignant | 40 | 59.7 |
| | Benign | 14 | 20.9 |
| 2. | Non-neoplastic | 13 | 19.4 |

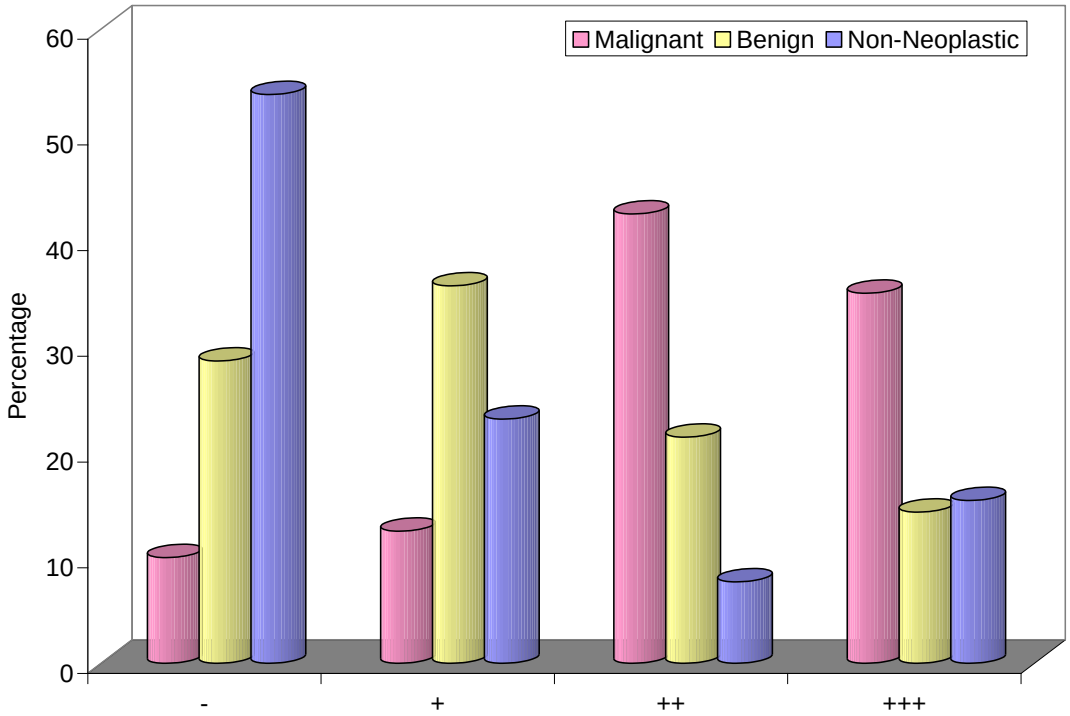



Majority of cases (n=54; 80.6%) were finally diagnosed as neoplastic. There were a total of 13 (19.4%) cases which were diagnosed as non-neoplastic. Among cases diagnosed as neoplastic – a total of 40 (74.1%) were malignant and 14 (25.9%) were benign whereas among those 13 cases diagnosed as non-neoplastic, a total of 8 (61.5%) were hyperplastic and remaining 5 (38.5%) were inflammatory lesions.

Maximum number of patients in non-neoplastic group was aged between 31-40 years whereas maximum numbers of malignant cases were aged between 41 to 50 years and maximum numbers of benign cases were aged between 21-30 years.

**Intensity and Diagnosis**

For scoring, it was observed that as compared to non-neoplastic, neoplastic lesions had higher scores (p=0.012). Similarly, more than three-fourth (77.5%) of malignant cases had scores ++ and +++ as compared to only 35.7% of benign and 23.1% of non-neoplastic cases, thus malignant cases showed a statistically significant difference from both benign as well as non-neoplastic lesions (p=0.042 and 0.002). With increasing intensity, a significant association with malignancy was evident. There were 31/40 (77.5%) of malignant cases, 5/14(35.7%) of benign cases and 3/13(23.1%) of non-neoplastic cases accorded with intensity 2 and 3.




**Scoring and Diagnosis**

**Table-3: Evaluation of IHC Gal-3 expression in thyroid neoplasm⁎**

| Diagnosis by Histopathology | Total No. | No. +ve of Gal-3 (%) | "p" value | Sens % | Spec % |
|---|---|---|---|---|---|
| A. Malignant Neoplasm | 40 | 31 (77.5%) | <0.001 | 77.5 | 69.2 |
| 1. Papillary thyroid carcinoma | | | | | |
| Classical | 09 | 07 (77.7%) | 0.201 | 77.8 | 43.1 |
| Follicular variant | 18 | 13 (72.2%) | 0.159 | 72.2 | 44.9 |
| Solid variant | 02 | 02 (100%) | 0.224 | 100.0 | 39.7 |
| Micropapillary | 01 | 01 (100%) | 0.393 | 100 | 40.9 |
| 2. Follicular thyroid carcinoma | 10 | 08 (80%) | 0.130 | 80 | 43.9 |
| B. Benign Neoplasm (Follicular adenoma and Hurthle Cell adenoma) | 14 | 05 (35.7%) | 0.055 | 35.7 | 34.0 |
| C. Non-neoplastic (Hyperplasia and inflammatory lesions) | 13 | 03 (23.1%) | 0.004 | 23.1 | 31.5 |

*Only those cases have been taken as positive who had scoring grade ++ or +++.

Gal-3 expression was identified in 76.7% (23/30) of PTC cases , and by histological subtypes of PTC Gal-3 expression was identified in classical, follicular variant, solid variant and micropapillary as 77.7%(7/9), 72.2% (13/18), 100%(2/2) and 100%(1/1) respectively .FTC 80% (8/10) cases showed positivity for Gal-3. Overall, Galectin-3 expression evaluated utilizing IHC techniques for thyroid malignancy shows sensitivity (77.5%). In benign and non-neoplastic lesion, Gal-3 expression was observed as 35.7% (5/14) and 23.1% (3/13) respectively.

**Evaluation of IHC Gal-3 Expression in Staining Pattern of Thyroid lesions**

Among malignancies, cytoplasmic Gal-3 expression was observed in 8/9 (88.8%) of classical PTC, 14/18 (77.8%) of FVPTC, and 1/1(100%) of MPC. FTC showed 5/10(50%) Gal-3 expression, both (nuclear+cytoplasm) Gal-3 expression was observed in 2/11(11.1%) of FVPTC, 2/2 (100%) of solid variant PTC, and 3/10(30%) of FTC. Extracellular matrix Gal-3 expression was observed in1/9(11.1%) of classical PTC and 1/18(9.09%) of FVPTC. No nuclear staining was observed. In Benign neoplasm and Non neoplastic lesions, cytoplasmic Gal-3 expression was observed in 7/14 (70%) and 6/13(46.2%) respectively. Both (nuclear+cytoplasm) Gal-3 expression was observed in 3/14 (30%) of benign neoplasm and extracellular matrix Gal-3 expression was observed in 2/13(15.4%) of non-neoplastic lesions. No nuclear staining was observed.

**Table-4: Evaluation of IHC Gal-3 Expression in Staining Pattern of Thyroid lesions**

| **Diagnosis by Histopathology** | **Total (n)** | **Cyto-plasm** | **Nucleus** | **Both (N+C)** | **ECM** |
|---|---|---|---|---|---|
| A. Malignant Neoplasm | 40 | | | | |
| 1. Papillary thyroid carcinoma | | | | | |
| Classical | 09 | 08 (88.8%) | - | - | 01 (11.1%) |
| Follicular variant | 18 | 14 (77.8%) | - | 02 (11.1%) | 1 (9.09%) |
| Solid variant | 02 | - | - | 02 (100%) | - |
| Micropapillary | 01 | 01 (100%) | - | - | - |
| 2. Follicular thyroid carcinoma | 10 | 05 (50%) | - | 03 (30%) | - |
| B. Benign Neoplasm (Follicular adenoma, Hurthle cell adenoma) | 14 | 07 (50%) | - | 03 (21.4%) | - |
| C. Non-neoplastic (Hyperplasia and inflammatory lesions) | 13 | 06 (46.2%) | - | - | 02 (15.4%) |

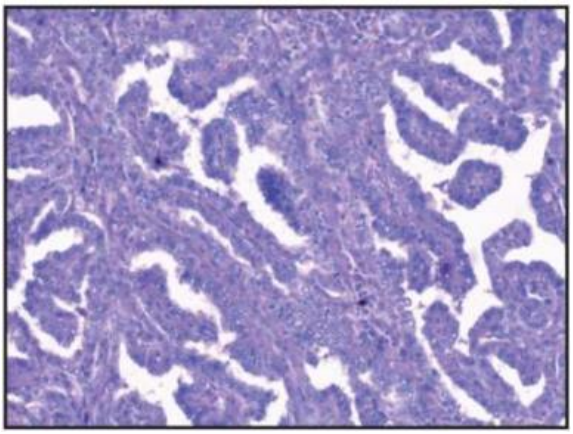


**Fig-1: Microphotograph showing classical papillary thyroid carcinoma (H&E, 20X)**

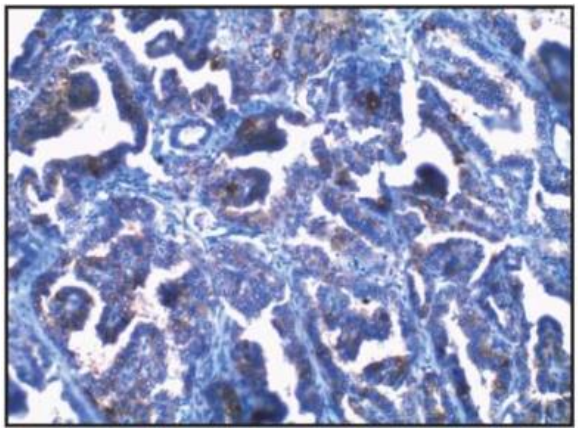


**Fig-2: Microphotograph showing gal-3 expression in classical papillary thyroid carcinoma (IHC, 20X). Score - +++, Intensity – 2, Pattern – Cytoplasm**

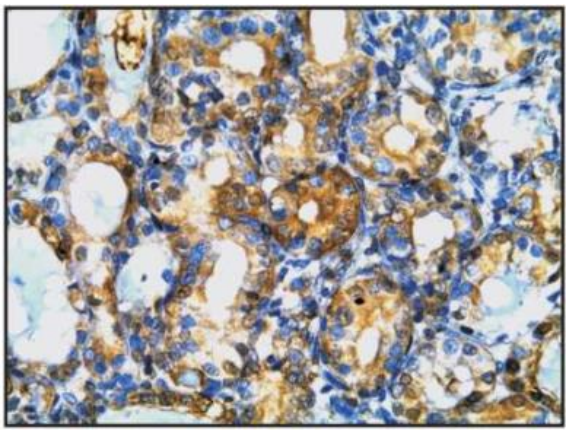


**Fig-3: Microphotograph showing gal-3 expression in follicular variant of papillary thyroid carcinoma (FVPTC) (IHC 20x)**

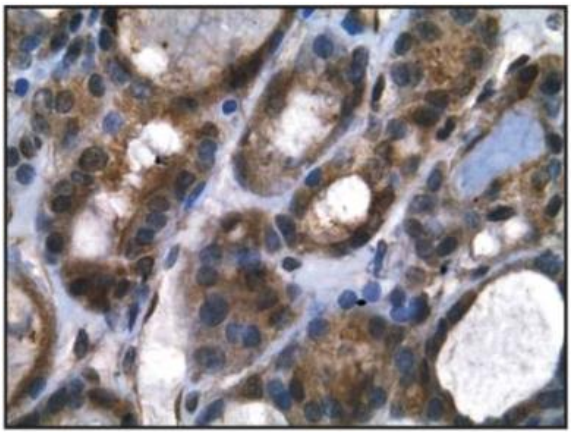


**Fig-4: Microphotograph showing gal-3 expression in follicular variant papillary thyroid carcinoma (FVPTC) (IHC 40X), Score - +++, Intensity – 2 , Pattern – Cytoplasm**

## DISCUSSION

Papillary thyroid carcinoma is the most frequent observed malignant tumour in the thyroid. In general the prognosis of PTC is favourable and ten-year survival rate for PTCs is greater then 90% [15]. However, about 20% of the differentiated thyroid cancer will present metastasis [16]. So accurate biomarker or immunohistochemical markers which can predict the aggressive behaviour of thyroid carcinoma is critical for clinical management [17]. Gal-3 could be an important tool for guiding therapeutic decision in patients with thyroid nodules [18]. On occasion cases of papillary thyroid hyperplasia can simulate papillary thyroid carcinoma and cause a diagnostic dilemma [19, 20]. In addition, PTC gives frequently rise to nodal metastasis via lymph vessels. Metastasis occurs in 20% of patients. In recent years, the development of PTC is influenced by many factors including genetic alterations, growth factors, and physical agents such as radiation. Galectin-3 a member of the B galactosil binding lectin family, for which normal function include cell-cell regulation, growth and differentiation in some studies. Finding that the sensitivity and specificity of gal-3 were 93% and 100% respectively, for papillary thyroid carcinoma [21-23].

In studies of PTC, Gal-3 expression has been reported in 58% to 100%. However, the majority of studies reported Gal-3 positivity in 90% to 100% of PTC cases [24]. Very few studies have reported Gal-3 expression in PTC by histological subtypes. Similarly, in our study, Gal-3 expression was identified in 77% (23/30) of PTC cases , and by histological subtypes of PTC Gal-3 expression was identified in classical, follicular variant, solid variant and micropapillary as 77.7%(7/9), 72.2% (13/18), 100%(2/2) and 100%(1/1) respectively. Expression of Gal-3 has also ranged from 20% to 100% in reported cases of FTC. The largest series, reported by Bartolazzi *et al.*, identified Gal-3 expression in 95% (54/57) of FTC cases [25]. Similarly, in our study, 80% (8/10) cases of FTC showed positivity for Gal-3.

Hence, Gal-3 is highly expressed in thyroid malignancies. There is no significant difference found in Gal-3 expression in PTC histological subtypes and FTC. Although it appears likely that a small proportion of follicular carcinomas are negative for Gal-3, likewise in our study 20% (2/10) of FTC cases were negative for Gal-3, it remains elusive whether the negativity is true or false. According to Kawachi *et al*. [26] primary lesions of papillary carcinomas with metastasis contained significantly higher concentrations of Gal-3 than tumours of this type without metastases. They explained further that Gal-3 down regulation in PTC may promote the release of some tumor cells from the primary tumor resulting in metastasis. In our single case of known metastatic PTC we found strong Gal-3 positivity. Follicular thyroid lesions have been rightly referred to as ‘the bane of the pathologist’ in a recent article by Baloch and LiVolsi [27]. The follicular variant of papillary thyroid carcinoma (PTCFV) often poses a diagnostic challenge in which the differential diagnosis includes other follicular patterned lesions such as follicular adenoma (FA) and follicular carcinoma. The distinction between these lesions is important because prognosis and management differ. Because FVPTC is diagnosed almost solely based on subjective cytologic criteria (nuclear grooves, nuclear clearing, nuclear overlap, and intranuclearpseudo inclusions) and no uniform minimal diagnostic criteria exist [28]. In our study, Gal-3 was expressed in 72.2%(13/18) of FVPTC, 80%(8/10) of FTC and 35.7%(5/14) of benign neoplasm ( follicular and hurthle cell adenomas).It has been suggested that Galectin-3 could also play role in the malignant transformation of thyroid cells and many studies have shown that PTC cases are characterized by strong, intense Gal-3 expression.In few studies Gal-3 also differentiated from papillary thyroid carcinoma and papillary hyperplasia ie positive rates of gal-3 were

97.4% in PTC and 16.7% in papillary hyperplasia. Their study believed that galectin-3 could be a valuable antibody for differential diagnosis of papillary carcinoma and papillary hyperplasia [22, 23]. Finaly conclude that galectin-3,a potential immunomarker, is accurate in making a preoperative distinction between PTC and non-PTC patients. In addition galectin-3 may provide more significant contributions in distinguishing PTC with or without lymph node metastasis. We suggest that a larger size and better studies should be conducted to confirm our results.

**REFERENCES**


1. Rosen JE, Stone MD. Contemporary diagnostic approach to the thyroid nodule. J Surg Oncol,2006;94(8):649-661.
2. De Lellis RA, Williams ED. Pathology of the thyroid and parathyroid.in: De Lellis RA, Lloyd RV, Heitz PU, Eng C ( eds). Pathology and genetics of tumours of endocrine organs, World health organization classification of tumours, IARC press, Lyon,2004,57-66.
3. Aiad HA, Kandil MA, Assad NY et al. Galectin-3 immunostaining in cytological and histopathological diagnosis of thyroid lesions. Journal of the Egyptian nat.cancer Inst.2008;20:36-46.
4. Fisher S, Asa SL. Application of immunohistochemistry to thyroid neoplasms. Arch Pathol Lab Med.2008;132:359-72.
5. Weber KB, Shroyer KR, Heinz DE, Nawaz S. et al. The use of a combination galectin-3 and thyroid peroxidase for the diagnosis and prognosis of thyroid cancer. Am J Clin Pathol.2004;122:524-31.
6. Fernandez PL, Merino MJ, Gomez M, Campo E. et al. Galectin-3 and laminin expression in neoplastic and non-neoplastic thyroid tissue. J Pathol,1997;181(1):80-86.
7. Barroeta JE, Baloch ZW, Lal P, Pasha T.et al. Diagnostic valu of differential expression of ck-19 , galectin-3 HBME-1,ERK, RET and P16 in benign and malignant follicular-derived lesions of the thyroid : an immunohistochemical tissue microarray analysis. Endocr Pathol,2006 ,17(3):225-234.
8. Prashad ML, Pellegata NS, Huang Y, Nagarja HN. et al. Galectin-3, fibronectin-1 , CITED-1 HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors.Mod Pathol,2005;18(1):48-57.
9. Rossi ED, Raffaelli M, Mule A, Meraglia A, et al. Simultaneous immunohistochemical expression of HBME-1 and galectin-3 differentiates papillary carcinoma from hyperfunctioning lesions of the thyroid. Histopathology.2006;48(7):795-800.
10. Park YJ, Kwah SH, Kim DC, Kim H, Choe G. et al. Diagnostic valu of galectin-3, HBME-1, cytokeratin 19, high molecular weight cytokeratin, cyclin D1, and P27(kip1) in the differential diagnosis of thyroid nodules. J Korean Med Sci,2007;22(4):621-628.
11. Paron I, Scaloni A, Pines A, Bachi A. et al. Nuclear localization of galectin-3 in transformed thyroid cells: a role in transcriptional regulation. BiochemBiophys Res Commun.2003;302:545-553.
12. Dabbs J David. Diagnostic immunohistochemistry: chapter 1:edition 2; Elsevier.2010:1-37.
13. Orlandi F, Saggiorato E, Pivano G, Puligheddu B, Termine A, Cappia S, et al. Galectin-3 is a presurgical marker of human thyroid carcinoma. Cancer Res. 1998;58:3015–20
14. Weber KB, Shroyer KR, Heinz DE et.al. The use of a combination of galectin-3 and thyroid peroxidise for the diagnosis and prognosis of thyroid cancer. Am J ClinPathol .2004;122:524-31.
15. Liu Z, Xun X, Wang Y, Mei L. et al. MRI and ultrasonography detection of cervical lymph node metastasis in differentiated thyroid carcinoma before reoperation. Am J Transl Res 2014;6:147-154.
16. Leboulleux S, Bastholt L, Krause T, Fouchardiere C. Vrnfrysnib in locally advanced or metastatic differentiated thyroid cancer : a randomized, double-blind, phase2 trial. Lancet Oncol 2012;13:897-905.
17. Vini L and Harmer C. Management of thyroid cancer. Lancet Oncol 2002;3:407-414.
18. Gomez Saez JM. Diagnostic usefulness of tumor markers in the thyroid cytological samples extracted by fine-needle aspiration biopsy. EndocrMetab Immune Disord Drug Targets 2010;10:47-56.
19. Casey MB, Lohse CM, Lloyd RV. Distinction between papillary thyroid hyperplasia and papillary thyroid carcinoma by immunohistochemical staining for cytokeratin 19,galectin-3, and HBME-1. EndorPathol 2003;14:55-60.
20. Cvejic D, Savin S, Petrovic I etal.Differential expression of galectin-3 in papillary projections of malignant and non-malignant hyperplastic thyroid lesions. ActaChirIugosl 2003;50:67-70.
21. Chen Y, Shen D, Sun K, et al. Expression of galectin-3, ck-19, HBME-1 and CD-56 and their significance in papillary thyroid microcarcinoma. Chinese journal of clinical and Experimental Pathology 2010;26:425-8.
22. Rossi ED, Raffaelli M, Mule A, et al. Simultaneous immunohistochemical expression of HBME-1 and galectin-3 differentiates papillary carcinoma from hyperfunctioning lesions of the thyroid. Histopathology 2006;48:795-800.
23. Beesley MF, Mc Laren KM. Cytokeratin 19 and galectin-3 immunohistochemistry in the differential diagnosis of solitary thyroid nodules. Histopathology 2002;41:236-43.

24. Connie GC, Scott S. Strugnell, Obil.G,Steven JM et.al. Diagnostic utility of gal-3 in thyroid cancer: The American journalof pathology, Vol. 176, No. 5, 2010
25. Bartolazzi A, Oralandi F, Saggiorato E, Volante M, Arecco F. et al. Galectin-3 expression analysis in the surgical selection of follicular thyroid nodules with indeterminate fine needle aspiration cytology: a prospective multicentre study. Lancet Oncol.2008;9:543-549.
26. Kawachi K, Matsushita Y, Yonezawa S, Nakano S. Galectin-3 expression in various thyroid neoplasms and its possible role in metastasis formation. Hum Pathol.2000;31:428-433.
27. Baloch ZW, Livolsi VA. Follicular–Patterned lesion of thyroid. The bane of the pathologist. Am J Clin Pathol.2002;117:143-50
28. Renshaw AA, Gould EW. Why there is the tendency to "overdiagnose the follicular variant of papillary thyroid carcinoma. Am J Clin Pathol.2002;117:19-21.