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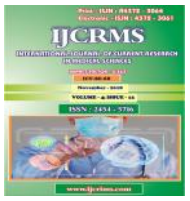

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# Diagnostic utility of Ki-67 as a proliferative marker & the expression of Galectin-3 in Neoplastic and Non-neoplastic lesions of thyroid.

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## Abstract

Thyroid neoplasms constitute the most commonly occurring endocrine tumors worldwide. Owing to the wide spectrum of clinical behaviour & varied therapeutic responsiveness, early diagnosis of thyroid tumors and appropriate management will prolong the survival rate of patients. However, distinguishing various thyroid lesions by hematoxylin and eosin sections alone is really challenging to a pathologist. The use of ancillary techniques like IHC is imperative for a definite diagnosis. The present study has used Galectin-3 for differentiating the neoplastic thyroid lesions from the non-neoplastic ones. Neoplastic thyroid lesions showed predominantly a strongly positive diffuse staining intensity with Galectin while non neoplastic thyroid lesions exhibited predominantly weak staining. Overall, the sensitivity and specificity of galectin -3 in distinguishing both neoplastic and non neoplastic thyroid lesions came to be 91.6% and 58.3% respectively. Positive predictive value and Negative predictive value was 68.7% and 77.7% respectively. Ki-67 labeling was found to be significantly higher in Neoplastic thyroid carcinomas than in non neoplastic tumors. Senstivity, specificity, positive predictive value and negative predictive value as 80.76%, 76.16%, 67.7%, and 70.16% respectively.

Conclusion: Gal-3 proves to be good candidate marker of malignancy especially in differential expression in neoplastic thyroid carcinomas when compared with non neoplastic thyroid lesions. Ki-67 immunohistochemical staining though can differentiate between neoplastic and non neoplastic thyroid lesions, it is not significantly helpful in differentiating between benign and malignant thyroid lesions.

**Keywords:** PTC, Follicular thyroid carcinoma, Galectin-3, Ki-67, IHC

## Introduction

Thyroid cancer is the most common malignancy of the endocrine system, representing 3.8% of all new cancer cases in the United States and is the ninth most common cancer overall.[1] Thyroid nodules commonly occur between 30-60 years of age. About 4% to 8% of adult women and 1% to 2% of adult men present with thyroid nodules that can be identified by physical examination. With the advent of ultrasonography, the detection rate has increased to 30%. Majority of the thyroid nodules are benign with malignant nodules comprising only 10%. Talking of the tissue of origin thyroid tumors can arise either from the epithelial cells lining the follicles or from parafollicular C cells. More than 95% of thyroid carcinoma originates from these follicular epithelial cells, whereas medullary carcinomas that originate from parafollicular C cells are rare, representing only about 3% of thyroid tumors.[2]

Papillary carcinoma is the most common malignant tumor constituting 80-85% of all the thyroid carcinomas and that too the classic type, followed by follicular carcinoma comprising 10-15%.But the mortality rate is only 6.5%. According to the surveillance and epidemiology, the 10 year survival rates for malignant thyroid tumors are Papillary carcinoma (98%), Follicular carcinoma (92%), Medullary carcinoma (80%) and Undifferentiated carcinoma (13%). [3,4]

Thyroid neoplasms have a wide spectrum of clinical behaviour & varied therapeutic responsiveness. Thus early diagnosis of thyroid tumors and appropriate management will prolong the survival rate of patients. However, distinguishing various thyroid lesions by hematoxylin and eosin sections alone is really challenging to pathologist.

Immunohistochemistry refers to the process of localizing proteins in the cells of a tissue section exploiting the principle of antibodies binding specifically to antigens in biological tissues. It is being applied and its utility in the diagnosis, treatment and prognosis of thyroid malignancies is being evaluated. Each marker differentially expressed in tumorous and non tumorous tissues represents a snapshot of the molecular events succeeding in the tissue environment. The use of combined immunohistochemical markers as a panel seems to be an alternative to aid some of the diagnostic challenges in surgical pathology and cytopathology of thyroid specimens.[5,6,7]

Ki-67 serves as a prognostic indicator in lymphoproliferative disorders, breast carcinoma and CNS tumours also. Ki-67 also finds its unique application in thyroid lesions for differentiating between follicular adenoma and follicular carcinoma which can be a challenge on H&E as capsular or vascular invasion is not always evident.[8]

Gal-3 has been found to be a promising molecular marker among the recent ancillary techniques for evaluation of thyroid neoplasms, however its exact role in thyroid tumour biology is still unknown. Thus, its sensitivity and specificity in detecting malignant neoplasms should be accurately confirmed and analysed.

Therefore the present study was aimed to evaluate thyroid gland lesions using H&E and Immunohistochemical expression of Ki-67 and Galectin-3 to differentiate between the benign and malignant lesions with confidence thereby helping the clinicians decide the optimal management approach for the patient.

AIM: To evaluate thyroid gland lesions using H&E and Immunohistochemical expression of Ki-67 and Galectin-3 to differentiate between the benign and malignant lesions with confidence thereby helping the clinicians decide the optimal management approach for the patient.

## Materials and Methods

The present study was conducted in 50 specimens of thyroid tissue received in the Department of Pathology, Government Medical College, Amritsar, after approval from the institutional thesis and ethics committee. Informed consent of the patient was taken (if required in vernacular language). Relevant history of the patient was taken as per the proforma attached along with.

Inclusion criteria: All specimens of thyroid tissue, diagnosed histologically as neopastic or non-neoplastic lesions of thyroid, were included irrespective of age. All the patients with secondary metastasis were excluded.

All the tissues were stained for H&E staining, and IHC staining using Ki-67 and galactin3 immunostaining and evaluated. Distribution and intensity of Gal-3 cytoplasmic signal interpretation was based on the guidelines followed by Weber KB et al., BS Sumana et al and Hermann ME et al. The staining intensity was graded on a scale of 0 to 3 where 0, 1+, 2+, and 3+ denote no staining, weak/slight staining, moderate staining and intense staining respectively, and the proportion of stained cells were interpreted as 1+ (< 10% of cells), 2+ (10% to 50% of cells) and 3+ (>50% of cells).[11,12,13]


Photomicrograph showing IHC kit (Biocare) for Galactin -3 & Ki -67 Immunostaining

Statistical analysis: Statistical analysis was done using 2x2 contingency table. Chi-square test with Yates correction was used to calculate p-value to ascertain statistical significance.

## Results

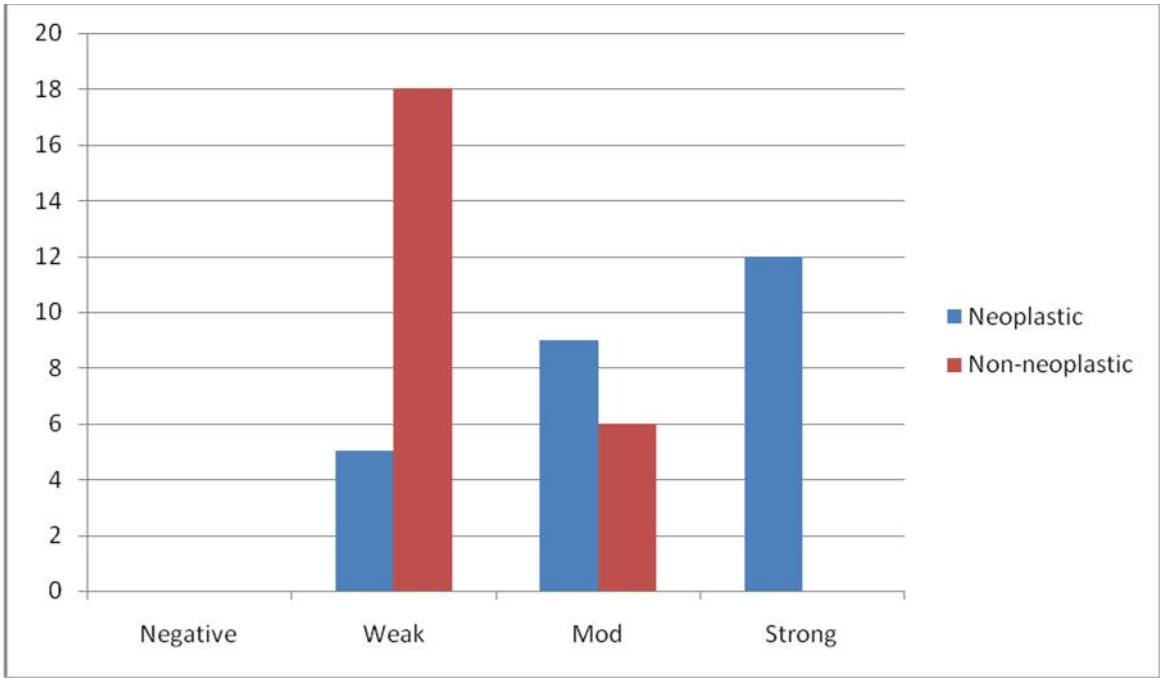
Results of the present study showed that thyroid nodules were most common in the age group between 20-40 years with female predominance. Female to male ratio was 2.5:1. Non-neoplastic (48%) comprised of Goitre (colloidal, adenomatous, nodular, multinodulor, n=24) and Neoplastic thyroid neoplasms category (52%) included Follicular adenoma (n=6), papillary thyroid carcinoma (n=16) , follicular carcinoma (n=3) and medullary carcinoma (n=1) cases.

Galactein-3 staining in Non neoplastic thyroid lesions i.e goiter showed overall weak staining (+1) in 75% of the samples and moderate staining (+2) in 25% of the cases. Absence of strong and diffuse staining intensity (score +3) was observed in non neoplastic lesions under study. further 58.3% cases of non neoplastic lesions showed staining positivity in less than 10% of the cells (+1), 37.5% (9 cases) showed upto 50% staining positivity in the epithelial cells (+2) and lastly only 4.1% (1 case) showed upto 80% staining positivity in the epithelium(+3). No case of >80% positivity in epithelium is seen in non neoplastic lesions of thyroid.(graph 1)

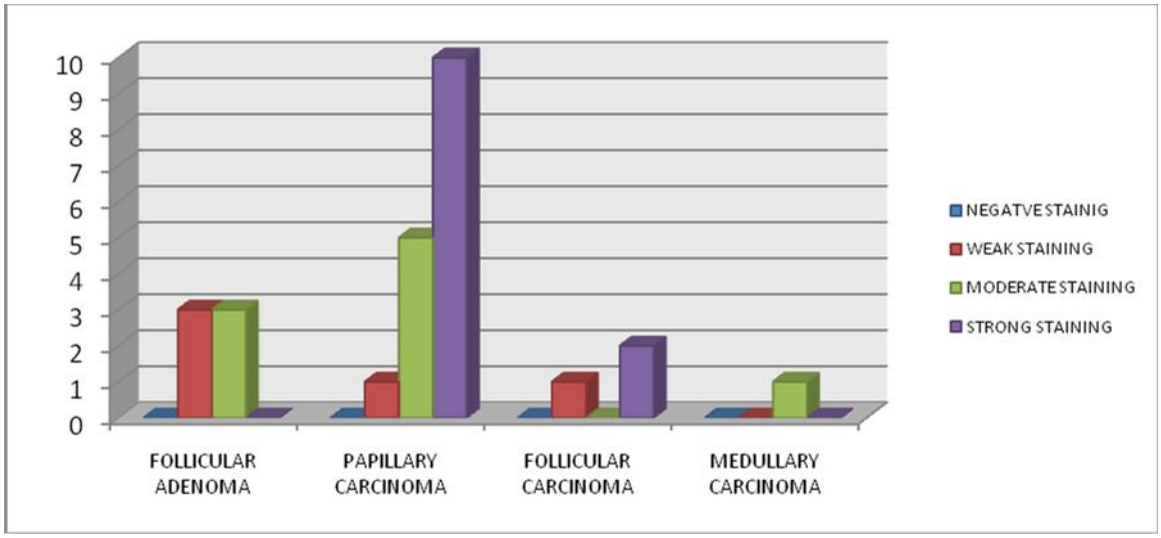
Galactein-3 in Neoplastic thyroid lesions showed overall strongly positive diffuse staining in the cytoplasm of cells in 46.1% of the samples and moderate staining in 34.6% of the cases and only 19.2% cases with weak staining. Thus, depicting that overall, neoplastic thyroid lesions showed predominantly a strongly positive diffuse staining intensity with Galactein-3. (graph 1).

Graph 2 also shows the quantity score for gal-3 and the maximum 38.4% cases showed staining positivity in greater than 80% (Score +4) of the cells, followed by 23.1% showed both 50- 80% staining positivity and 10- 50% staining positivity each in the epithelial cells and only 15.3% showed less than 10% stained cells.

Graph 1: Showing intensity of galactein 3 staining in non neoplastic and neoplastic thyroid lesions included in the study




Graph 2: Showing intensity of galactein 3 staining in neoplastic thyroid lesions included in the study



Further the results show that all cases of papillary carcinoma positive for lymphnode metastasis showed quality score of +3 and quantity score of +4. But no significant correlation was observed within Galactein 3 staining and the lymph node status of the carcinomas studied.

Overall, on comparision, the difference in galactein -3 staining between neoplastic and non neoplastic lesions of thyroid lesions came to be statistically significant.(*P*= .0015) (table 1)

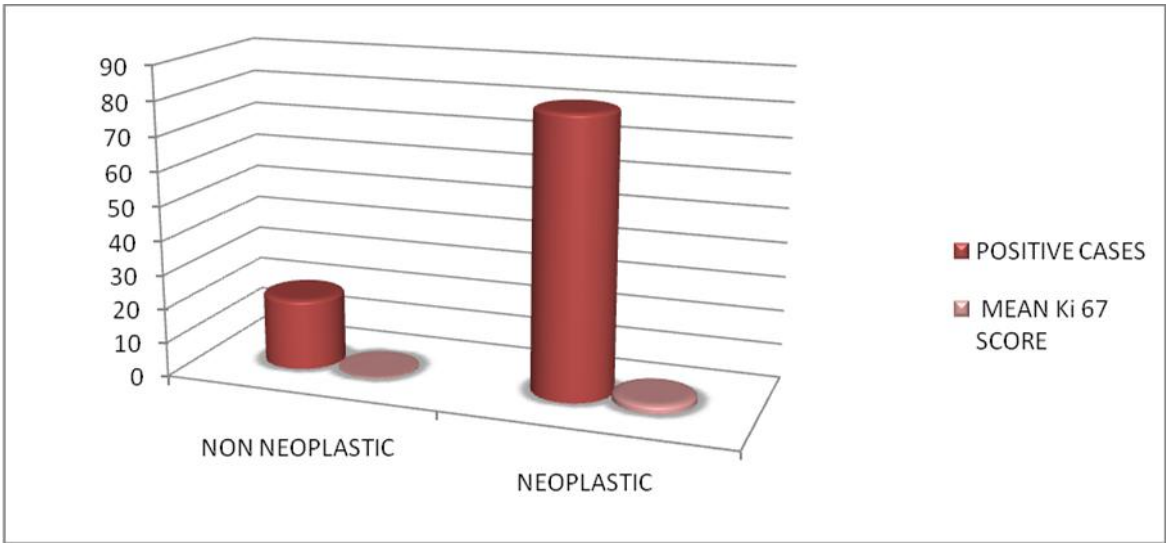
Table 1: Overall positive cases of non neoplastic and neoplastic lesions for galctein 3 staining

| Galactein-3 staining interpretation | Non neoplastic | Neoplastic |
|---|---|---|
| cases showing moderate and strong positivity | 10/24 | 22/26 |
| Cases showing weak positivity | 14/24 | 4/26 |

The sensitivity and specificity of galectin -3 in distinguishing both neoplastic and non neoplastic thyroid lesions came to be 91.6% and 58.3% respectively. Positive predictive value and Negative predictive value was 68.7% and 77.7% respectively.

The present study also observed the proliferation index in both benign and malignant thyroid lesions using Ki-67 IHC marker. It was observed that over all Ki 67 positivity was seen in 20.8% of Non neoplatic lesions of thyroid whereas 80.76% of neoplastic lesions of thyroid with a mean Ki67 score for Non neoplatic lesions of 0.375±1.05and for neoplatic lesions was 1.38 ±1.87.The difference in results between these two groups was found to be statistically significant ( *p*-value is <0.05). Senstivity, specificity, positive predictive value and negative predictive value for ki 67 came to be 80.76%, 76.16%, 67.7%, and 70.16% respectively.(table 2)

Graph 3: Overall mean ki-67 scoring in non neoplastic and neoplastic lesions within the sample.



## Discussion

The results of the present study demonstrated that, age wise distribution of incidence of thyroid nodules was most common in the age group between 20-40 years, which comprised of about 68% of the total cases in the study. Gender distribution showed female predominance with Female to male ratio observed was 2.5:1. Similar findings were also reported by BS Sumana et al[11] and Smriti Sudhanshu Dwivedi et al[14].

National Cancer Institute in 2013, analysed the proportion of various thyroid carcinoma and found that papillary thyroid carcinoma is the predominant malignancy constituting 70- 80% of all thyroid cancers. They are common in females between 30- 50 years as per their study. The next common malignancy is Follicular carcinoma constituting 10- 15% of all thyroid malignancies and is common in females in the age group of 40-60 years.[14] This predominance of papillary thyroid carcinoma is depicted in our sample as well.

Gal-3 has been found to be a promising molecular marker among the recent ancillary techniques for evaluation of thyroid neoplasms. The expression and distribution of Gal-3 between the nucleus and cytosol changes during cell differentiation and cancer development. It is also reported to exhibit an antiapoptotic activity, thereby promoting survival of malignant cells [16]

Our results depicted that neoplastic thyroid lesions showed predominantly a strongly positive diffuse staining intensity with Galactein-3 while non neoplastic thyroid lesions exhibited predominantly weak Galactein-3 staining. This was supported by Bartolazzi et al. who also reported similar findings in their study.[19]

Saleh et al. also reported that only 15.3% cases of non neoplastic lesions of thyroid included in study were positive for Galectin-3 with a significant differences in the immunoexpression in the benign non-neoplastic lesions, adenomas and carcinomas.[19]

In accordance to our results related to expression of galactein-3 in Papillary carcinoms, majority of authors like Cvejic D et al, Herrmann ME et al, Bartolazzi A et al, Prasad ML et al and Park YJ et al,[20,13,18,21,22] also reported Gal -3 positivity in 80% to 100% of papillary carcinoma cases. In a recent study by BS Sumana et al Gal -3 expression was also reported to be significantly higher (91.3%) in papillary carcinoma.[11] On comparing the results of expression of galactein 3 in Follicular thyroid carcinomas with other studies, it was seen that expression of Gal -3 ranged from 20% to 100% in reported cases of FTC. Xu XC et al., and Bartolazzi et al., identified Gal-3 expression in 100% and 95% of FTC cases respectively.[23,18]

Further in comparision to our results regarding expression of Galactein 3 staining in medullary carcinomas, BS Sumana et al, Fernandez et al and Bartolazzi et al reported expression in 50% cases of MTC, which is in contrary to our results as we reported 100% expression. This discrepancy can be explained on the basis that we had only 1 case of medullary carcinoma in our sample which is very less as compared to the other studies mentioned.[11,18]

The sensitivity and specificity of galactein -3 in distinguishing both neoplastic and non neoplastic thyroid lesions came to be 91.6% and 58.3% respectively. Positive predictive value and Negative predictive value was 68.7% and 77.7% respectively.

When compared berween follicular adenomas and follicular carcinomas, it was noticed that though there was difference in expression of galactein-3, but the difference was not statistically significant. Sensitivity and specificity of galactein -3 in comparision of both follicular adenomas and follicular carcinomas came to be 66.6% and 50% respectively. Also sensitivity and specificity of Galactein -3 to diagnose papillary carcinomas came to be 100% and 86% respectively. Thus, from the statistical analysis in this present study, it is found that Galactein -3 is a sensitive and specific marker in the diagnosis of papillary carcinoma.

Bartolazzi et al., the sensitivity and specificity of galectin-3 in thyroid carcinomas were 99% and 98%, respectively.[18] Orlandi F et al, have found Gal-3 to be the most sensitive and accurate marker for thyroid carcinoma.[24] Park et al., assessed IHC staining for six markers including Gal-3 in 295 thyroid lesions and concluded that Gal-3 is the most specific and sensitive marker of all the markers analysed.[22]

## Conclusion

In conclusion, Gal-3 proved to be good candidate marker of malignancy especially in differential expression in neoplastic thyroid carcinomas when compared with non neoplastic thyroid lesions and in differentiating follicular adenomas and follicular carcinoma. Ki-67 immunohistochemical staining though can differentiate between neoplastic and non neoplastic thyroid lesions, they are not significantly helpful in differentiating between benign and malignant thyroid lesions. thus using a combination panels of 2 or 3 of these IHC markers with morphologic evaluation are thus recommend as useful means to increases the likelihood of diagnosing various thyroid tumors specially thyroid carcinomas.

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