



## STUDY ON UTILITY OF KI-67 AS A PROLIFERATION MARKER IN THYROID LESIONS

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### ABSTRACT

**Objectives:** This study was conducted to assess the utility of Ki-67 as a proliferation marker in nonneoplastic and neoplastic lesions of thyroid. To study the role of Immunohistochemical proliferative marker Ki 67 in thyroid lesions.

**Summary:** The thyroid gland is unique among endocrine glands. It is the first endocrine gland to appear in the foetus. The thyroid gland is affected by a variety of pathological lesions that are manifested by various morphologies including developmental, inflammatory, hyperplastic and neoplastic pathology which are quiet common in the clinical practice. In the two and half year study period 1123 specimens were from various sites in head and neck region such as Scalp, periorbital region, ear, nose, cheek , lip, tonsil , tongue, thyroid, salivary glands and lymph nodes. Out of these 117 specimens were from thyroid and these cases were taken for this study. Ki-67 is an IgG1 type murine monoclonal antibody raised against a crude nuclear fraction of Hodgkin's disease-derived cell line L-428. Ki- 67 marker study may be helpful in distinguish undifferentiated areas from differentiated areas in a mixed type of thyroid cancer. Ki-67 labeling index (LI) show progressive increase from multinodular goiter to malignant neoplastic lesions.

### KEYWORDS :

#### Introduction:

The thyroid gland is unique among endocrine glands. It is the first endocrine gland to appear in the foetus. It is the largest of all endocrine glands weighing about 25grams and is the one which is amenable to direct physical examination because of its superficial location. The thyroid gland is affected by a variety of pathological lesions that are manifested by various morphologies including developmental, inflammatory, hyperplastic and neoplastic pathology which are quiet common in the clinical practice.

#### THYROID LESIONS

##### NON NEOPLASTIC LESIONS

##### Infectious Thyroiditis

- Acute Thyroiditis
- Chronic Thyroiditis

Hashimoto Thyroiditis

Subacute Thyroiditis

Grave's Disease

Goitre

Diffuse non toxic goiter

Multi Nodular goiter

##### NEOPLASTIC LESIONS

##### Benign

- Follicular adenoma
- Hurthlecell Adenoma

##### Malignant lesions

- Papillary Carcinoma
- Medullary Carcinoma
- Follicular Carcinoma
- Anaplastic Carcinoma

#### Role of Ki-67 as a proliferative marker in lesions of thyroid

- Ki-67 is an IgG1 type murine monoclonal antibody raised against a crude nuclear fraction of Hodgkin's disease-derived cell line L-428. The ki 67 was named after its place of production in West Germany at Kiel. The clone producing the Ki67 antibody was grown in the sixty seventh well of tissue culture plate. Ki-67 is a novel proliferative marker that can be readily detected by immunohistochemistry. Gerdes et al. have shown that all stages of the cell cycle will express Ki-67 except G-0 because resting cells entering from G-0 lack Ki-67 in early part of G1. Saad et al. determined the proliferative rate of normal human thyroid cells in different age groups using Ki-67 and found Ki-67 Labeling Index to be  $7.4 \pm 6.10\%$  in 25 fetal thyroids,  $0.23 \pm 0.15\%$  in 55 childhood thyroids and  $0.08 \pm 0.04\%$  in 37 adults at autopsy.

#### MATERIAL AND METHODS

In the two and half year study period 20908 specimens were received in the Department of pathology, Madurai Medical College, Madurai for histopathological examination from Government Rajaji Hospital, Madurai. Among these 1123 cases were from head and

neck lesions and 626 cases from thyroid gland lesions. 1123 specimens were from various sites in head and neck region such as Scalp, periorbital region, ear, nose, cheek , lip, tonsil , tongue, thyroid, salivary glands and lymph nodes. Out of these 117 specimens were from thyroid and these cases were taken for this study. The detailed clinical history of these 117 patients including the duration of swelling, pain, fever, loss of weight, loss of appetite and cough with expectoration etc. were obtained

The specimens of lobectomy, hemi thyroidectomy, near total thyroidectomy and total thyroidectomy with modified neck dissection were received for histopathological examination.

The specimens were fixed in 10% formalin for 24 – 48 hours. Then detailed gross examination including weight, measurement, shape, colour and consistency were noted. They were cut into parallel and longitudinal slices including the capsular invading areas. The additional features such as hemorrhage, cystic degeneration, calcification, necrosis and distance from line of resection were noted. The representative sections were taken from the lesions as shown in the table number.1

**Table 1**

Thyroid lesion	Number of sections <sup>1</sup>
For diffuse or inflammatory lesions	Three sections from each lobe and one from isthmus
Solitary encapsulated nodule	Sections from the entire circumference including tumor capsule and adjacent thyroid tissue
Multi nodular thyroid gland	One section from each nodule including adjacent thyroid tissue
Papillary carcinoma	Entire thyroid gland was blocked
Grossly invasive carcinoma (other than papillary carcinoma)	Three sections from tumor and three sections from non neoplastic gland and one from line of resection

The tissue slices were processed in various grades of alcohol and xylol and subsequently embedded in paraffin wax. Paraffin sections of 4  $\mu$ m thickness were subjected to haematoxylin and eosin staining. The histopathological study was done for 117 cases. Immunohistochemistry ki67 marker study was done for some selective cases and reports were recorded

Ethical Issues: To conduct the study permission was obtained from various department including Department of surgery, Department

of Ear, nose and Throat, Department of surgical oncology. Ethical clearance was obtained from Institutional Ethical Committee, Madurai medical College.

**Results**

Histopathological diagnosis of all cases tabulated in table number 2,3,4

**Table-2. histopathological diagnosis;**

LESION	Number of cases	Percentage
<b>NONNEOPLASTIC LESIONS</b>	73	62
<b>NEOPLASTIC LESIONS</b>	44	38

**Table-3. Nonneoplastic Lesions**

Diagnosis	Number of cases
Nodular goiter	54
Hashimotothyroiditis	18
Granulomatous thyroiditis	1
Total	73

**Table-4. Neoplastic Thyroid Lesions**

Diagnosis	Number of cases
<b>BENIGN NEOPLASTIC LESIONS</b>	
Follicularadenoma	25
<b>MALIGNANT NEOPLASTIC LESIONS</b>	
Papillary carcinoma	16
Medullary carcinoma	2
Anaplastic carcinoma	1
<b>Total</b>	<b>44</b>

**Immunohistochemistry**

Ki-67 Immunohistochemical staining was done for six different types of thyroid lesions such as Granulomatous thyroiditis , Hashimotothyroiditis, Nodular goiter, Follicular adenoma ,Papillary carcinoma and Anaplastic carcinoma .

An area with the maximum proliferation was chosen to evaluate the labeling index. Labeling index was expressed as percentage of positively stained cells (Brown granular nuclear reactivity) per 100 follicular epithelial cells after counting at least 1000 cells in each case. The staining pattern in various thyroid lesions tabulated in table number -5

**Table-5 .Ki-67 staining pattern in various thyroid lesions**

SNO	HPE DIAGNOSIS	Ki-67 staining
1	Granulomatous thyroiditis	Negative
2	Hashimato thyroiditis	Positive in germinal centre of follicles.
3	Multi Nodular goiter	Very few cells positive
4	Follicular adenoma	Positive
5	Papillary carcinoma	Positive(1 to 2%)
6	Anaplastic carcinoma	Strong positivity

In the present study, the mean values of Ki-67 Labeling index was increasing progressively from multi nodular goiter to Anaplastic carcinoma(Fig-1,2,3,4)

In 2010 Pujani M et al<sup>2</sup> reports that the mean values of Ki-67 Labeling Index increased progressively from multinodular goiter to follicular adenoma, papillary carcinoma and were the highest in undifferentiated carcinoma.

In 1998 Erickson et al.<sup>3</sup> observed the highest values for Ki-67 Labeling Index in anaplastic carcinoma which is followed by follicular and papillary carcinoma.

In 2002 Saiz et al<sup>4</sup> studied the immuno histochemical expression of Ki-67 and cyclin D1, E2F-1 in benign and malignant thyroid lesions .He found the highest expression of all the three markers in malignant tumors particularly in papillary carcinoma.

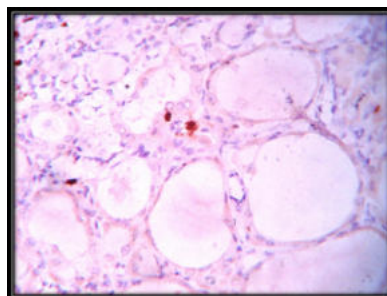
In 2008 Ziad et al.<sup>5</sup> studied immune expression of Ki-67 and thyroid

transcription factor-1 (TTF-1) in a coexistent Anaplastic and Follicular carcinoma and found a significantly higher Ki-67 Labeling Index in anaplastic areas in comparison with the follicular areas . Ki-67 and TTF-1 could provide useful information on the differentiation activities of thyroid tumor cells. It may be helpful to distinguish undifferentiated and well-differentiated areas in a mixed thyroid cancer.

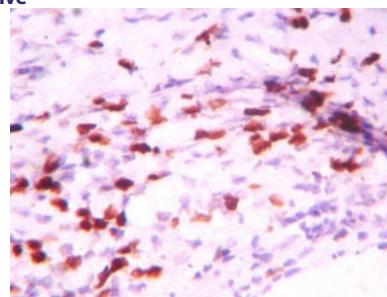
In the present study the mean values of Ki-67 Labeling Index is well correlating with other studies.

**Conclusion**

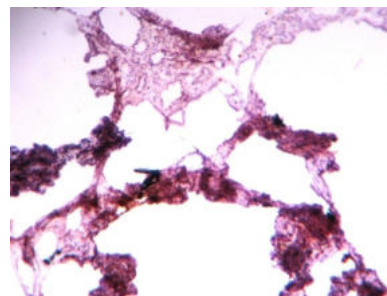
Ki- 67 marker study may be helpful in distinguish undifferentiated areas from differentiated areas in a mixed type of thyroid cancer. Ki-67 labeling index (LI) show progressive increase from multinodular goiter to to malignant neoplastic lesions.



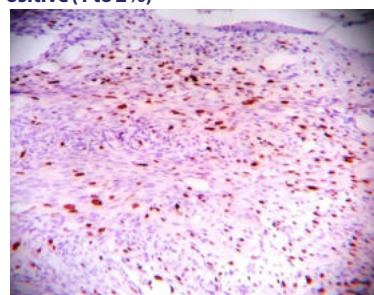
**Fig – 1. Ki-67 Immunohistochemical staining-MNG Very few cells positive**



**Fig - 2.Ki-67 Immunohistochemical staining- Follicular adenoma Positive**



**Fig - 3.Papillary carcinoma Ki-67 Immunohistochemical staining- Positive (1 to 2%)**



**Fig - 4. Anaplastic carcinoma Ki-67 Immunohistochemical staining- Strong Positivityx100**

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