

# Expression Immunohistochemistry Estrogen Receptor Alpha (ER $\alpha$ ) Of Papillary Thyroid Carcinoma (PTC) In Rumah Sakit Umum Pusat Haji Adam Malik Medan 2018

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DOI: 10.29322/IJSRP.10.05.2020.p10128

<http://dx.doi.org/10.29322/IJSRP.10.05.2020.p10128>

**Abstract:** Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, covers 80% of all thyroid cancers and often occurs in women than in men, the frequency of women is 3 times higher than in men. Several studies have shown that estrogen and its receptors are involved in the development of various types of malignant tumors including breast cancer, prostate cancer, ovarian cancer, endometrial cancer, colon cancer, lung cancer and thyroid cancer. Estrogen Receptor (ER) has been shown to increase PTC cell proliferation and cell line growth. Objective: To assess ER $\alpha$  immunohistochemistry expression in Papillary thyroid carcinoma. Materials and Methods: Formalin-fixed paraffin tissue blocks from 25 papillary thyroid carcinoma patients were used to examine the expression of immunohistochemistry ER $\alpha$ . The basic characteristics of the sample are obtained through medical records or pathology files. Of the 25 papillary thyroid carcinoma samples in this study, 14 cases (56.00%) showed positive expressions and 11 cases (44.00%) showed negative expressions of ER $\alpha$  immunohistochemistry staining. Of the 14 positive cases showing different intensities. ER $\alpha$  immunohistochemistry expression based on age was found most in the age group of 51 -60 years, namely as many as 8 cases (57.14%), whereas based on sex, ER $\alpha$  immunohistochemistry expression was found most positively in women, as many as 10 cases (71%). In this study at Adam Malik Hospital in Medan in 2018 that the highest ER $\alpha$  immunohistochemistry expression was in the age group of 51 -60 years which was 8 cases (57.14%), the positive ER $\alpha$  immunohistochemistry expression was found in most women in 10 cases (10 71%).

**Keywords:** Estrogen Receptor alpha (ER $\alpha$ ), Papillary thyroid carcinoma (PTC).

## I. INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for 80% of all thyroid cancers and is more common in women than in men.<sup>1-11</sup> PTC is a malignant epithelial tumor that shows differentiation of follicular

cells and has characteristic of nuclear features. Macroscopic images of PTC, usually appear in the form of an invasive solid mass of whitish gray with irregular boundaries. Some are calcified and can sometimes show bone formation in varying sizes with an average diameter of 2-3 cm.<sup>9-12</sup>

The characteristics of PTC nuclei are grouped into three categories: (1) changes in size and shape, (2) membrane abnormalities, and (3) chromatin characteristics. PTC nuclei are usually envelope-shaped, irregular and prominent pseudoinclusion or longitudinal grooves. Pseudoinclusion, is a cytoplasmic invagination into the nucleus, looks acidophilic, inclusions of a round structure, decomposes sharply and slightly eccentric, with a crescent shaped chromatin edge compressed on one side. Another feature of the PTC nuclei is clear nucleoplasm. Aspects in the core membrane are irregularly thickened by the apposition of chromatin material. This nuclei is described as optically clear and resembles ground glass. The appearance of ground glass appears in the paraffin-embedded process but it is not conspicuous or absent in frozen cuts.<sup>11,13,14</sup> The usual radiation therapy is surgery and removal of the thyroid intact with partial radioactive iodine, chemotherapy or combination therapy.<sup>15,16</sup>

Estrogen is a group of steroid compounds, which functions as the main female sex hormone and is important for the development and reproduction of women. There are three main types of estrogen in the human body: Estrone (E1), Estradiol (E2), and Estriol (E3). The classic genomic estrogen signaling pathway, estradiol (E2) -activated ER $\alpha$  translates to the nucleus, dimerizes, and binds to the 15-bp palindromic estrogen response element (ERE) or interacts with other transcription factors in the target gene, recruits coactivators, and stimulates gene transcription. There by increasing cell proliferation. Other mechanisms of estrogen action are faster and are called 'non-genomic' or 'membrane-initiated' because they involve E2 activation of plasma membranes related to ER $\alpha$  or ER $\beta$  and cause rapid activation of intracellular signaling pathways, for example, extracellular signal-regulated kinase 1/2 ( ERK1 / 2), and phosphatidylinositol 3-kinase / protein kinase B (PI3K / Akt). Non-genomic estrogen action is mediated by the interaction of ER $\alpha$  or ER $\beta$  with protein signaling in caveolae. G protein-coupled receptor 30 (GPR30) is a new membrane estrogen

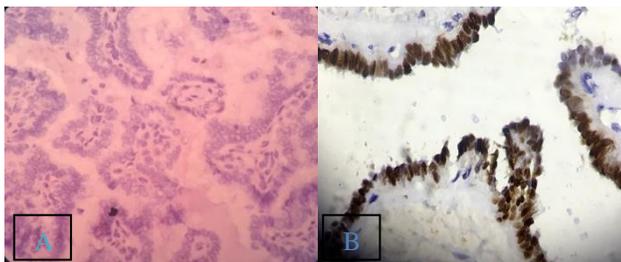
receptor that also activates ERK1 / 2 and PI3K / Akt signaling, although its role in estrogen action is still controversial.<sup>2,4,12,17,18</sup>

## II. MATERIAL AND METHODS

### Sample selection

This research is a descriptive staining study to assess the expression of ER $\alpha$  immunohistochemistry in papillary thyroid carcinoma (PTC). This research was conducted in the Department of Anatomic Pathology, Faculty of Medicine, Universitas Sumatera Utara and Anatomic Pathology Unit, H. Adam Malik General Hospital. Sample collection is collected by total sampling in 2018. The inclusion criteria in this study were all paraffin blocks originating from postoperative tissue which were diagnosed as papillary thyroid carcinoma (PTC) in an adequate and representative histopathology after staining with hematoxylin-eosin as well as having medical record data such as age / date of birth and type sex. Histopathological diagnosis based on the morphological features of cells using routine staining of hematoxylin-eosin. PTC is a type of thyroid carcinoma originating from the follicle and the nuclei has three categories: (1) changes in size and shape, (2) membrane abnormalities, and (3) chromatin characteristics.

ER $\alpha$  expression uses the Allred score method by looking at the percentage of colored cells in the nucleus and / or cytoplasm of tumor cells with proportion scores as follows: score 0 = 0, score 1 = <1% of colored cells, score 2 = 1 - 10% of cells that are colored colored, score 3 = 11 - 33% of colored cells, score 4 = 34 - 66% of colored cells, score 5 =  $\geq$  67% of colored cells. Staining intensity reaction as follows: 0 = none, 1 = weak color intensity, 2 = moderate color intensity, 3 = strong color intensity. The total score of ER $\alpha$  immunohistochemistry expression is the sum of proportion scores with intensity of staining, categorized as follows: negative = 0-2, positive = 3-8.<sup>2,12,19,20</sup>



Gambar 1. ER $\alpha$  Immunohistochemistry expression A. Negative ER $\alpha$  Immunohistochemistry expression B. Positive ER $\alpha$  Immunohistochemistry expression

### Data analysis

In this study the data obtained to assess the ER $\alpha$  immunohistochemistry expression of postoperative tissue that was diagnosed histopathologically as papillary thyroid carcinoma (PTC) is presented in a table form using a computerized program.

## III. RESULTS

### Basic characteristics of the sample

In this study the frequency distribution of PTC patients based on age and sex and ER $\alpha$  expression can be seen in table 1.

**Table 1 Basic Characteristics of the Sample**

Characteristics	Amount (n)	Percentage (%)
Age, mean $\pm$ SB,years	41,96 $\pm$ 15,43	
$\leq$ 20	2	8
21 – 30	5	20
31 – 40	3	12
41 – 50	5	20
51 – 60	8	32
61 – 70	2	8
> 70	-	-
Gender		
Female	18	72
Male	7	28
Expression ER $\alpha$ .		
Positive	14	56
Negative	11	44

Based on clinical data from medical records (table 1), the patients obtained in this study had an average age of 41.96 years, with the youngest age being 12 years and the oldest being 64 years old. The majority of cases are in the age group 51-60 years as many as 8 cases (32%), followed by the age group 41-50 years and 21-30 years as many as 5 cases (20%), then the age group 31-40 years 3 cases (12%) were followed by the age group of 61 -70 years and  $\leq$  20 years, respectively 2 cases (8.00%). While in the age group > 70 years, no cases or PTC were found. PTC are dominated by female in 18 cases (72%) while men are only 7 cases (28%). In this study from 25 PTC out of samples, there were 14 cases (56%) showing positive expressions of ER $\alpha$  immunohistochemistry staining and 11 cases (44%) showing negative.

### ER $\alpha$ expression distribution

#### Distribution of ER $\alpha$ immunohistochemistry expression based on age

While the distribution of ER $\alpha$  immunohistochemistry expression based on age can be seen in Table 2.

**Table 2 Distribution of ER $\alpha$  immunohistochemistry expression based on age**

Age (years)	Expression ER $\alpha$			
	Positive (n)	Percentage (%)	Negative (n)	Percentage (%)
$\leq$ 20	1	7,14	1	9,10
21 – 30	2	14,29	3	27,27
31 – 40	-	-	3	27,27
41 – 50	3	21,43	2	18,18
51 – 60	8	57,14	-	-
61 – 70	-	-	2	18,18
> 70	-	-	-	-
Total	14	100%	11	100%

The samples with positive ER $\alpha$  immunohistochemistry expression in the 51- 60 year age group had the highest number

of cases, 8 cases (57.14%) and the lowest number was the age group  $\leq 20$  years with 1 case (7.14%). ER $\alpha$  immunohistochemistry expression was negative with the highest number of cases in the age group 31 - 40 years and 21 - 30 years with 3 cases (27.27%) respectively, while the smallest number of cases were in the age group  $\leq 20$  years by 1 case. (9,10%).

#### Distribution of ER $\alpha$ immunohistochemistry expression based on sex

In this study, it can be assessed how the distribution of ER $\alpha$  immunohistochemistry expression (table 3).

**Table 3 Distribution of ER $\alpha$  immunohistochemistry expression based on sex**

Gender	Expression ER $\alpha$			
	Positive (n)	Percentage (%)	Negative (n)	Percentage (%)
Female	10	71,00	8	73,00
Male	4	29,00	3	27,00
Total	14	100%	11	100%

In 25 PTC samples, 10 cases (71.00%) were positively expressed in women and 8 cases (29.00%) in positive expressions in men, while 8 cases (73.00%) in expressions were negative in women and negative expression 3 cases (27.00%) in men (Table 3).

#### IV. DISCUSSION

In this study, from 25 with samples of casus PTC patient the most female 18 and male only 7 casus with a ratio of 1: 2.6 between men and women. In this study a little lower with the existing literature, but it still remains the most suffered by female sex, namely the incidence of PTC sufferers in women is about 3 times the incidence in men, but this difference decreases with increasing patient age.<sup>1,12,21</sup> This study is the same as the study of Widhiasih, et al. in Denpasar the ratio of PTC patients between male and female sexes was 1: 2.5.<sup>22</sup> Study of Kawabata, et al. in Japan with samples 1990 to 2000 stated that of 100 cases of PTC found 79 cases in women and 21 cases in men. When compared, about 1: 3.76 among men and women with PTC.<sup>23</sup> This study also suffered the most by female sex and was more the same as this study. Reza, et al. in Iran, out of 92 patients with PTC who were 79 female and 13 male patients.<sup>24</sup> When compared, about 1: 6.1, this ratio was very high between men and women, still dominated by female sex. This proves that there is a tendency for the influence of sex hormones on thyroid lesions, especially estrogen in the pathogenesis and / or development of PTC disease.<sup>23</sup>

PTC is a thyroid cancer that is often found in adults and children. The average age of PTC patients when diagnosed was 50 years, and 91% of patients were diagnosed at the age of 20-74 years. PTC with 1 children, 12 years old. Whereas 50 years old PTC sufferers in this study (group of patients aged 51-60 years) were 8 people and were the most age group suffering from PTC. While the mean age of PTC sufferers in this study was 41.96 years old, this is the same as the study of Widhiasih, et al. in Denpasar with a mean age of PTC sufferers of 45.07 years which is around the age of forties.<sup>22</sup>

Some researchers have shown that ER $\alpha$  is present in thyroid tissue with thyroid tumors and also in normal thyroid tissue.<sup>23</sup> The expression of ER isoforms in normal tissue and PTC is still controversial.<sup>26</sup> In this study the assessment of 25 PTC samples found 11 samples were negative (44%) and 14 samples were rated positive (56%). This study is in line with the study of Dai, et al. states out of 218 PTC samples with negative results of 6 samples and positive results of 212 samples and counted as low as 109 samples and as high as 109 samples. This is consistent with this study that every ER immunohistochemistry expression is not monotonous or not all have the same expression with high or low intensity and even negative ones, but in Dai, et al. negative ER $\alpha$  immunohistochemistry expressions are grouped into low expressions, whereas in this study differentiated between negative and positive with low, moderate and strong intensity. Dai, et al. also stated that ER $\alpha$  immunohistochemistry was expressed in PTC, hyperplasia nodules and normal thyroid tissue and the level of ER $\alpha$  expression was significantly higher in PTC than hyperplasia nodules and hyperplasia nodules higher than in normal thyroid tissue.<sup>1</sup>

#### V. CONCLUSION

In this study in RSUP H Adam Malik Medan in 2018 that sufferers of papillary thyroid carcinoma predominantly suffered by female sex that is as much as 72%. In this study it can be seen that 92% of papillary thyroid carcinoma sufferers are aged 20 - 70 years. By obtaining a positive ER $\alpha$  immunohistochemistry expression in this papillary thyroid carcinoma sample proves that there is a relationship between ER $\alpha$  and papillary thyroid carcinoma

#### VI. COMPETING INTERESTS

The author has no financial interests relevant to the product or company described in this article.

#### VI. ACKNOWLEDGMENT

We would like to thank all staff of the Department of Anatomical Pathology, University of North Sumatra, Private hospitals and private clinics in Medan, Indonesia for all their assistance and cooperation.

#### VII. ETHICAL APPROVAL

Health Research Ethical Committee, Universitas Sumatera Utara, Medan, Indonesia approved this study.

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