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What is the meaning of ki67 expression in papillary thyroid cancer.

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Abstract

In this study, we investigated the effect of Ki67 on PTC, PTMC and thyroid disease as well as on the clinicopathological values in PTC and PTMC patients.

Keywords: Endocrine cancer, Thyroid carcinoma, Tumors, Immunohistochemical.

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Introduction

Since the 1990s, the incidence of thyroid carcinoma is increasing with the effect of environmental factors. Currently, it is known that the most common carcinoma of endocrine cancers is thyroid carcinoma. In the female population, thyroid cancer was ranked 14th among all cancers 20 years ago, while it is now the 5th most common cancer. Papillary thyroid carcinoma is the majority of these cases. However, recently papillary microcarcinomas have also increased significantly. The majority of papillary thyroid cancers have a good prognosis. In some patients with aggressive tumors, the prognosis is quite poor [1]. Unfortunately, this aggressive condition is present even in papillary microcarcinomas. The role of Ki67 on papillary thyroid cancer and thyroid diseases is still unknown, but studies are still underway.

Materials and Methods

Between June 2017 and December 2018, 64 patients with PTK and benign thyroid disease underwent thyroidectomy in the general surgery unit of Kanuni Sultan Süleyman Training and Research Hospital. Thyroid adenomas and thyroid nodular goiter were present in benign thyroid disease. There were 31 patients in the PTC group and 33 patients in the benign group.

There were 31 cases in the PTC group, including 1 male and 30 female. The mean age was 46.61 ± 11.72 years. The mean tumor size in the PTC group was 1.71 ± 1.46 cm. Total thyroidectomy was performed to all patients, including patients with papillary microcarcinoma and patients with limited tumor in the single lobe of the thyroid. Central Lymph Node Dissection (CLND) was not routinely performed for PTC patients in our hospital. Lymph node dissection was planned in patients with suspicious lymph node involvement for metastasis in neck US imaging. Central, ipsilateral and contralateral lymph node dissection was performed according to localized lymph node localization [2]. Parathyroid glands and recurrent laryngeal nerve were carefully separated during surgery.

All specimens were examined by experienced pathologists and pathology parameters such as tumor multifocality, multicentre, extrathyroidal spread, capsule invasion, necrosis, surgical margin, lymphovascular invasion and lymph node metastasis were recorded.

In this study, when two or more tumor foci were observed in the same or different lobes of the gland, the tumors were considered as very focused. Tumor size was accepted as the dominant nodule diameter. Clinical pathological staging was based on 2014 NCCN guidelines. The following parameters were collected: age, gender, surgical margin, tumor size, multifocality, multicentrite, extrathyroidal extension and lymph node metastasis.

Ki67 expression was determined by immunostaining with monoclonal antibodies. Monoclonal antibodies to Ki67 were purchased from Cell Marque Company Limited in California, United States. Paraffin-embedded tissue samples were used. Immunohistochemical analysis was performed using bond polymer refine detection on an automated Leica Bond Max instrument. Epitope retrival was performed with 20 min edta. Protocol peroxide block; 10 min, marker; 25 min, postprimer; 8min, polymer; 8 min, DAB refine; made in 6 minutes. All slide images were obtained by scanning the 3DHistech Pannoramic 250 Flash III Scanner at 40x size and saved in mrxs file format. Ki67 counting was done with Virapath Ki67 Algorithm digital image analysis program. The digital analysis program was run in large areas that were annotated by a specialist pathologist around the tumoral areas classified as benign and malignant. The anodized areas were determined to cover at least half of the tissue remaining around the tumoral region. In the small tissues, all tissue around the tumor area was studied. The fields in the tables are also specified in mm square. Lymphocytes and other inflammatory cells were not separated by the analysis program and were not included in the count. Ki67 positivity index was calculated automatically by the algorithm as the ratio of the number of ki67 positive cells to the total number of cells.

All patients in the study were recorded. SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Quantitative data were presented as mean ± SD and compared with a Mann-Whitney test. Pearson linear correlation was used to evaluate the correlations. P<0.05 showed significant differences.

Results

Table 1 shows a comparison of Ki67 expression intensity between the PTC group and the benign thyroid disease group.Mann-Whitney test showed that the expression density of Ki67 in the PTC group was significantly higher than the group of benign thyroid disease (P<0.014) (Table 1).

Type	Case	Expression intensity (%)	P value
PTC	31	5.771 ± 5.5467	<0.014
Benign	33	3.181 ± 2.3616	

Table 1. *Ki67 expression intensity comparison between the benign thyroid disease group and PTC group.*

Table 2 summarizes the clinical and pathologic characteristics of the PTC patients. There were 30 women (96%) and 1 man (4%) in the PTC group; The mean age was 46.61 ± 11.72 years. The mean tumor size in the PTC group was 1.71 ± 1.46 cm. Four of these patients (13%) had PTC with extrathyroidal extension. Multifocality was detected in eight patients (25.8%) and multicentricity was found in 7 patients (22.5%) independently. In two patients (37.3%), lateral lymph node metastasis was present together with the central lymph node [3]. In 8 other patients with lymph node dissection, neither the central region nor the lateral region had metastasis.In PTC group, clinical and pathological characteristics were compared according to Ki67 expression intensity. Clinicopathological factors were listed in (Table 2).

Clinical characteristic		Case(n)	Expressionintensity (%)	P value
Gender	Male	1	1.17	0.484
	Female	30	5.57 ± 5.529	
Age	<45 years	16	6.44 ± 7.0076	0.652
Tumour size	<1cm	10	5.98 ± 6.7408	0.732
	>1cm	21	5.66 ± 5.0663	
Multifocality	Yes	8	5.96 ± 3.1962	0.133
	No	23	5.70 ± 6.2198	
Extrathyroidal extension	Yes	4	9.86 ± 8.4112	0.653
	No	27	5.16 ± 4.9372	-
Lymph node metastasis	Yes	2	5.61 ± 2.6022	0.075
	No	29	5.78 ± 5.7202	-
Surgical margin	Pozitive	4	4.24 ± 0.9423	0.837
	Negative	27	5.99 ± 5.9148	-
Capsul invasion	Yes	8	5.86 ± 3.8684	0.416
	No	23	5.74 ± 6.0983	-
Lenfovascular invasion	Yes	6	4.56 ± 1.6202	0.635
	No	25	6.06 ± 6.1203	-

Table 2. *Comparison of the clinical and pathologic characteristics in PTC (n=31).*

The Ki67 expression intensity was not statistically significant compared to the density in a tumor greater than or equal to 1 cm in a tumor smaller than 1 cm. Of course, as is known, Ki67 expression intensity in thyroiditis group was statistically higher than that of non-thyroiditis group (P=0.005). The Ki67 expression intensity did not show significant differences in clinical and pathological features in the PTC disease group.

Discussion

The most common type of papillary thyroid carcinoma in endocrine cancers, especially the microcarcinoma subtype, is rapidly increasing in recent years. For many years, preoperative diagnostic fine needle aspiration biopsy combined ultrasound has been used to differentiate benign or malignant thyroid nodules. Nowadays, most centers frequently use metastatic lymph nodes due to malignancy [4]. Although this approach is considered to have a high accuracy percentage compared to most researchers, it still cannot differentiate

malignancy in some exceptional cases. As is known, many approaches to diagnosis and prognosis of thyroid cancer have low specificity. For this reason, researchers have made considerable efforts to diagnose thyroid cancer and to determine their prognosis, and in recent years they have time to find reliable biomarkers.

Ki67 is a DNA binding protein that is mainly distributed in the nucleus and is related to cell proliferation. Ki67 is a large protein of 395 kDa encoded by approximately 30,000 base pairs. Ki67, one of the important markers of cell proliferation, is widely used in the treatment and investigation of various types of tumors such as breast cancer. Ki67 is generally distributed in the nucleus and its main role is to protect the DNA structure in cell mitosis. While Ki67 protein is subjected to phosphorylation and phosphorylation during mitosis, it is also susceptible to proteasites and regulated by proteolytic pathways. Furthermore, the structure of Ki67 is similar to that of some proteins involved in cell cycle regulation. Ki67 does not exist in calm cells (G0), but begins to appear in the core in G1 phase. Subsequently, in the S and G2 phases, Ki67 protein expression increases gradually along the M phase and peaks, followed by a rapid decrease over the M phase.

The expression of Ki67 is closely related to tumor cell proliferation and growth and is widely used as a proliferation marker in routine pathology studies. It is widely known that high Ki67 expression is associated with poor prognosis in breast cancer and prostate cancer.

However, only a limited number of studies have examined the relationship between Ki67 and thyroid cancer. Ito et al assessed the prognostic significance of Ki67 labeling index in papillary thyroid cancer and showed that Ki67 was an independent prognostic factor for disease-free survival in PTC patients.

This study showed that Ki67 expression intensity in papillary thyroid cancer and microcarcinoma group was significantly higher than in benign thyroid disease group. However, the inability of the patient sample showed that Ki67 expression was a relatively low diagnostic value. Therefore, Ki67 cannot be used as a single predictive factor in determining papillary thyroid cancer and determining its behavior. A combination of some factors should be used to increase the accuracy of detection of malignancy. Previous studies have suggested that evaluation of TERT promoter mutations, BRAFV600E mutation, or thyroglobulin mating time may be good strategies for predicting the prognosis of papillary thyroid cancer. Recent research has also shown that periostine matrix protein can also be an ideal biomarker to predict the prognosis of the disease. In the future, Ki67 should be tested combined with another biomarker.

Our study showed that Ki67 expression intensity was significant in patients with papillary thyroid carcinoma and microcarcinoma compared to patients with benign disease. However, Ki67 expression intensity was not associated with gender, age, multicentricity, multicentricity, extrathyroidal spread, capsular invasion, surgical margin, lymphovascular invasion and lymph node metastasis. This result showed that Ki67 expression was associated with extrathyroidal extension and lymph node metastasis and that Ki67 expression intensity in tumors larger than or equal to 1 cm. It was found to be higher and not compatible with the study found that the tumor size correlated linearly with the Ki67 expression intensity. Considering the number of samples in this sense, the number of samples in our study was not as adequate as in the other two studies. However, neck lymph node dissection is not routinely performed in our center. The short-term may also be misleading as the results in thyroid cancer require long-term follow-up.

The expression Ki67 is largely associated with thyroiditis. Although the mechanism is still unknown, the relationship between Ki67 and inflammation has been reported. A study of the molecular mechanisms of Ki67 revealed that Ki67 plays an important role in the early stages of ribosomal RNA synthesis, and that the Ki67 protein may be associated with a variety of signaling pathways which may in turn induce the Ki67 question. In addition, there was a relationship between thyroiditis and Ki67 expression for the first time. In this study, Ki67 expression level was significantly higher in papillary thyroid cancer, but it was not associated with clinicopathological factors. We accept the limits of our investigation [5]. Our study was retrospective, the follow-up period was short, the number of samples was less than the other studies. A long-term follow-up study is needed to confirm the outcome.

Conclusion

Our study confirmed that Ki67 is highly expressed in papillary thyroid carcinoma and can be used to differentiate PTC from benign thyroid disease. The expression intensity of Ki67 in PTC was not associated with prognostic factors. In this study, firstly, the relationship between Ki67 and papillary thyroid carcinoma in Turkish society was mentioned. Therefore, we think that Ki67 can be combined with other diagnostic materials in addition to biomarkers used in the diagnosis of papillary thyroid cancer. We recommend further work on this subject.

Conflict of Interest

The authors declare that there is no conflict of interest.

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