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Research Article

The Role of p27kip1 in the Aggressiveness of Papillary Thyroid Carcinoma: A Clinicopathological Analysis.

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Abstract:

Background: Cell-cycle-regulating proteins, including cyclin-dependent kinase inhibitor 1B *p27*^{kip1}, have been researched in different malignancies, including thyroid carcinoma, and their association with tumor aggressiveness and recurrence has been examined in many tumors.

Objective: This research aimed to examine the clinicopathological relevance of reduced cyclin-dependent kinase inhibitor 1B *p27*^{kip1} expression in papillary thyroid carcinoma and its association with the clinicopathological parameters indicative of papillary thyroid carcinoma aggressiveness.

Methods: Formalin-fixed, paraffin-embedded tissue blocks were obtained from histologically confirmed cases of papillary thyroid carcinoma diagnosed between June 2022 and June 2023 at the National Center for Teaching Laboratories, Medical City Complex, Baghdad, Iraq. A total of 60 papillary thyroid carcinoma samples were included in the study. Immunohistochemical analysis was performed to assess the expression of the p27 protein. The study further evaluated the association between cyclin-dependent kinase inhibitor 1B *p27*^{kip1} expression and various clinicopathological parameters, including patients' age, sex, papillary thyroid carcinoma subtypes, tumor size, capsular invasion, multifocality, extrathyroidal extension, and lymph node metastasis.

Results: A decrease in the expression of cyclin-dependent kinase inhibitor 1B *p27*^{kip1} of less than 10% was observed in 37 out of 60 cases (61.7%). The correlation with clinicopathological parameters revealed a significant decrease in expression of cyclin-dependent kinase inhibitor 1B *p27*^{kip1} associated with female sex, classical variant PTC, infiltrative tumors, large tumor size (2-2.5 cm), and multifocal lesions.

Conclusion: Reduced expression of cyclin-dependent kinase inhibitor 1B *p27*^{kip1}; (<10%) was observed at a relatively high rate in papillary thyroid carcinoma. A significant correlation was found between decreased cyclin-dependent kinase inhibitor 1B *p27*^{kip1} expression and several clinicopathological features, including infiltrative pattern tumors, large tumor size, and multifocality. These findings suggest that reduced cyclin-dependent kinase inhibitor 1B *p27*^{kip1} expression may be linked to more aggressive tumor behaviour and could potentially serve as a prognostic marker in PTC.

Keywords: Clinicopathological parameters: Cyclin-dependent kinase inhibitor *p27*^{kip1}; Immunohistochemistry; Papillary thyroid carcinoma; Tumor aggressiveness.

Introduction:

Papillary thyroid carcinoma (PTC) is the most prevalent and treatable form of thyroid neoplasms (1-4). Papillary thyroid carcinoma accounts for 70–90% of reported thyroid carcinoma. The prevalence of papillary carcinoma has significantly risen in several nations since the 1970s (5-7). The increased detection rate is attributed to the widespread implementation of ultrasonic examination (8-10). The majority of PTC cases have a slow progression in comparison with other malignant thyroid tumors (follicular, medullary, and anaplastic thyroid carcinoma) (11-13). Nevertheless, some exhibit aggressive behavior, and specific clinicopathological parameters, including advanced age, large size of tumor, extrathyroidal extension, and lymph node metastases, are proposed as an unfavorable predictive indicator (14-16).

Papillary thyroid carcinoma comprises several histological variants, each with distinct morphological and clinical characteristics. The classical variant is the most common and typically exhibits indolent behavior, while the follicular variant may mimic follicular neoplasms and shows variable prognostic outcomes. Other less frequent but clinically significant variants include the tall cell, diffuse sclerosing, and hobnail variants, which are often associated with more aggressive behavior and poorer prognosis. Accurate identification of PTC subtypes is essential, as variant-specific features may influence treatment decisions and patients' outcomes (17). A tumor arises from the accumulation of several molecular mutations; alteration of the cell cycle is regarded as an unequivocal characteristic of cancerous cells.

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Cyclin-dependent kinases (CDKs), a class of protein serine/threonine kinases in human cells, regulate cell cycle progression. They are activated by attaching to a group of similar proteins known as cyclins. CDKs (1, 2, 4, and 6) and cyclins (A, B, D, and E) perform important functions throughout the cell cycle (18). p27 protein, encoded by cyclin-dependent kinase inhibitor 1B (CDKN1B), is a key regulator of the cell cycle that inhibits CDK-cyclin complexes and cell cycle progression, and thus controls cell cycle progression at G1. The tumor suppressor gene *p27^{kip1}*, located on chromosome 12p13, is a member of the Cip/Kip family. The degradation of this protein, which is triggered by its CDK-dependent phosphorylation and subsequent ubiquitination by SCF complexes (Skp1-Cul1-F-box protein complex), is required for the cellular transition from quiescence to the proliferative state. (19, 20)

The incidence of PTC in Iraq has been observed to be increasing significantly over the years (21). According to the annual report of the Iraqi Cancer Registry 2020 (22), thyroid carcinoma was classified as the second most common carcinoma in females. PTC is the most common type of thyroid carcinoma, occurring in 83.47% of cases. This trend highlights a growing public health concern, particularly as thyroid cancer ranks as one of the top cancers in the country, especially among women. According to previous studies, there is a correlation between decreased expression of the *p27^{kip1}* protein and poorer prognosis outcomes, as well as increased tumor aggressiveness and metastasis to lymph nodes in PTC (14, 23, 24). This study aimed to evaluate the immunohistochemical expression of the cell cycle regulator p27^kip1 in PTC and its association with clinicopathological features, to explore its potential as a predictor of tumor aggressiveness in the Iraqi population.

Materials and methods

This study is a retrospective cross-sectional analysis of formalin-fixed paraffin-embedded tissue blocks (FFPE) from registered cases of histologically confirmed papillary thyroid carcinoma referred to the National Centre for Teaching Laboratories, Medical City Complex, Baghdad, Iraq. The tissue samples included 60 cases of PTC. The final histological identification of PTC encompasses several variants. The inclusion criteria were all samples with a definitive diagnosis of PTC, irrespective of patient age and sex. The exclusion criteria encompassed the papillary microcarcinoma subtype, owing to their generally low-risk clinical behavior, in addition to any samples that were compromised, improperly stored, or devoid of comprehensive clinical or pathological data. Aggressive features of tumors were detected by using numerous parameters, including age, sex, histopathologic type, tumor size (maximum tumor diameter), multifocality, encapsulation, lymph node metastasis, and the existence of extrathyroid extension. Blocks of paraffin were collected for all cases of PTC, sectioned, and stained with hematoxylin and an Eosin stain (H and E). Subsequently, all slides were re-evaluated, and the findings were recorded.

Immunohistochemical staining: Immunohistochemical (IHC) staining was conducted on paraffin-embedded samples. Embedded sections were sectioned to a thickness of 4 µm to provide optimal resolution post-staining. p27 antibodies (catalog No. BSB 5835, BiO SB.USA) are mouse monoclonal; this antibody is designed for immunohistochemical usage on FFPE, cellular preparations, and frozen sections. The type of antibody is monoclonal (clone SX53G8, isotype IgG1/K, localization nuclear). Anti-p27^{kip1} is obtained from the cell culture supernatant that has been diluted in a buffer with a pH of 7.5. Anti-p27 is pre-diluted and ready for use.

Immunohistochemical protocol: Air-dried tissue sections, deparaffinized tissue sections with xylene, dehydrated and rehydrated with alcohol, immunoDNA retriever with citrate or EDTA added after heat treatment, peroxidase blocking, Added the primary antibody (anti-P27): aliquot 50 µl of the pre-diluted primary and secondary antibodies, add the substrate chromogen reagent (DAB substrate solution), then stain with hematoxylin and examine the slide under a light microscope.

IHC interpretation of p27^{kip1} expression: Tumors were classified as immunopositive or immunonegative according to their percentages, utilizing a threshold value. The cutoff threshold for p27kip1 was established at 10% (≥10% or <10% defined as <10% positive tumor cells), where results below 10% signify immunological negativity or underexpression, and values equal to or over 10% denote overexpression, often observed in normal and benign thyroid lesions (25, 26).

Statistical Analysis: The collected data were coded, entered, presented, and analyzed by IBM Statistical Package for Social Sciences, Chicago, IL, USA (IBM-SPSS) version 29. Data were presented using basic statistical measures (descriptive statistical measures), including frequency, percentage, mean, standard deviation, and range (minimum and maximum values). The importance of the disparity between various means (quantitative data) was assessed utilizing the Student's *t*-test for the difference between two independent means. The significance of the differences among various percentages (qualitative data) was assessed using the Pearson Chi-squared test (χ^2-test), applying Yates' adjustment or the Fisher exact test when appropriate. Statistical significance was deemed present when the *P* value was less than or equal to 0.05.

Results:

The mean age of the patient in the current study was 46.6 ± 14.0 years, with a range of 23 to 85 years. Regarding sex, the female sex represented 47/60 (78.3%), as shown in (Table 1**).** The classical variant

was evident in 43/60 (71.7%). The variants of PTC detected in this study were shown in **(**Figure 1). Infiltrative tumors were evident in 40/60 (70%). Regarding the size of the tumor, the highest rate was at tumor size (2-2.5cm), comprising 13/60 (21.7%). Multifocal tumors were present in 30/60 (50%), an extrathyroid extension was established in only 3 (5%), while lymph node (LN) metastasis was evident in 17/60 (28.3%), as shown in (Table 2**).**

Table 1: **Age and sex distribution in PTC samples**

		PTC samples		*P* value
		N=60	%	
Age (year)	<30	3	5.0	0.273
	30-39	19	31.7	
	40-49	12	20.0	
	50-59	18	30.0	
	60-69	3	5.0	
	≥70	5	8.3	
	Mean±SD (Range)	46.6±14.0 (23-85)		0.555
Sex	Male	13	21.7	0.535
	Female	47	78.3	

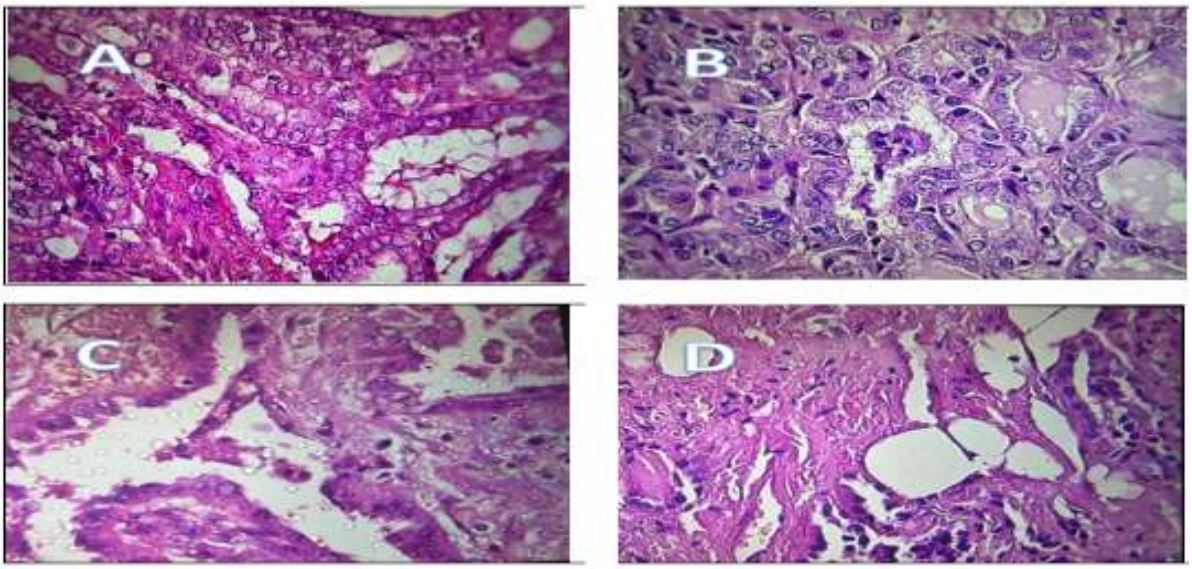

Figure 1: (A) classical variant PTC (40X), (B) follicular variant PTC (40X), (C) hobnail variant PTC (40X), and (D) sclerosing variant PTC (10X), (H&E stain).

Table 2: **Clinicopathological parameters in PTC samples**

		PTC samples	
		N = 60	**%**
Type of PTC*	Classical	43	71.7
	Follicular	16	26.7
	Sclerosing	1	1.7
Presence of a capsule	Infiltrative	42	70.0
	Encapsulated	18	30.0
Size (cm)*	1.0-<1.5	11	18.3
	1.5-<2.0	14	23.3
	2.0-<2.5	13	21.7
	2.5-<3.0	5	8.3
	3.0-<3.5	6	10.0
	3.5-<4.0	5	8.3
	4.0≥	6	10.0
Multiplicity	Unifocal	30	50.0
	Multifocal	30	50.0
Extra thyroid extension	Positive	3	5.0
	Negative	52	86.7
	Not identified	5	8.3
LN* metastasis	Positive	17	28.3
	Negative	34	56.7
	Not identified	9	15.0

PTC (papillary thyroid carcinoma), cm (centimeter), LN* (lymph node)

P27^{kip1} decreased expression was established in the PTC samples in 37/60 (61.7%) (p-value = 0.071), as shown in (Table 3). The expression of p27 protein in PTC samples is shown in (Figure 2).

Table 3: **Expression level of *p27^{kip1}* in PTC samples**

		Patients			*P* value
		No.	%	95%Confidence limit	
P27 expression level	<10%	37	61.7	49.1% -73.2%	0.071
	≥10%	23	38.3	26.8% - 50.9%	

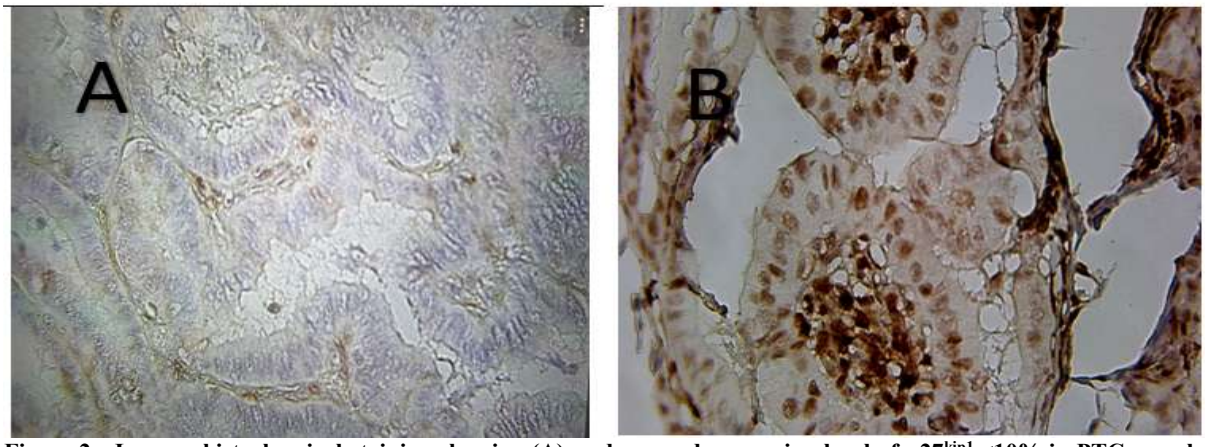

Figure 2: Immunohistochemical staining showing (A): a decreased expression level of p27^{kip1} <10% in PTC samples (40X), (B): an increased *p27^{kip1}* expression level ≥10% in PTC samples (40X).

Regarding correlation with clinicopathological parameters, decreased expression of p*27^{kip1}* was significantly correlated with female sex in 33/37(89.2%), also with classical variant PTC 31/37(83.8%), Infiltrative tumors were established in 30/37 (81.1%), size of the tumor, the *p27^{kip1}* was significantly correlated with decreased expression and tumor size (2-2.5 cm) 11/37(29.7%), and multifocal tumors were evident in 23/37(62.2%). The age of patients, extrathyroid extension, and LN metastasis were statistically not significant, as shown in (Table 4**).**

Table 4: Correlations between clinicopathological parameters and *p27^{kip1}* expression in PTC samples

		P27				*P* value
		< 10% (n=37)		≥ 10% (n=23)		
Clinicopathological parameter		No.	%	No.	%	
Age (year)	<30	3	8.1	-	-	0.247
	30 -39	9	24.3	10	43.5	
	40 -49	9	24.3	3	13.0	
	50 -59	12	32.4	7	30.4	
	60 -69	2	5.4	-	-	
	≥70	2	5.4	3	13.0	
Sex	Male	4	10.8	8	34.8	0.024
	Female	33	89.2	15	65.2	
Type of PTC	Classical	31	83.8	12	52.2	0.015
	Follicular	6	16.2	10	43.5	
	Sclerosing	-	-	1	4.3	
Presence of a capsule	Infiltrative	30	81.1	12	52.2	0.018
	Encapsulated	7	18.9	11	47.8	
Size (cm)	1.0-<1.5	5	13.5	6	26.1	0.039
	1.5-<2.0	4	10.8	10	43.5	
	2.0-<2.5	11	29.7	2	8.7	
	2.5-<3.0	4	10.8	1	4.3	
	3.0-<3.5	5	13.5	1	4.3	
	3.5-<4.0	4	10.8	1	4.3	
	≥4.0	4	10.8	2	8.7	
Multiplicity	Unifocal	14	37.8	16	69.6	0.017
	Multifocal	23	62.2	7	30.4	
Extra thyroid extension	Positive	2	5.4	1	4.3	0.659
	Negative	31	83.8	21	91.3	
	Not identified	4	10.8	1	4.3	
LN metastasis	Positive	14	37.8	3	13.0	0.077
	Negative	17	45.9	17	73.9	
	Not identified	6	16.2	3	13.0	

PTC=papillary thyroid carcinoma; cm =centimeter; LN=lymph node.

Discussion

Papillary thyroid carcinoma is a particularly common malignant tumor. Cell proliferation and cell cycle entry are regulated through a complex interaction between cyclins and cyclin-dependent kinases (CDKs). *p27kip1* is essential for G1/S phase cell-cycle control. Moreover, the p27kip1gene is an atypical tumor suppression gene whose encoded proteins block the cell cycle by inducing G1 phase cessation (27, 28). Thus, diminished expression of *p27kip1*signifies a reduction in tumor suppression. Decreased expression of p27 protein in thyroid parenchymal tissue is clinically linked to the malignant nature and aggressiveness of tumors (29, 30).

In this study, the expression levels of p27 were evaluated in PTC samples, with a particular focus on identifying the proportion of cases showing reduced expression and its potential clinical relevance. among the 60 patients analyzed, decreased nuclear expression of *p27kip1* (defined as <10% positive tumor cells) was observed in 61.7%. Although the difference approached statistical significance, the *P*-value was 0.071.

Reduced expression of *p27kip1* has been previously implicated in the pathogenesis and progression of several malignancies (31), including thyroid cancer, due to its role as a cyclin-dependent kinase inhibitor involved in cell cycle regulation. The observed increasing rate of low *p27kip1* expression in the current study supports the hypothesis that loss of *p27kip1* may contribute to tumor progression in a substantial subset of PTC cases.

The borderline p-value (0.071) may reflect limitations in sample size or interobserver variability in immunohistochemical scoring. Further studies with larger sample sizes or additional molecular correlations may help clarify whether decreased *p27kip1* expression has independent prognostic value in PTC. The current study finding is comparable with Guerra *et al.* (32), who reported a decreased expression in 72 (66.7%) of the Italian population using immunohistochemistry. Decreased expression of *p27kip1* was detected in Do *et al.* (29) in Korea. The decreased expression of *P27kip1* in PTC was detected in 81/107 (75.7%), with a significant p-value of 0.019. P27 protein was detected by the immunohistochemical technique, Erickson *et al.* (33), *p27kip1* decreased expression was detected in 30/32 (94%), also detected by immunohistochemical staining. In Özbek *et al.* (34), in the Turkish population, P27kip1 expression was detected in 94.1% by the immunohistochemical technique. There was variation in levels of expression of *p27kip1* in this study, although all studies detected the P27 protein by the same technique. This may be due to interobserver variability in immunohistochemical scoring (some studies used a quantitative method while others used a qualitative method), variation in sample size and sample selection (high-risk variants such as tall cell variants and columnar not evident in the study, papillary microcarcinoma excluded), and geographical variation. Since all studies showed an increased rate of decrease in *P27kip1* expression in PTC, as in our study; this indicates that *P27kip1* is an important genetic marker for the assessment of PTC. The rate of loss of *p27kip1* expression in patients with PTC in eligible studies varied from 10.2% to 92.3%, according to a meta-analysis in Nae *et al.* (35).

Regarding the clinicopathological parameters, decreased P27 expression was most evident in the age group 50-59 years (32.4%), which may highlight that decreased expression of *P27kip1* may be related to the older age group. In contrast, higher *p27kip1* expression was more common in patients aged 30–39 years (43.5%). Although no significant association was observed, this pattern may reflect age-related changes in tumor biology. In Pešutić-Pisac *et al.* (36), the correlation with older age was not significant.

A significant correlation was found between reduced *P27*kip1 expression and female sex. This likely reflects both the predominance of females in the study sample and the higher incidence of PTC in women, suggesting a potential role of sex hormones in *P27kip1* regulation during thyroid tumorigenesis. Valdi Pešutić-Pisac *et al.* (35), there was a significant correlation with female gender. A strong correlation was also observed between *p27kip1* expression and tumor variant. The classical variant of PTC was more frequently associated with reduced *p27kip1* expression (83.8%) and was significantly associated with the ≥10% *p27kip1* group, while the follicular variant showed relatively higher expression (43.5%). This may reflect differences in molecular pathways driving tumor behavior in different histological subtypes (many of these follicular variant tumors were encapsulated, with low-risk behavior). In Valdi Pešutić-Pisac *et al.* (36), there was a significant correlation with high-risk subtypes. Regarding tumor invasiveness, the majority of cases with low *p27kip1* expression were infiltrative tumors (81.1%), whereas encapsulated tumors were more common in the high-expression group (47.8%). This suggests a potential role for *p27kip1* downregulation in promoting local invasion and loss of tumor capsule integrity. In Valdi Pešutić-Pisac *et al.* (36), there was a significant correlation of *P27kip1* with infiltrative tumors. Tumor size also demonstrated a clear association with p27 expression. More specifically, tumors measuring 1.5 cm were present in 43.5% of high p27 cases, while tumors ≥2.0 cm were predominantly seen in the low-expression group. This inverse relationship between tumor size and *p27kip1* expression supports the role of *p27kip1* in tumor aggressiveness. In Pešutić-Pisac *et al.*. 2008 (36), the association with the large size of the tumor was not significant.

In terms of tumor multifocality, multifocal tumors were more commonly observed in the low-expression group (62.2%) compared to 30.4% in the higher expression group, suggesting that reduced

p27^{kip1} expression may be associated with an aggressive behavior of the tumors. Likewise, lymph node metastasis was more frequent among patients with low *p27^{kip1}* expression (37.8%) compared to those with higher expression (13.0%), and extrathyroidal extension was infrequent in both groups. The extrathyroid extension and lymph node metastasis in the current study were not significant; this might be related to the number of samples as a whole and the number of samples that were reported to have LN involvement and extrathyroid extension. Since the samples were randomly chosen, in Valdi Pešutić-Pisac *et al.*. 2008, , both LN metastasis and extrathyroid extension were significant, Büşra Özbek *et al.* 2024 (34), weak staining was detected in 50% of positive LN involvement in PTC. This is also recorded in Kim NY *et al.* 2017 (35). So, the current results may serve as additional data that support previous studies on decreased *p27^{kip1}* expression and tumor aggressiveness, and may play a role in tumor prognosis.

Limitation

This study was limited by a small sample size, which affected the generalizability of results. Cost constraints and the difficulty of obtaining quality FFPE (Formalin-Fixed, Paraffin-Embedded) samples, manifested as tissue degradation in some samples, have impacted immunohistochemical analysis. Additionally, limited resources restricted the use of more advanced, higher-sensitivity molecular techniques such as NGS (Next-Generation Sequencing) and digital PCR (Polymerase Chain Reaction).

Conclusion

The present study demonstrated that reduced expression of p27^{kip1} was evident in papillary thyroid carcinoma at a high rate and was associated with several indicators of aggressive tumor behaviour. These findings suggested that decreased p27 expression may serve as a potential marker of tumor aggressiveness and could have prognostic value in the clinical assessment of PTC patients.

Authors' declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the National Center for Teaching Laboratories, Medical City Complex, Baghdad (issue No. 11582 dated 19 March 2023) and from the Research Ethics Committee in the Department of Pathology and Forensic Medicine, College of Medicine, University of Baghdad (issue No. 197-B, dated 24 December 2023).

Conflicts of Interest: None.

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Data availability: Upon reasonable request, the corresponding author will make the data sets generated and/or analyzed during the current work available.

Authors' contributions:

Study conception & design: (Wafaa Khalel Ibrahim). Literature search: (Wafaa Khalel Ibrahim). Data acquisition: (Wafaa Khalel Ibrahim). Data analysis & interpretation: (Wafaa Khalel Ibrahim & Khitam Razzaq Alkhafaji), Manuscript preparation: (Wafaa Khalel Ibrahim). Manuscript editing & review: (Wafaa Khalel Ibrahim).

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دور بروتين p27kip1 في عدوانية سرطان الغدة الدرقية الحليمي: تحليل سريري مرضي

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الخلاصة

الخلفية:درست البروتينات المنظمة لدورة الخلية، بما في ذلك p27^kip1، في أنواع مختلفة من الأورام الخبيثة، ومنها سرطان الغدة الدرقية، وذلك بسبب ارتباطها المحتمل بعدوانية الورم واحتمالية تكراره.

الهدف: هدفت هذه الدراسة إلى تقييم العلاقة بين انخفاض التعبير عن بروتين p27^kip1 والعوامل السريرية والمرضية المرتبطة بسلوك سرطان الغدة الدرقية الحليمي (PTC)، ولا سيما المؤشرات التي تدل على عدوانية الورم.

المواد والطرق: تم الحصول على كتل أنسجة محفوظة بالبارافين ومثبتة بالفورمالين (FFPE) من حالات مثبتة نسيجيا من سرطان الغدة الدرقية الحليمي، والتي شخصت خلال الفترة من يونيو 2022 إلى يونيو 2023 في المركز الوطني للمختبرات التعليمية، مجمع مدينة الطب، بغداد، العراق. شملت الدراسة 60 حالة من سرطان الغدة الدرقية الحليمي. اجرى تحليل مناعي نسيجي لتقييم مستوى التعبير عن بروتين p27^kip1. كما جرى تحليل العلاقة بين مستوى تعبير هذا البروتين وعدد من العوامل السريرية والمرضية، بما في ذلك عمر المريض، الجنس، النمط النسيجي للورم، حجم الورم، وجود غزو كبسولي، التعدد البؤري، الامتداد خارج الغدة، ونقائل العقد اللمفاوية.

النتائج: سجل انخفاض في التعبير عن p27^kip1 بنسبة أقل من 10% في 37 من أصل 60 حالة (61.7%).كما وقد أظهرت التحليلات وجود علاقة معنوية إحصائيا بين انخفاض التعبير عن p27^kip1 وبعض العوامل السريرية والمرضية، وتشمل: الجنس الأنثوي ، النمط الكلاسيكي من سرطان الغدة الدرقية الحليمي ، الأورام ذات النمط التسللي او الارتشاحي ، زيادة حجم الورم ، والتعدد البؤري.

الاستنتاج: لوحظ انخفاض تعبير p27kip1 (<10٪) بمعدل مرتفع نسبيا في سرطان الغدة الدرقية الحليمي، ووجد ارتباط كبير بين انخفاض تعبير P27kip1 وعدة سمات سريرية مرضية، بما في ذلك نمط الأورام الارتشاحي، وحجم الورم الكبير، والتعددية البؤرية. تشير هذه النتائج إلى أن انخفاض تعبير P27kip1 قد يكون مرتبطا بسلوك الورم الأكثر عدوانية ويمكن أن يكون بمثابة علامة إنذارية في سرطان الغدة الدرقية الحليمي.

مفتاح الكلمات: المؤشرات السريرية المرضية، مثبط كيناز معتمد على الدورات الخلوية p27kip1 ، الكيمياء النسيجية امناعية، سرطان الغدة الدرقية الحليمي، عدوانية الورم.