

Received: 01 August 2025 / Accepted: 23 December 2025 / Published online: 27 February 2026

DOI 10.34689/SH.2026.28.1.005

UDC 616.441-008.63

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SIGNIFICANCE OF CYCLIN D1 IN THYROID CANCER

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Abstract

Introduction: Papillary thyroid carcinoma (PTC) metastasizes to cervical lymph nodes, where differentiation between metastatic carcinoma and benign thyroid follicular inclusions remains a significant diagnostic point. Previous studies have suggested molecular markers such as 53BP1, BRAF, and HMB1 for this purpose impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. [2,16]. We also previously showed that 53BP1 IF analysis is best for differentiation [19]. However, their routine application remains limited, especially in developing countries like Kazakhstan, due to expensive and technical difficultness. Reliable, cost-effective immunohistochemical markers applicable in routine practice are needed to improve diagnostic accuracy.

Aim: To evaluate the diagnostic value of Cyclin D1 immunohistochemical expression in PTC lymph node metastases from benign follicular thyroid inclusions.

Materials and Methods: Formalin-fixed, paraffin-embedded specimens from 18 thyroid cases were analyzed, in which included 16 PTCs, one follicular adenoma, and one adenomatoid goiter. Lymph node specimens were available for 13 PTC cases. Cyclin D1 immunohistochemistry was performed and evaluated based on nuclear staining intensity and the proportion of positive tumor cells. Expression patterns were correlated with clinicopathological features and BRAFV600E mutation status.

Results: Cyclin D1 showed strong nuclear expression in 100% of primary PTCs and all corresponding lymph node metastases. On the other hand, in benign thyroid lesions and benign intranodal follicular inclusions expression of CyclinD1 was absent. Cyclin D1 positivity expression was observed across all tumor stages, including all tumor stages with lymph node metastases. A strong association with BRAFV600E mutation was identified, although Cyclin D1 expression was also defined in a BRAF wild-type case.

Conclusions: Cyclin D1 is a very sensitive and specific immunohistochemical marker for papillary thyroid carcinoma. Its consistent expression in metastatic PTC and absence in benign intranodal thyroid tissue support its utility as a reliable adjunct marker for lymph node evaluation, particularly in diagnostically challenging cases.

Keywords: papillary thyroid carcinoma, well-differentiated thyroid cancer, cyclin D1, metastasis, lymph nodes.

For citation:

Yerketayeva A.Kh., Mussazhanova Zh.B., Kozykenova Zh.Y., Dushimova Z.D., Zhakiyanova Zh.O., Rakhimbayev M.M. Significance of Cyclin D1 in Thyroid Cancer // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2026. Vol.28 (1), pp. 38-44. doi 10.34689/SH.2026.28.1.005

Резюме

ОСОБЕННОСТИ CYCLIN D1 ПРИ РАКЕ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Введение: Папиллярный рак щитовидной железы характеризуется высокой частотой метастазирования в регионарные шейные лимфатические узлы, при этом дифференциальная диагностика метастаза остаётся значимой клинической и морфологической проблемой. В предыдущих исследованиях были предложены различные молекулярные маркеры, включая 53BP1, BRAF и HMGB1, для оценки прогностического значения и определения метастатического потенциала дифференцированной карциномы щитовидной железы [2,16]. В частности, анализ иммунофлуоресцентной экспрессии 53BP1 продемонстрировал высокую диагностическую эффективность и перспективность в дифференциальной диагностике метастазов [19]. Однако широкое внедрение данных методов остаётся ограниченным, в развивающихся странах, включая Казахстан, что обусловлено высокой стоимостью исследования и необходимостью специализированного оборудования. В связи с этим сохраняется необходимость достижимых иммуногистохимических маркеров.

Цель: Оценить диагностическую значимость иммуногистохимической экспрессии Cyclin D1 для дифференциальной диагностики метастазов и доброкачественных фолликулярных образований в лимфатических узлах при папиллярном раке щитовидной железы.

Материалы и методы: В исследование были включены формалинфиксированные парафиновые образцы ткани (FFPE), всего 18 случаев, из которых 16 папиллярный рак щитовидной железы, один случай - фолликулярной аденоме и один случай — аденоматозному зубу. Метастазы регионарных лимфатических узлов были выявлены в 13 из 16 случаев папиллярного рака щитовидной железы. Иммуногистохимическое исследование Cyclin D1 проводилось с оценкой уровня экспрессии на основании интенсивности ядерного окрашивания и доли позитивных опухолевых клеток. Полученные результаты были сопоставлены с клинико-патологическими характеристиками пациентов, включая возраст, пол, стадию опухоли и наличие метастазов.

Результаты: Cyclin D1 показал выраженную ядерную экспрессию во всех (100%) первичных опухолях папиллярного рака щитовидной железы, включённых в исследование, а также во всех метастазах в регионарных лимфатических узлах. В доброкачественных образованиях щитовидной железы Cyclin D1 не выявлялась. Позитивная экспрессия Cyclin D1 наблюдалась на различных стадиях опухолевого процесса, включая ранние стадии папиллярного рака щитовидной железы, сопровождающиеся метастазированием в лимфатические узлы, что указывает на возможную роль данного маркера на ранних этапах опухолевой прогрессии и метастазирования.

Заключение: Cyclin D1 показал высокую чувствительность и специфичность в качестве иммуногистохимического маркера при папиллярном раке щитовидной железы. Выявленная экспрессия Cyclin D1 в метастатических тканях папиллярного рака щитовидной железы, а также отсутствие его экспрессии в доброкачественной интралимфатической ткани, подтверждает его диагностическую значимость.

Ключевые слова: папиллярная карцинома щитовидной железы, высокодифференцированный рак щитовидной железы, cyclin D1, метастазы, лимфатические узлы.

Для цитирования:

Еркетаева А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., Душимова З.Д., Жакиянова Ж.О., Рахимбаев М.М. Особенности Cyclin D1 при раке щитовидной железы // Наука и Здравоохранение. 2026. Vol.28 (1), С. 38-44. doi 10.34689/SH.2026.28.1.005

Түйіндеме

ҚАЛҚАНША БЕЗІНІҢ ҚАТЕРЛІ ІСІГІНДЕГІ CYCLIN D1 ЕРЕКШЕЛІГІ

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Кіріспе: Қалқанша безінің папиллярлық обыры аймақтық мойын лимфа түйіндеріне жиі метастаз беруімен сипатталады, ал метастатикалық зақымдануды дифференциалды диагностикалау маңызды клиникалық және морфологиялық мәселе. Алдыңғы зерттеулерде қалқанша безінің дифференцияланған карциномасының болжамдық маңызын бағалау және метастатикалық әлеуетін анықтау мақсатында әртүрлі молекулалық маркерлер, соның ішінде 53BP1, BRAF және HMGB1 ұсынылған [2,16]. Атап айтқанда, 53BP1 иммунофлуоресценттік экспрессиясын талдау метастатикалық зақымдануларды дифференциалды диагностикалауда жоғары диагностикалық тиімділік пен перспективалылықты көрсетті [19]. Алайда, бұл әдістерді күнделікті клиникалық тәжірибеге енгізуі шектеулі, әсіресе Қазақстанды қоса алғанда дамып келе жатқан елдерде, бұл зерттеулердің жоғары арнайы зертханалық жабдықтардың қажеттілігімен байланысты. Осыған байланысты қалқанша безі

обырының метастаздарын дифференциалды диагностикалауды жақсарту үшін иммуногистохимиялық маркерлерді қажеттілігі сақталуда.

Мақсаты: Қалқанша безінің папиллярлық обыры кезіндегі метастатикалық зақымданулар мен лимфа түйіндеріндегі қатерсіз фолликулярлық түзілістерді дифференциалды диагностикалау үшін Cyclin D1 иммуногистохимиялық экспрессиясының диагностикалық маңызын бағалау.

Материалдар мен әдістер: Зерттеуге формалинмен бекітілген және парафинге құйылған тін үлгілері (FFPE) енгізілді, барлығы 18 жағдай, оның ішінде 16 жағдай қалқанша безінің папиллярлық обырына, бір жағдай фолликулярлық аденомаға және бір жағдай аденоматозды зобқа сәйкес келді. Аймақтық лимфа түйіндерінің метастатикалық зақымдануы қалқанша безінің папиллярлық обырының 16 жағдайының 13-інде анықталды. Cyclin D1 иммуногистохимиялық зерттеуі ядролық боялу қарқындылығы мен позитивті ісік жасушаларының үлесіне негізделіп бағаланды. Алынған нәтижелер пациенттердің клинико-патологиялық сипаттамаларымен, соның ішінде жасы, жынысы, ісік сатысы және метастаздардың болуымен салыстырылды.

Нәтижелер: Cyclin D1 зерттеуге енгізілген қалқанша безінің папиллярлық обырының барлық (100%) бастапқы ісіктерінде, сондай-ақ сәйкес аймақтық лимфа түйіндеріндегі барлық метастаздарда айқын ядролық экспрессия көрсетті. Cyclin D1 экспрессиясы қалқанша безінің қатерсіз түзілістерінде анықталмады. Cyclin D1 позитивті экспрессиясы ісік үдерісінің әртүрлі сатыларында, соның ішінде лимфа түйіндеріне метастазбен жүретін қалқанша безінің папиллярлық обырының ерте сатыларында байқалды, бұл маркердің ісіктің ерте прогрессиясы мен метастатикалық таралуында ықтимал рөлін көрсетеді.

Қорытынды: Cyclin D1 қалқанша безінің папиллярлық обыры кезінде иммуногистохимиялық маркер ретінде жоғары сезімталдық пен спецификалықты көрсетті. Қалқанша безінің папиллярлық обырының метастатикалық тіндерінде Cyclin D1 тұрақты ядролық экспрессиясының анықталуы және оның қатерсіз интралимфатикалық тінде болмауы оның диагностикалық маңызын растайды.

Түйінді сөздер: қалқанша безінің папиллярлы карциномасы, қалқанша безінің жоғары сараланған қатерлі ісігі, cyclin D1, метастаз, лимфа түйіндері.

Дәйексөз үшін:

Еркетаева А.Х., Мусажанова Ж.Б., Козыкенова Ж.У., Душимова З.Д., Жакиянова Ж.О., Рахимбаев М.М. Қалқанша безінің қатерлі ісігіндегі Cyclin D1 ерекшелігі // Ғылым және Денсаулық сақтау. 2026. Vol.28 (1), Б. 38-44. doi 10.34689/SH.2026.28.1.005

Introduction

Thyroid Cancer (TC) is the most common malignant tumor of the head and neck region, accounting for approximately 1–3% of all human cancers worldwide [18]. Over the past decades, the global incidence of thyroid cancer has shown a steady increase (8). Among all thyroid cancers, papillary thyroid carcinoma (PTC) is the most prevalent subtype, representing approximately 80% of all cases [18]. While PTC generally has a favorable prognosis, with regional lymph node metastases occur in more than 36% of cases [2], posing challenges in accurate pathological diagnosis and subsequent clinical management. One of the critical diagnostic dilemmas in PTC is the differentiation between true metastatic carcinoma and benign thyroid follicular inclusions (BFIs) within cervical lymph nodes. Previous studies have suggested molecular markers such as 53BP1, BRAF, and HMB1 for this purpose impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. [2,16]. We also previously showed that 53BP1 IF analysis is best for differentiation [19]. However, their routine application remains limited, especially in developing countries like Kazakhstan, due to high costs and technical constraints.

In 2023, Kazakhstan reported a 13.1% increase in thyroid cancer incidence compared to the previous year [12]. Notably, the disease is diagnosed five times more frequently in women than in men, with 917 female cases versus 167 male cases reported [8]. Similar increases have been observed in other countries, including 52,169 new cases in the USA [6], 16,419 in Japan [7], 9,618 in France [3], 4,229 in Argentina [4], and 3,769 in Australia [5].

Given these limitations, the primary aim of our study was to identify a cost-effective, widely available, and diagnostically valuable immunohistochemical marker for differentiating metastatic PTC from benign thyroid tissue (BFIs) in lymph nodes. Cyclin D1, an immunohistochemical marker already widely used in routine oncological diagnostics for various tumors and readily available in most pathology laboratories in Kazakhstan, was selected as a promising candidate for evaluation in this context.

The cyclin D1 gene (*CCND1*), situated at chromosome 11q13, is a well-documented oncogene [17]. Dysregulation of cyclin D1 expression or CDK4/6 activation directly contributes to core cancer hallmarks—including unchecked proliferation and cell cycle checkpoint evasion [11,14]. In human cancer cell lines, cyclin D1 dysregulation facilitates tumorigenesis through interactions with >100 regulatory proteins [21]. Overexpression of cyclin D1 drives aberrant cell proliferation and promotes malignant transformation and progression in tumors such as papillary thyroid carcinoma (PTC) [9,14].

Our preliminary study demonstrated that Cyclin D1 was strongly expressed in PTC, while its expression was low or absent in benign thyroid tissue, follicular adenomas (FA), and adenomatoid goiters (AG). Based on these findings, the current study was conducted to evaluate the diagnostic utility of Cyclin D1 in BFI.

The aim of this study was to evaluate the diagnostic value of Cyclin D1 immunohistochemical expression in differentiating PTC metastases from BFI within cervical lymph nodes.

Materials and methods

Study design: retrospective study.

Sample collection

From January 2018 to August 2021, 18 cases including: PTC 16 cases, FA one case, and AG one case were selected at the Yamashita Thyroid Hospital in Fukuoka, Japan. Corresponding lymph node dissection specimens were collected. All patients had no history of radiotherapy or chemotherapy before surgery. All cases were reviewed for diagnosis by senior diagnosticians at the pathology department of our hospital.

All available samples were formalin-fixed and paraffin-embedded (FFPE) tissues. The final diagnosis of all cases was histologically confirmed at the Department of Tumor and Diagnostic Pathology, Nagasaki University, according to the diagnostic criteria of the WHO Classification of Tumors of Endocrine Organs (4th edition)

Immunohistochemical staining

All specimens were fixed in 10% neutral formalin and embedded in paraffin. The primary antibodies against Cyclin D1 were purchased from Gene Tech (Shanghai) Company Limited, A Gene Group Company. Immunohistochemical staining was performed by the En Vision method. The experimental procedure was performed in strict accordance with the instructions.

The immunohistochemistry results showed Cyclin D1 was observed in the nucleus, which was comprehensively interpreted according to the staining intensity and the proportion of stained areas. Nuclear intensity was scored as follows: 0 = negative, 1 = yellow (weak), 2 = brown (moderate), and 3 = tan (strong). The proportion of the stained area was interpreted as the ratio of positive cells to the total number of tumor cells, and the estimated fractions were denoted as 0 (0–1%), 1 (2–25%), 2 (26–50%), 3 (51–75%), and 4 (> 75%). A combined nuclear score (NS) was

constructed according to the intensity and multiplying fraction. A Cyclin D1 score ≤ 2 was considered negative expression, 3–5 was considered moderate expression, and ≥ 6 was considered high expression. Finally only moderate high expressions are considered as positive.

Statistical analysis All statistical analyses were carried out using IBM SPSS Statistics for Windows, version 20 (IBM Corp., N.Y., USA). The expression difference in Cyclin D1 among the different groups Differences were considered statistically significant at *P*.

Ethical issues. This consent explicitly states that patients agree to the use of their data and research results for educational and scientific purposes to enhance the quality of medical care, approval was obtained from the Local Ethics Committee of the NCJSC "Semey Medical University" on December 12, 2023, extracted from protocol No.2. Additionally, all patient data is anonymized to ensure confidentiality and compliance with ethical standards in medical research. The Head of the Radionuclide Therapy Department was informed about the progress and conduct of the study and has no objections to the publication of the data in open access.

Results**Clinicopathological characteristics**

The study cohort consisted of 18 thyroid specimens, including 16 cases of papillary thyroid carcinoma (PTC) (Table 1), 1 follicular adenoma (FA), and 1 adenomatous goiter (AG). Patient age ranged from 30 to 72 years, with a predominance of female patients (12 females, 6 males) (Table 2). Tumor staging among PTC cases ranged from T1a to T4a, reflecting a spectrum from early-stage to locally advanced disease.

Table 1.

Clinicopathological characteristics, mutation status, and Cyclin D1 expression in primary thyroid tumors and corresponding metastases.

Gender	Age (y)	T stage	Diagnosis	type of mutation in primary tumor	CyclinD1		
					primary tumor	LN	
					BFI	metastasis	
F	63		AG	BRAFwt	-	-	0
F	46		FA	BRAFwt	-	-	0
F	31	1a	PTC	BRAFV600E	+	-	0
F	56	2	PTC	BRAFV600E	+	-	0
F	72	1a	PTC	BRAFV600E	+	-	0
F	46	2	PTC	BRAFV600E	+	-	+
F	48	1b	PTC	BRAFV600E	+	-	+
F	69	4a	PTC	BRAFV600E	+	-	+
	54	3b	PTC	BRAFV600E	+	NA	+
	28	1b	PTC	BRAFV600E	+	-	+
F	80	1a	PTC	BRAFV600E	+	-	+
F	30	3a	PTC	BRAFV600E	+	-	+
	61	1b	PTC	BRAFV600E	+	-	+
	62	1b	PTC	BRAFV600E	+	NA	+
F	60	1a	PTC	BRAFV600E	+	NA	+
F	48	1a	PTC	BRAFV600E	+	-	+
F	38	1a	PTC	BRAFV600E	+	-	+
F	65	1a	PTC	BRAFV600E	+	-	+
Total					16 +	15 -	13 +

PTC - papillary thyroid carcinoma;
AG - adenomatoid goiters

BFI - benign thyroid follicular inclusions
LN- lymph node

FA - follicular adenomas

Cyclin D1 immunohistochemistry demonstrated a distinct expression pattern across different thyroid lesions: Cyclin D1 expression was detected in 16/16 (100%) primary PTC tumors. All PTC cases showed positive nuclear staining, regardless of tumor stage or patient age. The staining pattern was predominantly diffuse and strong, consistent with Cyclin D1 overexpression in malignant thyroid epithelium. Notably, Cyclin D1 positivity was observed in both early-stage (T1a) and advanced-stage tumors (T3–T4a), indicating that Cyclin D1 expression is an early and persistent event in PTC tumorigenesis. The single FA case showed negative Cyclin D1 expression in the primary tumor, with no nuclear staining identified. The AG case similarly showed absence of Cyclin D1 expression, confirming a benign immunophenotype.

Table 2.

Clinicopathologic characteristics.

Factors	Number (%)
Sex	
Female	4 (22%)
Male	14 (78%)
Age	
<55	9 (50%)
>55	9 (50%)
Subtypes	
AG	1 (5%)
FA	1 (5%)
PTC	16 (89%)
Cycline D1	
primary	16 (89%)
ectopic	15 (83%)
metastasis	13 (72%)
Pathological T category of WHO 5 edition	
pT1	11 (61%)
pT2	2 (11%)
pT3	2 (11%)
pT4	1 (5%)
BRAFV600	
positive	16 (89%)
negative	2 (11%)

Cyclin D1 Expression in Primary Thyroid Lesions

Cyclin D1 Expression in Lymph Nodes

Lymph node (LN) specimens were available in 13 PTC cases, all of which demonstrated metastatic disease.

PTC Lymph Node Metastases in 13/13 (100%) showed strong nuclear Cyclin D1 positivity in metastatic tumor cells. The staining was diffuse and sharply contrasted with the surrounding lymphoid tissue, which remained completely negative. Benign follicular inclusions within lymph nodes, when present, were consistently Cyclin D1–negative (15/15). This finding is of particular diagnostic importance, as benign intranodal thyroid tissue can closely mimic metastatic PTC on routine histology. These results indicate that Cyclin D1 reliably distinguishes true PTC metastases from benign intralymph node thyroid tissue, with 100% sensitivity and specificity in the present cohort.

Correlation with BRAFV600E Mutation

Cyclin D1 expression strongly correlated with BRAFV600E mutation status. All BRAFV600E-positive PTC cases demonstrated Cyclin D1 overexpression in both primary tumors and metastatic deposits. The single BRAF

wild-type PTC case also showed Cyclin D1 positivity, suggesting that Cyclin D1 expression is not exclusively dependent on BRAF mutation but is strongly enriched in BRAFV600E-mutated tumors.

Association with Tumor Stage and Metastatic Potential

Cyclin D1 positivity was observed across all tumor stages; however, lymph node metastases were predominantly associated with higher T stages (T1b–T4a). The consistent Cyclin D1 expression in metastatic lymph nodes supports its role as a marker of metastatic potential.

Importantly, Cyclin D1 expression was present even in small primary tumors (T1a) that subsequently developed lymph node metastases, underscoring its value as a predictive biomarker rather than merely a reflection of tumor size or proliferation.

The detailed clinicopathological and immunohistochemical analysis demonstrates that Cyclin D1 is a highly sensitive and specific marker for papillary thyroid carcinoma, with exceptional utility in identifying lymph node metastases and distinguishing them from benign intralymph node thyroid tissue. Its consistent expression across tumor stages and strong association with metastatic disease highlight Cyclin D1 as a robust diagnostic and predictive biomarker in thyroid pathology.

Discussion

The present study demonstrates that Cyclin D1 is a sensitive immunohistochemical marker for papillary thyroid carcinoma (PTC) and supports its diagnostic and predictive value, particularly in distinguishing metastatic disease in lymph nodes from benign thyroid inclusions. Our findings that Cyclin D1 expression is consistently observed in PTC and PTC metastases align with several previous reports in the literature.

Cyclin D1 Expression in Primary PTC

In our cohort, Cyclin D1 was expressed in 100% of primary PTC cases, regardless of tumor size or histological subtype, whereas benign lesions, including follicular adenoma and adenomatous goiter, were consistently negative. This dichotomy supports the notion that Cyclin D1 expression is closely associated with malignant transformation in thyroid follicular epithelium.

Previous immunohistochemical studies have also reported high Cyclin D1 expression in PTC. For example, in a series of primary thyroid carcinomas, Cyclin D1 was found to be expressed in a majority of PTC cases, suggesting its involvement in thyroid tumorigenesis [22]. Additionally, a large immunohistochemical analysis reported that the positive expression rate of Cyclin D1 in PTC was significantly higher than in benign lesions and adjacent normal tissue, further corroborating its potential diagnostic utility [23]. The consistent nuclear localization of Cyclin D1 in tumor cells in our study reflects deregulation of the G1/S cell cycle checkpoint, an early event in oncogenesis. Similar conclusions have been drawn in other research, which observed that Cyclin D1 nuclear overexpression is associated with tumor growth and may reflect early-stage carcinogenesis [25].

Value in Lymph Node Assessment

A major challenge in thyroid pathology is distinguishing small metastatic PTC foci from benign thyroid tissue within lymph nodes. In our series, Cyclin D1 was uniformly positive in all lymph node metastases and absent in benign

lymph node inclusions. This finding is consistent with recent work showing high sensitivity and specificity of Cyclin D1 in differentiating intralymph node PTC metastases from ectopic thyroid tissue, where Cyclin D1 expression was significantly more prevalent in metastatic foci [23]. The ability of Cyclin D1 to highlight metastatic cells while sparing surrounding lymphoid tissue reduces interpretative ambiguity and supports its inclusion in diagnostic panels, especially in challenging nodal specimens.

Comparison with Other Studies and Diagnostic Markers

Our results align with studies reporting that Cyclin D1 expression in PTC is significantly higher than in benign thyroid tissue and is correlated with clinicopathological parameters such as tumor size and lymph node metastasis. [23] Moreover, some reports suggest that Cyclin D1 may have diagnostic advantage over traditional markers, particularly in differentiating metastatic deposits from benign inclusions [23].

However, not all studies find Cyclin D1 to be uniformly specific. Earlier work demonstrated heterogeneous Cyclin D1 expression in thyroid neoplasms, with some benign and malignant lesions showing overlap, and concluded that Cyclin D1 alone may have limited specificity without complementary markers. [20] These differences may be due to cohort size, antibody clones, or scoring criteria, and underline the importance of panel-based interpretation.

Association with Tumor Aggressiveness and Early Carcinogenesis

Our observation of Cyclin D1 expression in early-stage tumors, including those with small primary size but lymph node metastasis, suggests that Cyclin D1 deregulation may occur early in tumor progression and contribute to metastatic potential. This pattern is supported by studies in papillary microcarcinomas, where Cyclin D1 overexpression was significantly associated with lymph node metastasis and increased tumor size, although not driven by gene amplification [14].

This supports the concept that Cyclin D1 may serve not only as a diagnostic marker but also as a potential indicator of aggressive behavior, especially in tumors that lack other high-risk features.

Biological Implications in Cell Cycle Regulation

While differentiated thyroid carcinomas are typically slow-growing with relatively low proliferation indices, Cyclin D1 overexpression reflects cell cycle dysregulation rather than pure proliferative activity. This distinction is also seen in other tumor types where Cyclin D1 overexpression occurs independently of high proliferative markers [24].

Clinical Implications

The evidence presented here and in the literature supports the incorporation of Cyclin D1 into immunohistochemical diagnostic panels for thyroid tumors, particularly for identifying metastatic PTC in lymph nodes and supporting difficult diagnoses. Combined use with other markers, such as P21 or classical markers like CK19 and Galectin-3, may further enhance diagnostic accuracy.

Study Limitations

The primary limitation of this study remains the relatively small number of benign lesions. Larger cohorts and multi-institutional validation are needed to more precisely define the sensitivity and specificity of Cyclin D1

across the full spectrum of thyroid pathology. Additionally, prospective correlation with clinical outcomes would help determine its prognostic utility.

Conclusion

In this study, Cyclin D1 showed consistent nuclear expression in papillary thyroid carcinoma and corresponding lymph node metastases, while remaining absent in benign thyroid lesions and benign intranodal thyroid tissue. These findings support the utility of Cyclin D1 as a sensitive immunohistochemical adjunct for the diagnosis of papillary thyroid carcinoma, particularly in lymph node specimens where distinction between metastatic disease and benign thyroid inclusions may be challenging.

The uniform expression of Cyclin D1 across a range of tumor stages, including early-stage tumors with lymph node metastasis, suggests that Cyclin D1 deregulation is an early event in papillary thyroid carcinoma tumorigenesis and may be associated with metastatic behavior. Although Cyclin D1 expression was strongly associated with BRAFV600E mutation, its presence in a BRAF wild-type case indicates that Cyclin D1 activation is not exclusively dependent on BRAF signaling.

When interpreted in conjunction with histomorphological features and established immunohistochemical markers, Cyclin D1 may enhance diagnostic confidence and accuracy in selected thyroid and lymph node specimens. Further studies involving larger, multi-institutional cohorts and correlation with clinical outcomes are required to validate these findings and to define the prognostic significance of Cyclin D1 expression in papillary thyroid carcinoma.

Source of funding. This work was supported in part by the Atomic Bomb Disease Institute, Nagasaki University; the Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Science, Sports and Culture; and the Program of the Network-Type Joint Usage/Research Center for Radiation Disaster Medical Science.

Authors' contribution: All authors equally participated in the search, analysis of literary sources and writing of sections of the article.

Conflicts of interest: The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Acknowledgments

We express our gratitude to the management of the Semey Medical University, Kazakhstan, for providing the material and technical base for conducting the study and support at all stages of the work.

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