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ارتباط تعبير جين *DLL3* بانتقال العقد اللمفاوية لدى المرضى العراقيين المصابين بسرطان الغدة الدرقية النخاعي المتفرق

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المستخلص:

يُعدّ سرطان الغدة الدرقية النخاعي (MTC) ورمًا عصبيًا صماويًا نادرًا وشديد العدوانية يصيب الغدة الدرقية. تُشكّل الحالات المتفرقة نحو ثلاثة أرباع مجموع الحالات، وفي ٥٠% من هذه الحالات توجد طفرات جسدية في الجين الأولي الورمي RET. مؤخرًا، برز الليغاند الشبيه بدلتا ٣ (*DLL3*)، الذي يُعبَّر عنه على نطاق واسع في الأورام العصبية الصماوية، بوصفه جزيئًا هدفًا جديدًا. لذلك، فإن تحليل العلاقة بين فرط تعبير جين *DLL3* وقيمته السريرية يحظى باهتمام كبير. في هذا العمل، تمّت دراسة ٦٩ عينة من سرطان الغدة الدرقية النخاعي المتفرق محفوظة بالفورمالين ومضمّنة بالبارافين. ومن بين هذه العينات، كانت ٤٨ حالة معروفة مسبقًا بأنها مرتبطة بانتقالات مؤكدة إلى العقد اللمفاوية، في حين كانت ٢١ حالة في المرحلة الأولى أو الثانية من MTC دون إصابة عقدية. تم تقييم تعبير جين *DLL3* باستخدام تقنية RT–qPCR وربطه بالعوامل السريرية والمرضية. وُجد أن ارتفاع تعبير جين *DLL3* يرتبط بشكل ملحوظ بإصابة العقد اللمفاوية، بينما أظهرت الأورام التي لا تحتوي على تليف سدى الورم (stromal desmoplasia) غيابًا ثابتًا لتعبير *DLL3*. تؤكد هذه البيانات دور جين *DLL3* في سرطان الغدة الدرقية النخاعي وارتباطه بشدة عدوانية المرض. ويبدو أن DLL3 يُعدّ واسمًا بديلًا دقيقًا لوجود انتقالات العقد اللمفاوية، كما قد يعكس بالمثل شدة عدوانية

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المرض. ونظرًا للدور الواعد نظريًا لـ *DLL3* في علاج أورام أخرى تُعبّر عن هذا الجين، فقد يعمل *DLL3* أيضًا كهدف علاجي بديل في سرطان الغدة الدرقية النخاعي.

لكلمات المفتاحية: سرطان الغدة الدرقية النخاعي؛ DLL3؛ نقائل العقد اللمفاوية؛ أورام الغدد الصماء العصبية؛ سرطان الغدة الدرقية.

Association of *DLL3* Gene Expression with Lymph Node Metastasis in Iraqi Patients with Sporadic Medullary Thyroid Carcinoma

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ABSTRACT

Medullary thyroid carcinoma (MTC) is a rare and highly aggressive neuroendocrine tumor of the thyroid gland. Around three-fourths of cases are sporadic, and in 50% of these cases, there are somatic mutations in the RET proto-oncogene. Recently, delta-like ligand 3 (*DLL3*), which is broadly expressed in neuroendocrine tumors, emerged as a new target molecule. Therefore, the current analysis of the correlation of the overexpression of the *DLL3* gene and its clinical value is of great interest. In this work, a total of 69 formalin-fixed, paraffin-sectioned sporadic medullary thyroid carcinoma samples were studied. Among those, 48 cases were already known to be associated with confirmed lymph node metastases, and 21 cases were stage I or stage II MTC without nodal involvement. Expression of the *DLL3* gene was evaluated by RT-qPCR and correlated with clinical and pathological factors. High *DLL3* gene expression was remarkably correlated with lymph node involvement, whereas tumors without stromal desmoplasia consistently

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exhibited an absence of *DLL3* expression. These data emphasize the role of the *DLL3* gene in MTC and its correlation with disease aggressiveness. It appears that *DLL3* is an accurate surrogate marker for the presence of lymph node metastases and may similarly reflect disease aggressiveness. Given the theoretically promising role of *DLL3* in the treatment of other tumors that express the gene, *DLL3* may also serve as an alternative therapeutic target in MTC.

Keywords: medullary thyroid carcinoma; *DLL3*; lymph node metastasis; neuroendocrine tumors; thyroid cancer

1. Introduction

Medullary thyroid carcinoma (MTC) is a rare yet highly aggressive neuroendocrine malignancy originating from parafollicular C cells of the thyroid. Despite representing only a small fraction (2–3%) of thyroid cancers, MTC contributes disproportionately to thyroid cancer–related mortality, accounting for nearly 15% of deaths [1, 2]. Less than one-third of MTC cases are hereditary and occur within multiple endocrine neoplasia (MEN) syndromes, specifically MEN2A and MEN2B, driven by germline RET proto-oncogene mutations. The remaining cases are sporadic, approximately half of which exhibit somatic RET mutations. Unlike hereditary disease, sporadic MTC develops independently of background C-cell density, although non-MEN2-related C-cell hyperplasia has been reported [3, 4]. In MEN-associated disease, MTC evolves from an established neoplastic form of C-cell hyperplasia. Differentiation between neoplastic C-cell hyperplasia and early invasive hereditary micro-MTC lesions measuring less than 1 cm remains difficult, as true malignancy is defined by the invasive behavior of transformed C cells [5, 6]. Treatment options for advanced MTC are limited, and surgical resection with central and lateral cervical lymph node dissection remains the cornerstone of current management strategies [2, 7-10].

Advanced cases of MTC with a large tumor burden, for which there would not be any further surgical treatments available, may start with systemic therapy with the involvement of tyrosine kinase inhibitors being

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put into place [8]. The long-term outlook would strongly depend on the stage of the disease, with advanced stage IV MTC. This would be categorized based on severe local aggression along with the involvement of lymph node metastases or distant metastases, in addition to having a profoundly reduced ten-year survival of around 21% [2]. The NOTCH signaling pathway is an integral modulator underlying the pathogenesis of medullary thyroid carcinomas. Being an active signaling mechanism within its physiological environment, it has an important role in the regulation of C-cell division and differentiation of thyroid cells [11]. This pathway is commonly disrupted as neuroendocrine malignancies progress. The NOTCH receptor, which would be localized to the cell surface of neuroendocrine cells, would commonly interact with varied ligands. Its action would also be cell-specific, with varied theories articulating its role either as a suppressor of the tumor or an oncogenic mediator. The delta-like ligand 3 (*DLL3*) would particularly represent an inhibitor of the NOTCH signaling pathway. Being an important mechanism in the setting of aggressive neuroendocrine cancers, it would include varied entities such as those of small cell lung cancer, small cell bladder carcinoma, and metastatic neuroendocrine cancers of the prostate [11-13].

According to immunohistochemical analysis, high expression levels of *DLL3* are found in neuroendocrine cells, which depict strong membrane reactivity, while low levels are in non-neuroendocrine cells [14]. In small-cell lung cancer, high *DLL3* expression (measured by the presence of reactivity in more than 50% of tumor cells) is associated with slow tumor progression, which is a prognostic indicator. These findings establish the therapeutic potential for *DLL3* in *DLL3*-positive neuroendocrine carcinomas [14,15]. Currently, no published study has assessed *DLL3* expression in MTC in association with multiple clinicopathological parameters.

This study assessed *DLL3* expression in sporadic medullary thyroid cancer using RT-qPCR on formalin-fixed, paraffin-embedded tumor specimens from an Iraqi patient cohort. The expression of *DLL3* was analyzed in relation to major clinicopathological features, including lymph

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node metastasis, tumor grade, and stromal desmoplasia. This study examines the relationship between *DLL3* expression and metastatic potential to determine the prognostic significance of *DLL3* and assess its feasibility as a therapeutic target in medullary thyroid carcinoma.

2. Materials and methods

2.1 Samples collection

69 archival specimens of sporadic medullary thyroid carcinoma fixed in formalin and embedded with paraffin were evaluated from patients at Al-Yarmook Hospital from 2020 to 2024. The diagnosis was verified in accordance with the World Health Organization criteria issued in 2017, as explained in the paper's references concerning the expertise of the thyroid pathologists KWS and ST [15].

2.2 Gene expression techniques

2.2.1 Samples preparation

Tissue samples (5-10 µm thickness) were placed in 1 mL of xylene in an Eppendorf tube, vortexed for 10 sec, left at room temperature for 10 minutes, and then spun for 2 minutes. After which, the supernatant was removed, and the tissue pellet was then washed with ethanol. Lysis of tissues was performed through the addition of lysis buffer and proteinase K, then digestion at 56 °C for 30 minutes. The processed samples were next frozen at -20 °C for future analysis of *DLL3* gene expression.

2.2.2 Total RNA extraction

The RNA, including mRNA, was isolated from the samples using the Qiagen RNeasy FFPE kit according to the manufacturer's guidelines (Thermo Fisher, USA).

2.2.3 RNA quantitation by Qubit 4.0

To assess the RNA content, we used the Qubit RNA HS Assay Kit. The assay range varied from 4.7 to 46.1 ng/µL. The total RNA content was

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not remarkably different between the control and cancer tissues; however, a slight difference in the presence of RNA purity was observed.

2.2.4 Complementary DNA (cDNA) synthesis for *DLL3*

Reverse transcription of the total RNA was conducted to synthesize the complementary DNA (cDNA), which targets *DLL3* and uses the SuperScript™ IV VILO Master Mix from Takara; the reaction took place in 20 µL. The volume of RNA for each procedure was 5 µL, as shown in Table 1. The quality of cDNA synthesis can be determined by the quality of results obtained from the following RT-qPCR.

Table 1. Reverse transcription PCR reaction components and volumes.

Material	Volume (µL)
RNA	5 (50 ng)
SuperScript™ IV VILO master mix	10
Primer	1
Nuclease-free water	Up to 20

DLL3 gene primers, detailed in Table 2, were produced by Macrogen (South Korea) and kept lyophilized until needed for the experiments.

Table 2. The primer sequence

Primer	Sequence	Reference
Forward primer *DLL3*	5´-AGGCTGCTGCTACTACTTCC -3´	[16]
Reverse primer	5´-TGGAGGTAGAGGATGGTGGT- 3´	

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DLL3		
Forward primer *TBP*	5´- GTGGTGTTGTGAGAAGATG-3´	[17]
Reverse primer *TBP*	5´-GGCAGCGCTGCCCAGATAGCAG-3´	

2.2.5 Quantitative reverse transcriptase PCR (qRT-PCR)

Patient samples, both metastatic and non-metastatic, were analyzed by RT-qPCR for the expression of the *DLL3* gene using relative quantification [18]. Expression normalization was performed using the housekeeping gene *TBP*. The $2^{-\Delta\Delta CT}$ method was then employed to calculate the relative expression level of the *DLL3* gene. The expression of *DLL3* was assessed by quantitative reverse transcription PCR (RT-qPCR), which uses fluorescent signals to quantify specific cDNA levels. The housekeeping gene *TBP* was used to normalize *DLL3* expression. RT-qPCR reactions were conducted on a Smart Cycler real-time PCR system (Bioer, Japan) as shown in Table 3, and gene expression fold changes were calculated from Ct values utilizing the Wizbio Pure™ SYBR qPCR reagents. The reaction compositions and volumes are detailed in Tables 3 and 4.

Table 3. Components used in RT-qPCR for *DLL3* and *TBP* experiments

Components	Volume (µL)	Concentration
Master mix syper green	10 µL	
Forward primer	0.5 µL	10 pmol
Reverse primer	0.5 µL	10 pmol
cDNA	6 (50 ng)	

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Nuclease-free water	Up to 20 µL	

Table 4. Thermal profile for gene expression of *DLL3*.

Cycle step	Temperature (°C)	Time	Cycles
Initial denaturation	95	8 sec	1
denaturation	95	15 sec	50
Extension	60	30 sec	
Melt curve	60	40 min	1

Relative changes in gene expression were determined using the $2^{-\Delta\Delta Ct}$ method, following the approach described by Livak and Schmittgen (2001) [19]. All statistical analyses were conducted with GraphPad Prism version 9.

2.3 Ethical approval

The Ethics Committee of the Iraqi Ministry of Health approved the protocol of this research. Informed consent was taken from all participants in this study. A systematic questionnaire was used to find personal details of all patients and normal individuals. All participants and their families were appropriately informed about this research. The Scientific Committee of the College of Biotechnology at Al-Nahrain University and Baghdad Teaching Hospital in Baghdad Medical City permitted to further carry out scientific work of the number T.H.J./4 on 5/11/2025.

3. Results and discussions

3.1 Demographical distribution of samples

3.1.1 Age distribution

Age at diagnosis plays a crucial role in the clinical presentation, genetic background, and prognosis of medullary thyroid carcinoma (MTC). Younger patients are more likely to have hereditary MTC, which is associated with germline RET proto-oncogene mutations and often occurs as

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part of MEN2 syndromes [20]. In these cases, MTC may develop during childhood or early adulthood, particularly in MEN2B, which represents the most aggressive form and presents at a very early age. Sporadic MTC, however, typically presents in a later life span, in the majority of instances between the age group of 40 to 60 years. In elderly individuals, more aggressive cancer, which is marked by greater size, lymph node metastasis, or systemic metastasis, is supposed to be strongly associated. Hence, age is proving to be an impartial prognostic factor, in which younger individuals achieve a greater survival advantage over the elderly.

The age-MTC connection has important clinical implications. In the earlier form of this condition, genetic screening for RET mutations is needed, while in the latter form of the condition, a full staging procedure is needed [21]. Thus, not only does the age of a patient indicate the cause of the condition of MTC, but it is also a contributing factor to the patient's form of treatment, as illustrated in Table 5 below.

Table 5. Clinicopathological data of MTC patients' age

Sex	*Total number of MTC*	*Metastasis*	*Non-metastasis*
Male			
Age: median (range)	30 54.1	28	2
Female	39	20	19
Age: median (range)	56.9		

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3.1.2 The BMI:

The Body Mass Index (BMI) was calculated for all participants using recorded weight and height measurements, determined by dividing weight (kg) by height squared (m^2). This score is frequently utilized to assess nutritional status, encompassing obesity and protein-energy deficiency [22]. The results indicated that the majority of persons diagnosed with medullary thyroid cancer were classified as overweight or obese, as outlined in Table 6.

Table 6. Correlations between the Body Mass Index of thyroid cancer patients.

Group	*Total number of MTC*	*BMI*
MMTC	48	27.1 ± 0.8
NonM-MTC	21	26.7 ± 0.3

It has long been recognized that being overweight can increase the risk of falling ill and dying from various chronic diseases. Rates of obesity and overweight have surged in the last few decades across the world [23], and this trend parallels the rise in the incidence of DTPC. Most likely, there is an association between the two rates [24, 25]. However, the association between the two conditions has long been subject to debate, particularly due to varying definitions and calculations in the assessment of obesity in different studies. The World Health Organization has adopted the BMI, calculated by dividing the weight in kilograms by the square of the person's actual height in meters, as the only universally recognized way of measuring body fat. A BMI of 18.5 to 24.9 is regarded as normal, while that of 25 to 29.9 indicates obesity and the likely increasing risk of associated conditions, and finally, over 30 indicates obesity and the presence of moderate to severe

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health conditions, particularly associated with obesity [26]. In medical literature, obesity can also be determined through the estimation of waist circumference, the ratio of hips to waist, and the amount of visceral and subcutaneous fat deposition in the body. However, the BMI has certain inaccuracies, primarily the point that the BMI differentiates between actual and muscular body fats, particularly the fact that one formula is insufficient in the determination of obesity in an individual, particularly across ethnic variations [27].

3.1.3 Grade of disease:

Grade refers to the degree of difference tumor cells have from regular cells, with high grades reflecting cells of poor differentiation. In thyroid cancer, tumor grading assists in estimating how aggressive thyroid cancer may be, including its possibility of spreading to other locations. Findings from this research revealed that grade III thyroid carcinoma tissue was predominantly found, accounting for 56% of the relevant cases, with only 10% of cases registering Grade I thyroid carcinoma tissue. There were no key variations among malignant thyroid carcinoma tissue grades, as reflected in Table 7.

Table 7. Distribution of the sample study according to the grade of disease in the thyroid cancer patients' group.

Grade	No. (%)
I	7 (10%)
II	23 (34%)
III	39 (56%)

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3.2 Expression of *DLL3*

DLL3 gene expression was analyzed following normalization to the reference gene *TBP*. Amplification curves for *DLL3* and *TBP* were examined to obtain accurate Ct values for each target (69 out of 76 samples, chosen based on their accepted results). The results demonstrated a significant upregulation of *DLL3* expression in MTC patients with lymph node metastases relative to non-metastatic cases, as illustrated in Figure 1 and Tables 8 and 9. Consistently, *DLL3* fold expression was very highly elevated in metastatic MTC samples.

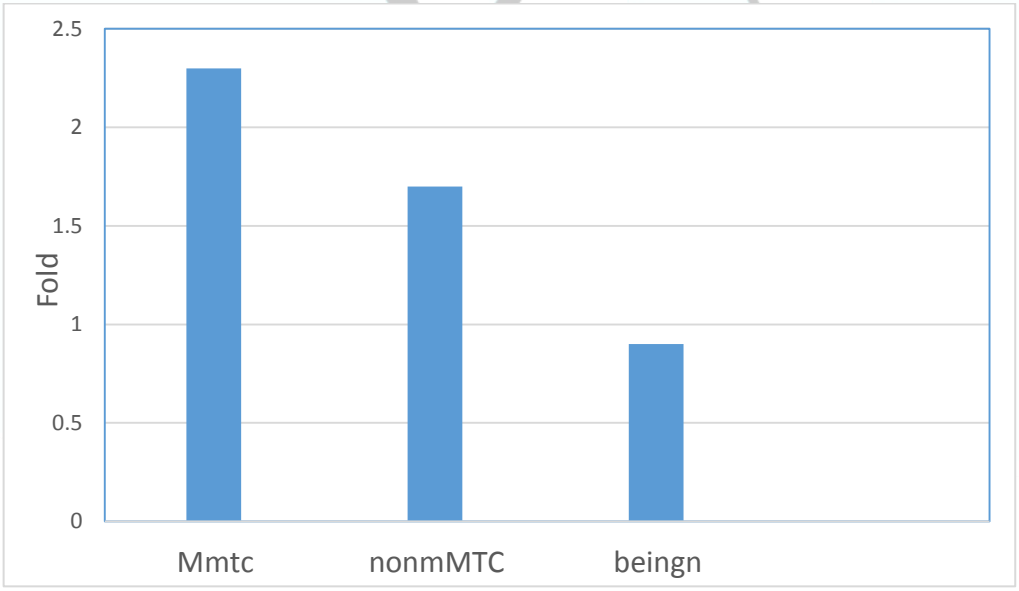

Figure 1. Fold change of *DLL3* gene expression.

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Table 8. Relative *DLL3* gene expression normalized to *TBP*.

Group	Reference gene	Relative *DLL3* expression ($2^{-\Delta\Delta Ct}$)	Control
Metastatic MTC (M-MTC)	*TBP*	~2.3	Benign tissue
Non-metastatic MTC (Non-MTC)	*TBP*	~1.7 Benign tissue	Benign tissue
Benign thyroid tissue	*TBP*	1.0	-

Table 9. RT-qPCR Ct analysis of *DLL3* normalized to *TBP*.

Group	Mean C_t *DLL3*	Mean Ct of *TBP*	ΔCt	ΔΔCt	Relative expression
Metastatic MTC (M-MTC)	25.2	22.0	3.2	-1.20	~2.3
Non-metastatic MTC	26.0	22.1	3.9	-0.75	~1.7
Benign thyroid tissue	27.3	22.2	5.1	0.00	1.0

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Our study assessed the expression level of *DLL3* in sporadic MTC using RT-qPCR and explored its relationship to clinicopathological factors, with special emphasis on lymph node metastasis. The data obtained show that *DLL3* is in MTC with lymph node metastasis compared to those without metastatic disease, suggesting that there is a very good relationship between *DLL3* expression and metastatic disease, in keeping with existing data showing that *DLL3* is changed in highly malignant neuroendocrine neoplasms, including small cell carcinoma of the lung and neuroendocrine prostate cancer, in which it is closely correlated with aggressive tumor behavior and unfavorable prognosis in MTC. The data show that there is a very good positive relationship between *DLL3* expression and lymph node metastatic disease, lending efficacy to its proposed hypothesis in predicting and contributing to tumor cell dissemination in MTC [12].

The biological relevance of *DLL3* expression in MTC can be appreciated as *DLL3* is known to act as an inhibitory ligand for the NOTCH signaling pathway, which is established to control the differentiation and proliferation of neuroendocrine cells. Dysfunction of the NOTCH signaling pathway has been established to contribute to the development of neuroendocrine tumors, and *DLL3* overexpression is postulated to promote the maintenance of a dedifferentiated and aggressive tumor phenotype. The high expression of *DLL3* in metastatic MTC observed in our study suggests that *DLL3* may serve as a surrogate marker for NOTCH pathway inhibition and tumor aggressiveness [2, 14].

In addition, the current study is consistent with previous histopathologic findings, which showed aggressive MTC characteristics, stromal desmoplastic, and lymph node metastases to be associated with each other. Although the current study aimed at gene expression evaluation, not immunohistochemistry, the positive correlation between the level of *DLL3* and the presence of metastases is consistent with the hypothesis regarding its use as a marker for the invasive phenotype of MTC [26,12].

From the technical perspective regarding the use of FFPE tissue and RT-qPCR, the method was shown to possess efficacy in analyzing the

expression levels of the *DLL3* gene despite the challenges posed by RNA degradation in FFPE tissue. To standardize the research findings and obtain relative quantification values, the *TBP* housekeeping gene was used. By using small fragments in the RT-qPCR reactions, the test became more sensitive. Although the identification of the potential biomarker *DLL3* related to the lymph node metastases may exhibit immense prognostic values and treatment strategies in the clinical setting, the method may present immense potential to treat patients with overexpressed *DLL3* due to the proven successful outcomes achieved using anti-*DLL3* targeted ADC in the treatment of some neuroendocrine cancers [15, 27].

One key finding of the study is that *DLL3* levels are typically absent or very low in tumors without desmoplastic stroma. Desmoplastic stroma is a well-established histopathological marker associated with aggressive disease and lymph node metastasis in MTC. The association of *DLL3* overexpression with desmoplastic stroma and lymph node metastasis further substantiates the potential of using *DLL3* as a molecular marker of invasive disease [10]. From a methodological standpoint, the study also validates the utility of RT-qPCR in FFPE tissue sections as a reliable approach for measuring DLL3 expression levels in tumors, despite the RNA degradation problems associated with FFPE tissue sections [2, 12]. The use of TBP as a normalization control gene also enabled accurate and reliable quantification of DLL3 expression levels. From a practical standpoint, the establishment of *DLL3* as a marker associated with lymph node metastasis has several implications [14]. Firstly, the level of *DLL3* could be a useful tool in stratifying disease risk and determining appropriate surgical interventions. Secondly, in the context of the recent successes of *DLL3*-targeting therapies in other neuroendocrine cancers, the study also has implications for the potential of using *DLL3* as a therapeutic target in advanced MTC. To conclude, the study provides robust evidence supporting the association between DLL3 overexpression and lymph node metastasis and a poor prognosis in sporadic medullary thyroid carcinoma [2, 14].

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4. Conclusion

It is concluded from this study that the level of *DLL3* is much higher in sporadic MTC with lymph node metastases compared with those without metastases. It is also evident that the level of *DLL3* corresponds with more aggressive tumor behavior and could potentially be used as a prognostic marker and a gold standard for lymph node metastases in MTC patients. Thereby, the evaluation of *DLL3* could improve risk stratification and decision-making in MTC patients. As well as, given the restricted role of *DLL3* in neuroendocrine tumors and its rapidly expanding role as a target for therapy, *DLL3* is a promising candidate for future targeted therapies for MTC patients. Future studies in larger patient cohorts at the protein level would be valuable for validating current observations and exploring the therapeutic efficacy of anti-*DLL3* therapies.

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Conflict of Interest

The author has no known conflicts for this work.

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