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Original Article

Expression patterns and diagnostic efficacy of cytokeratin 19 and galectin-3 in thyroid neoplasms

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Abstract: Background: Thyroid cancer is the world's most prevalent endocrine malignancy and a major health issue. With population aging and environmental influence, its incidence is increasing significantly. Highly specific and sensitive biomarkers to differentiate it from other thyroid diseases are crucial in clinical diagnosis. Identifying thyroid cancer types accurately is essential for personalized treatment, better survival, and improved prognosis. Methods: This study was to demonstrate the survival prognosis of Cytokeratin19 (CK19) and Galectin-3 in thyroid cancer through the Kaplan-Meier plotter. Simultaneously, KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway database was used to detect the associated signaling pathways of CK19 and Galectin-3. Furthermore, a retrospective analysis was performed on 55 cases of thyroid tumor, including papillary thyroid carcinoma (PTC) and nodular goiter (NG), using immunohistochemistry (IHC) for these proteins. The ROC curve evaluated the diagnostic ability of CK19 and Galectin-3 expressions. Results: Lower levels of CK19 and Galectin-3 were associated with a poor overall survival prognosis (OS, $P < 0.05$). The KEGG pathway database demonstrated that the signaling pathways related to CK19 and Galectin-3 play a vital function in controlling the cell cycle. The research revealed that CK19 and Galectin-3 expressions were greater in PTC compared to NG ($P < 0.01$). Furthermore, in PTC, the positive expression of Galectin-3 was increased in the subgroup aged 55 years and above ($P < 0.01$). A positive correlation of PTC was identified between the expressions of CK19 and Galectin-3. Moreover, lymph node metastasis correlated positively with tumor size in PTC ($P < 0.01$). Both CK19 and Galectin-3 proteins have predictive values in predicting PTC ($P < 0.05$). Meanwhile, the AUC value for the optimal cut-off of combined CK19 and Galectin-3 is more statistically significant ($P < 0.05$). Conclusion: CK19 and Galectin-3 are likely to be involved in the pathogenesis of thyroid neoplasms, manifesting distinct functions across diverse PTC subtypes. Furthermore, they may function as highly specific and sensitive biomarkers for differentiating pathological diagnoses, thus offering substantial value in the precise identification of thyroid-related pathologies.

Keywords: Cytokeratin19 (CK19), Galectin-3, thyroid carcinoma pathology, biomarkers

Introduction

Thyroid cancer is the most common endocrine glands neoplasm [1]. Benign thyroid neoplasms outnumber malignant ones, with ratios such as 10:1 in the United States [2], 3:1 in Addis Ababa, Ethiopia [3], and Zaria, Nigeria [4] and 4:1 in Accra-Ghana [5]. According to statistics from the International Agency for Research on Cancer (IARC), approximately 586,000 new cases are expected in 2020 [6, 7]. However, thyroid carcinoma incidence has increased recently, and papillary thyroid carcinoma (PTC) is the most common thyroid malignancy [8-10]. The International Histological Classification of tumors [11, 12] offers a detailed and in-depth explanation of PTC. Thyroid tumors are classified as benign or malignant. However, traditional diagnostic methods like ultrasound and fine-needle aspiration biopsy have limitations in certain cases and the limitations of intraoperative frozen pathology contribute to these difficulties. Tumor markers play a vital role in the diagnosis and grouping of thyroid neoplasms. Cytokeratin19 (CK19), and Galectin-3 are among the markers that have been extensively studied in thyroid pathology [13].

CK19 belongs to the type I cytokeratin family and is a low molecular weight cytokeratin. In

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normal thyroid tissue, the expression levels of CK19 are rather low. However, during the complex process of thyroid tumor development, its expression often changes significantly [14]. It is composed of intermediate filament proteins that play an important role in maintaining cellular structural integrity, cell motility, and signaling [14, 15]. CK19 has been detected as positive in a wide range of malignancies, including those in the anal region, Paget disease, endometrial, cholangiocarcinoma, breast, hepatoid adenocarcinoma, pancreatic ductal, squamous cell and thyroid carcinomas [16].

Galectin-3, Galectin protein, is critical for cell-cell and cell-matrix communication. This, in turn, allows them to play a significant role in numerous cellular processes, including cell proliferation, cell maturation, neovascularization, and apoptosis [17]. In recent times, a number of studies have delved into its significance in cell proliferation and the complex process of tumor formation [1].

In recent years,certain immunohistochemical (IHC) markers have been validated as effective in discriminating between non-neoplastic lesions and thyroid cancer. These markers include TG, Ki67, BRAF, CK19, Galectin-3, calcitonin, HBME-1, TTF-1, and RET [18]. Despite the fact that numerous studies [14] have thoroughly explored the utility of these markers, either in isolation or in various combinations, a unified and universal consensus has yet to be achieved. Additionally, the diagnostic value of CK19 and Galectin-3 in differentiating PTC from nodular goiter (NG) remains undetermined. Therefore, in our present and ongoing study, CK19 and Galectin-3 have exhibited promising value in the diagnosis, differential diagnosis, and prognostic evaluation of thyroid tumors. This potential holds great promise for improving the clinical management and patient outcomes related to thyroid-related diseases.

Materials and methods

Clinical samples

Patients were from a hospital-based retrospective study. The patients received surgical procedures from Nov. 2020 to Oct. 2024 at the Tianjin Nankai Hospital (TNH), China. All patients provided consent for use of their tissue samples and corresponding clinical information. The Ethics Review Board of TNH approved the retrieval of formalin-fixed, paraffin-embedded surgical specimens from the Department of Pathology archives and the collection of corresponding clinical pathology data (a total of 55 cases were included, consisting of 23 cases of papillary thyroid micro-carcinoma (PTMC), 13 cases of PTC, and 19 cases of NG) (**Figure 1**).

Patients ranged from 25 to 73 years of age at the time of diagnosis, with the median age 50.58 ± 12.27 years. A total of 55 patients (11 male patients and 44 female patients) underwent histologic analysis in accordance with the World Health Organization Classification [19].

Inclusion criteria: (1) All patients admitted to our hospital for the first time underwent intraoperative frozen pathology and paraffin pathology; (2) Clinical and pathological data are complete. Exclusion criteria: (1) A history of metastatic thyroid tumor or other malignant metastatic tumor; (2) Pathologic diagnosis is unclear or the number of tumor cells is extremely small.

Hematoxylin-eosin (H&E) and immunohistochemical (IHC) technique

All 55 patients with difficult-to-diagnose thyroid tumor were retrospectively analyzed by H&E examination. With the streptavidin-peroxidase (SP) method, 4-5 μm thick cross-sections of formalin-fixed, paraffin-embedded clinical specimens were subjected to IHC. The antibodies and kits were prepared strictly in accordance with the instructions.

CK19 and Galectin-3 protein expressions were appraised in reference to the percentage of cells of interest (scoring 0 as absent, 1 as positive cells < 25%, 2 as positive cells between 25%-50%, 3 as positive cells between 50-75%, and 4 for positive cells > 75%) and the intensity of staining (scoring 0 as negative, 1 as weak, 2 as moderate, and 3 as strong), following the method described by Wa Kammal et al [19, 20].

Overall scores, calculated as cell percentage and intensity summed, were further analyzed using statistical software.

Statistical analyses

The data were presented as the range, mean ± standard deviation, the median, counts (by the

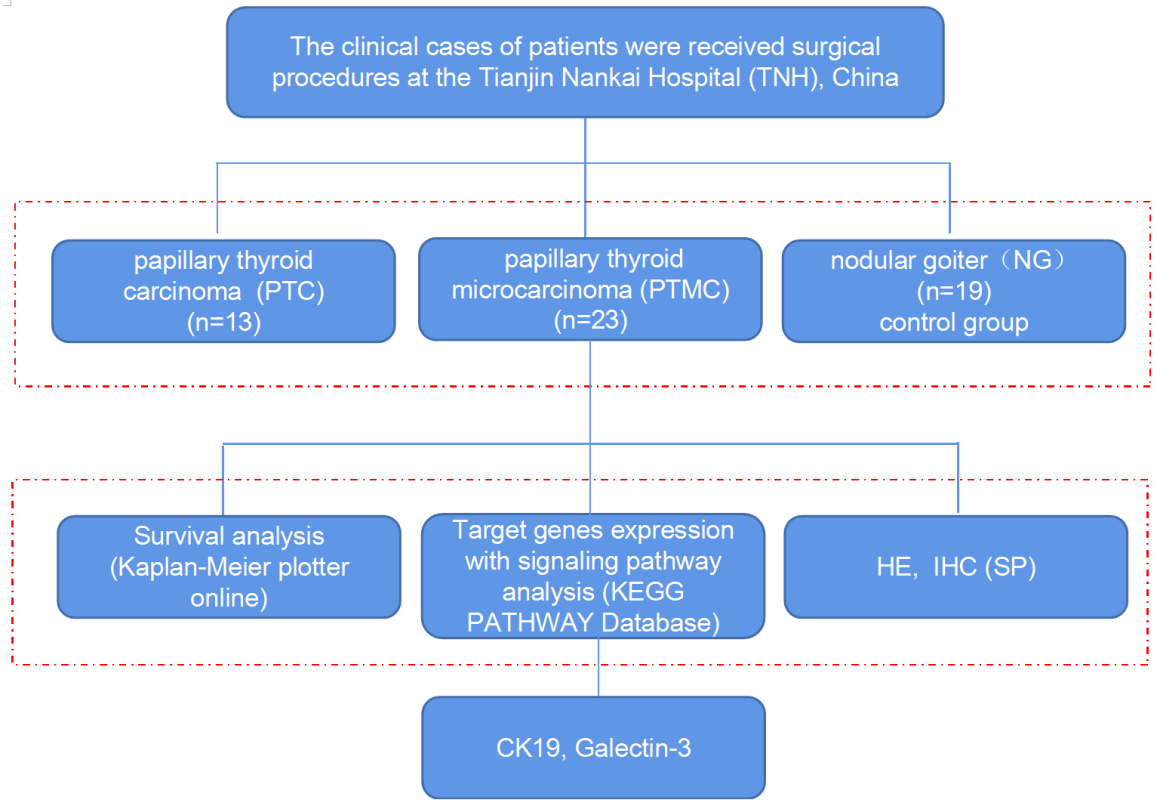

Figure 1. Flow chart illustrating the experimental design of this study.

number), and relative counts (%). Analysis of variances for multiple variables was performed using one-way ANOVA. Associations between categorical variables were assessed by Chi-square tests. Survival analyses of overall survival (OS) and recurrence free survival (RFS) were executed using Kaplan-Meier plotter from a public database. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value for a variable and the area under the curve (AUC) was used to reflect its predictive power. Graph-Pad Prism version 5.0 and SPSS 22.0 software were employed for statistical analyses. For all statistical analyses, $P < 0.05$ was regarded as significant.

Computational expression data and signaling pathway

RNA Sequencing expression data for 502 thyroid carcinoma samples and their corresponding database were retrieved from the public database (http://kmplot.com). The expressions of CK19 and Galectin-3 were then correlated with patient OS and RFS. To ascertain the correlation between CK19 and Galectin-3 and signaling pathways, the KEGG Pathway Database was used.

Ethical consideration

The institutional ethical approval was aquired and sanctioned by the Medical Ethics Committee of Tianjin Nankai Hospital. The approval number is NKYY_YXKT_IRB_2024_107_01.

Results

Survival analysis of CK19 and Galectin-3 genes in thyroid carcinoma

We used the online Kaplan-Meier plotter (www.kmplot.com), which was used to assess the effects of *CK19* and *Galectin-3* on patient survival in the public database of thyroid carcinomas. The patients were divided into two groups using the RNA expression levels of *CK19* and *Galectin-3* as the cut-off line. The results showed that patients with higher *CK19* expression had significantly higher OS ($P = 0.034$, log-rank test) but worse RFS rate ($P = 0.31$) compared to patients with lower *CK19* expression

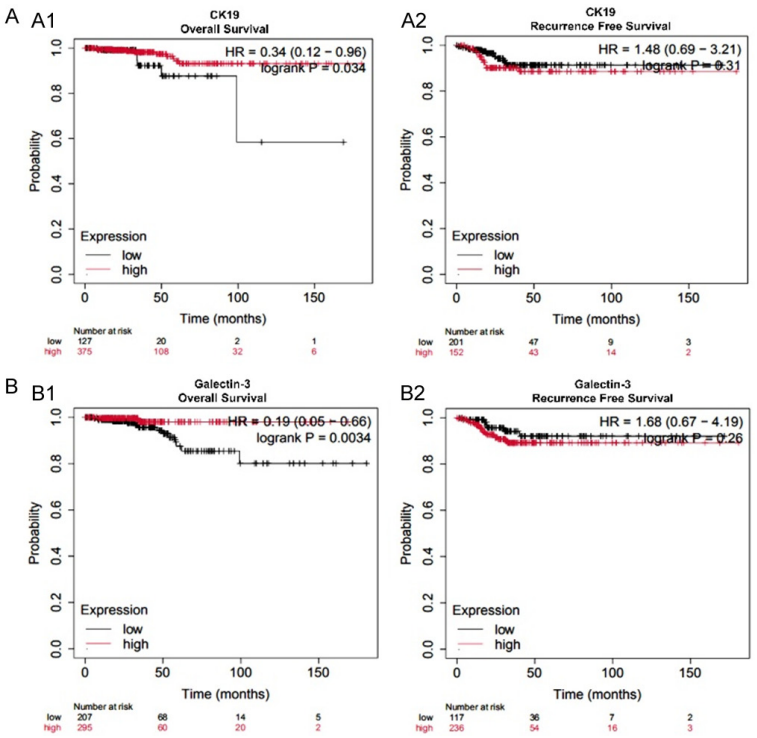

Figure 2. Survival analysis of *cytokeratin19 (CK19)* and *Galectin-3* gene expression in thyroid carcinomas. (A) Survival analysis of CK19 in thyroid carcinoma indicated that patients with higher CK19 expression had a significantly higher OS (P = 0.034, A1), but a worse RFS rate (P = 0.31, A2). (B) Survival analysis of Galectin-3 in thyroid carcinoma indicated that patients with higher Galectin-3 expression had a significantly higher OS (P = 0.034, B1), but a worse RFS rate (P = 0.26, B2).

in thyroid cancer (**Figure 2A1**, **2A2**). Similarly, patients with higher *Galectin-3* expression had significantly higher OS (P = 0.034, log-rank test), while worse RFS (P = 0.26) than those with lower *Galectin-3* expression in thyroid cancer (**Figure 2B1**, **2B2**).

The role of CK19 and Galectin-3 genes in the signaling pathway

To determine the association among *CK19, Galectin-3* and signaling pathways, the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway database was used in this study. The analysis showed that the *CK19* target gene was significantly enriched in the estrogen signaling pathway (**Figure 3**). The results of the analysis demonstrated that extracellular heparin-binding epidermal growth factor (HB-EGF) exerts its effect on its receptor, the epidermal growth factor (EGFR), located on the cell membrane. It enters the cytoplasm to induce the e2-er-ras-erk signaling pathway, thereby activating cells. Estrogen (ER) in the nucleus combines with coenzyme A (CoA) to activate *keratin19* (*KRT19*) during DNA translation, ultimately influencing cell cycle regulators, pro-apoptotic proteins, cell adhesion molecules, and cell membrane and cytoplasmic signaling.

It was also found that the target gene expression of *Galectin-3* (α3) was enriched in the proteasomal pathway (**Figure 4**). The protein binds to the regulatory particles that recognize the multi-ubiquitin chain tag attached to the protein, initiating a degradation process known as the ubiquitin-proteasome system. The proteasome degradation pathway encompasses many aspects of the cell cycle, regulation of gene expression, and oxidative stress, and is critical for many cellular processes.

CK19 and Galectin-3 expression in PTC and NG

The presence of brownish-yellow and/or tan-stained granules in the envelope and cytoplasm is considered positive for CK19 expression. The result of the study demonstrated that the expression of CK19 in PTC and PTMC was significantly higher than that of NG (P < 0.01) (**Table 1**). This analysis was conducted using Graph-Pad Prism 5.0 (**Figure 5E**). The expression of Galectin-3 was called positive if brown-yellow and/or tan staining granules appeared in the envelope and cytoplasm. The results demonstrated that the expression of Galectin-3 in PTC and PTMC was significantly higher than that of NG (P < 0.01) (**Table 1**). This analysis was also performed with Graph-Pad Prism 5.0 (**Figure 5F**).

CK19 and Galectin-3 expression and clinicopathologic characteristics in PTC

Subsequently, subgroup analyses were performed for PTC patients, taking into account various factors such as patient gender, age, the presence of multiple lesions, lymph node metastasis, and tumor size. The results demon-

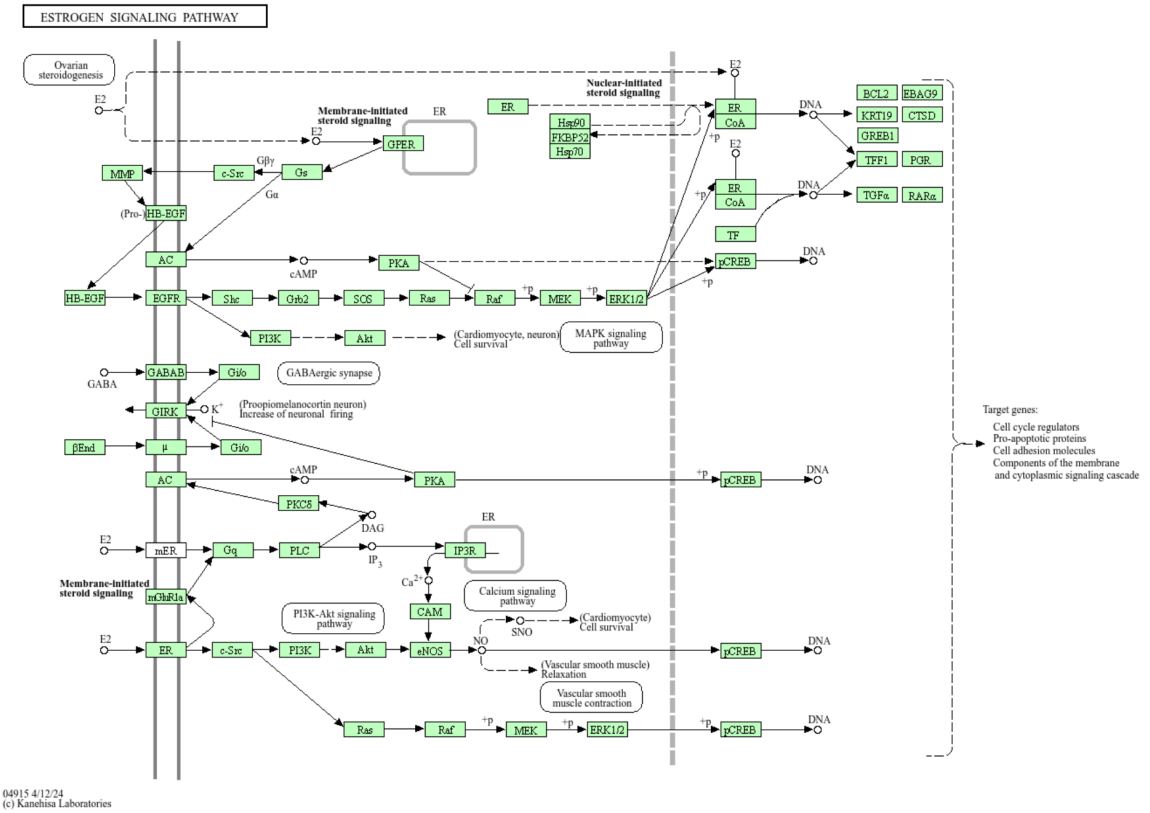

Figure 3. Target genes of *CK19* (*KRT19*) in the Estrogenic signaling pathway.

strated that there were no significant differences in the levels of CK19 and Galectin-3 among these subgroups ($P > 0.05$). However, positive expression of Galectin-3 was significantly elevated in a subgroup of patients aged 55 years and older ($P < 0.05$) (**Table 2**).

Correlation analysis with CK19 and Galectin-3 expression in PTC and PTMC

Pearson correlation analysis is a statistical method used to measure the linear relationship between two variables. In PTC and PTMC, Pearson correlation analysis revealed a positive correlation between the expressions of CK19 and Galectin-3 ($P < 0.01$) (**Table 3**). Additionally, lymph node metastasis was also positively correlated with tumor size in PTC and PTMC ($P < 0.01$) (**Table 4**).

ROC curves for CK19, Galectin-3, and the combination of CK19 and Galectin-3 in PTC

The area under the curve (AUC) for CK19 predicted PTC was 0.762 (95% CI: 0.628-0.866), while the area under the curve for Galectin-3 predicted PTC was 0.850 (95% CI: 0.728-0.932). CK19 and Galectin-3 were both proteins of predictive value in the prediction of PTC ($P < 0.05$). The optimal cut-off for combined use of CK19 and Galectin-3 was 0.45455 (specificity 89.47%, sensitivity 80.56%), and the AUC value was 0.882 (95% CI: 0.766-0.935) ($P < 0.05$) (**Figure 6**).

Discussion

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy worldwide [21]. Between 2005 and 2022, there were significant increases in the incidence of thyroid neoplasms in both genders. The incidence rate in females rose from 2.4 to 3.8, and in males, it increased from 0.9 to 1.2 [22], and the male-to-female incidence ratio reported by various research groups varies, mostly between 1:3 and 1:12 [23]. In our study, the male-to-female incidence ratio of PTC precisely aligned with the majority of literature reports, standing at 1:3. Other studies show that patients over 45 with differentiated thyroid cancer may have a poor prognosis [24].

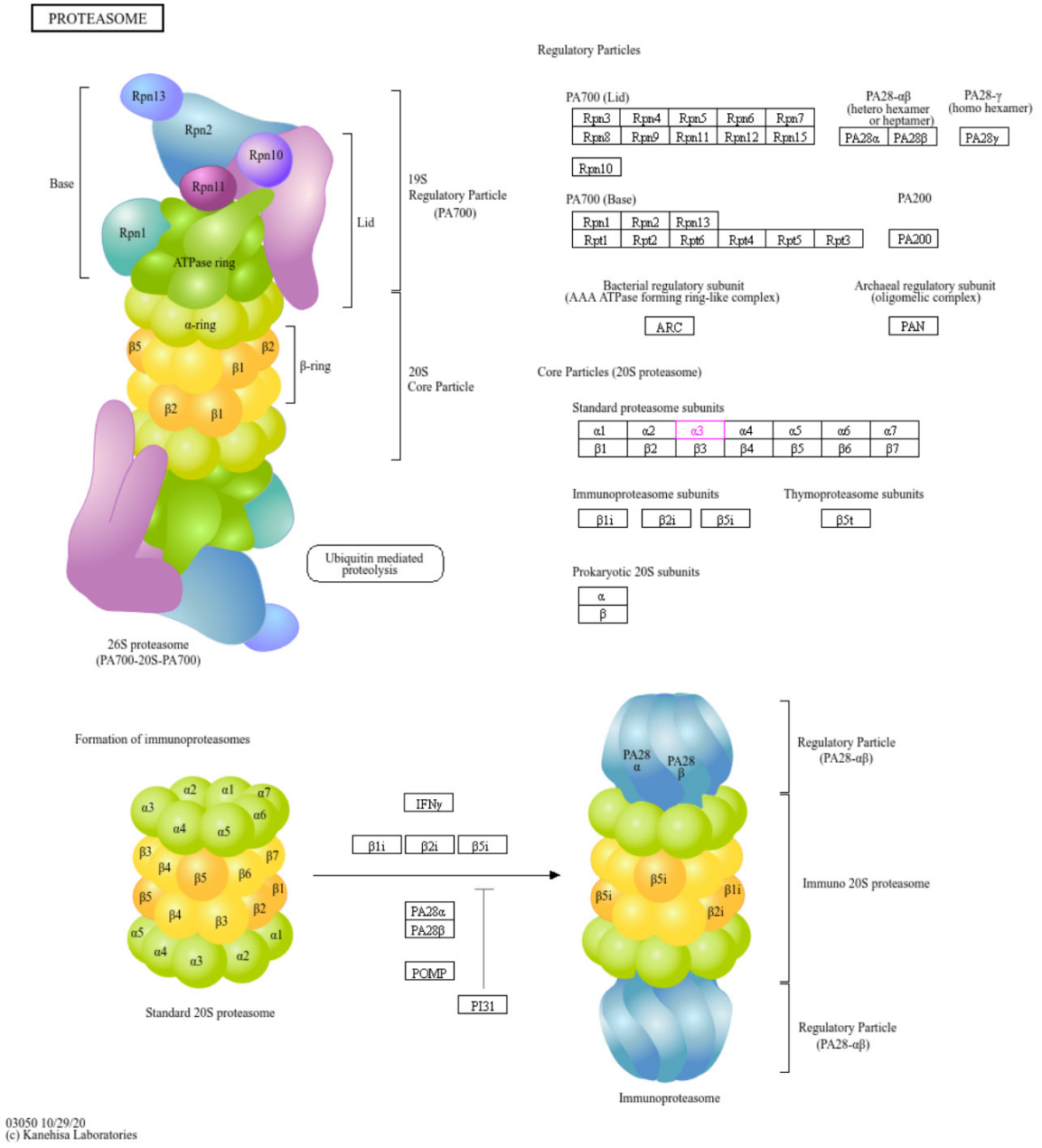

Figure 4. Target genes of *Galectin-3* (α3) in the Ubiquitin-Proteasome pathway.

Table 1. Analysis of the association of CK19 and galectin-3 expression levels in thyroid tumors

Groups		CK19		Positive rate (%)	P	Galectin-3		Positive rate (%)	P
		Positive	Negative			Positive	Negative		
PTMC	23	21	2	91.30	< 0.01	18	5	78.26	< 0.01
PTC	13	13	0	100.00		11	2	84.62	
NG	19	8	11	42.11		2	17	10.53	
Total	55	42	13	76.36		31	24	56.36	

PTC = Papillary thyroid cancer, PTMC = Papillary thyroid microcarcinoma, NG = Nodular goiter, CK19 = Cytokeratin19.

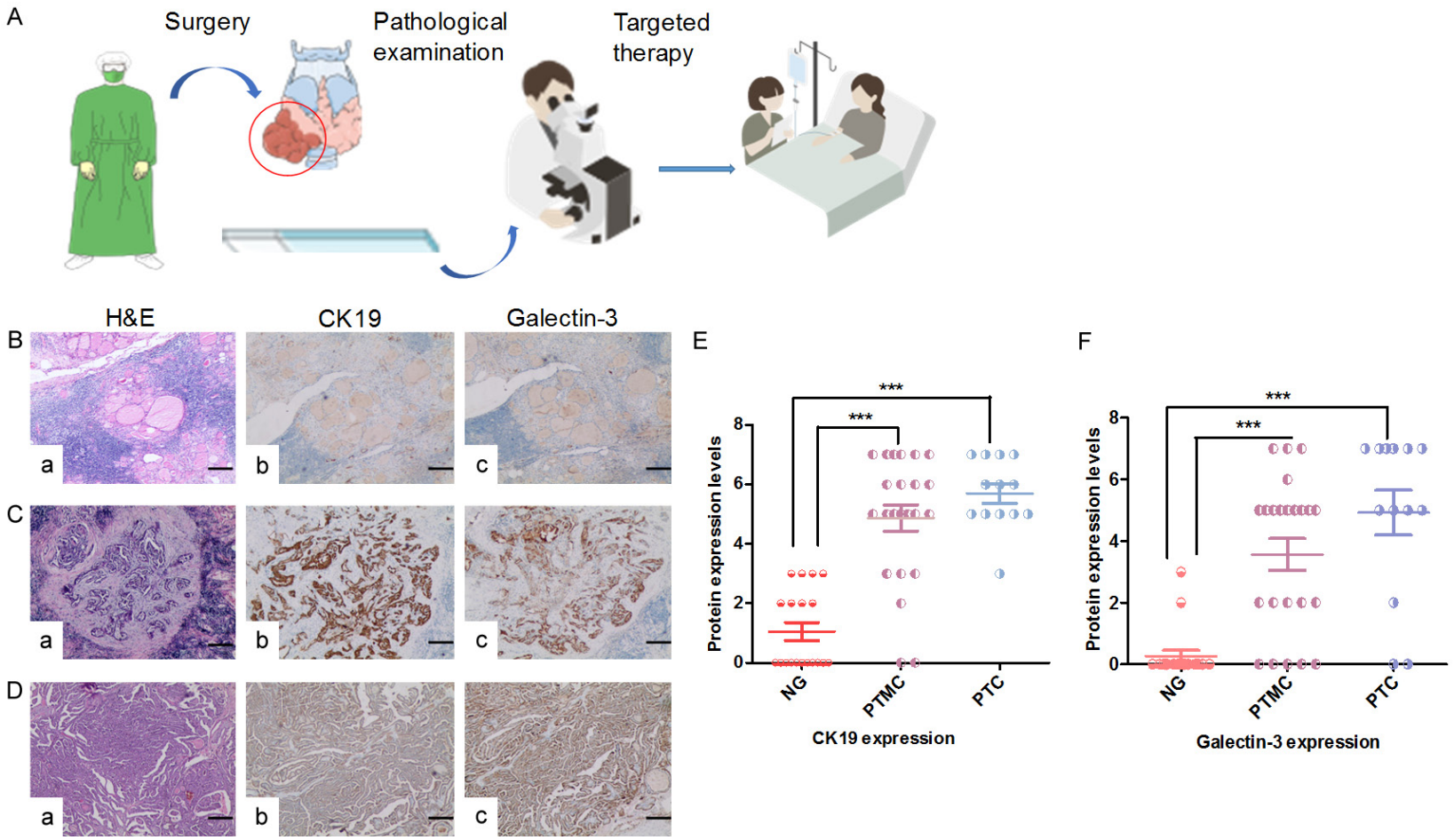

Figure 5. A. Schematic of thyroid tumor resection and pathological diagnosis. B. Negative expression of CK19 and Galectin-3 in NG (Bar = 50 μm, HE*400, IHC*400). C. Strong positive expression of CK19 and Galectin-3 in PTMC (Bar=50 μm, HE*400, IHC*400). D. Strong positive expression of CK19 and Galectin-3 in PTC (Bar = 50 μm, HE*400, IHC*400). E. Protein expression levels of CK19 in thyroid tumors were significantly different ($P < 0.001$, indicated with ***). F. Protein expression levels of Galectin-3 in thyroid tumors were significantly different ($P < 0.001$, indicated with ***). PTC=Papillary thyroid cancer, PTMC=Papillary thyroid microcarcinoma, NG=Nodular goiter.

Table 2. Association of CK19 and galectin-3 expression in PTC and PTMC with clinicopathologic features

Items	n	CK19		χ^2	P	Galectin-3		χ^2	P
		Positive	Negative			Positive	Negative		
Gender									
Male	9	9	0	0.706	0.401	9	0	2.897	0.089
Female	27	25	2			20	7		
Age (years)									
< 55	24	22	2	1.059	0.303	17	7	4.345	0.037
≥ 55	12	12	0			12	0		
Lesion									
Positive	10	10	0	0.814	0.367	7	3	0.985	0.321
Negative	26	24	2			22	4		
Lymph node									
Positive	8	8	0	0.605	0.437	5	3	2.141	0.143
Negative	28	26	2			24	4		
tumor size (cm)									
< 1	23	21	2	1.197	0.274	18	5	0.214	0.644
≥ 1	13	13	0			11	2		

Table 3. The correlation between the expression of CK19 and Galectin-3 in PTC and PTMC

Galectin-3	CK19		Total	χ^2	p
	Positive	Negative			
Positive	29	0	29	8.773	0.003
Negative	5	2	7		
Total	34	2	36		

Table 4. Correlation between lymph node metastasis and tumor size in PTC and PTMC

Lymph node	Tumor size (cm)		Total	χ^2	p
	< 1	≥ 1			
Positive	2	6	29	6.742	0.009
Negative	21	7	7		
Total	23	13	36		

Research shows some seemingly benign nodules can be or become malignant multifocally. Yokozawa et al [25] found 15.9% of < 10 mm cancer tissues had thyroid invasiveness and 20.0% of PTC had occult lymph node metastasis. Small benign lesions with papillary/atypical hyperplasia have similar microfeatures, which need IHC markers for diagnosis. Given thyroid cancer's complexity, we chose sensitive and specific CK19 and Galectin-3 for accurate differential diagnosis.

CK19, keratin protein, is highly expressed in both normal and neoplastic tissues. In normal thyroid follicular cells, CK19 is typically absent in expression, but in the case of PTC, a positive and diffuse staining pattern is clearly observable. In follicular adenomas as well as follicular thyroid carcinoma, the staining shows a focal pattern and is significantly less intense [26, 27]. This current study, using a detailed analysis, revealed that, in addition to focal positive expression of CK19 in normal thyroid follicular epithelium, some focal atypical hyperplasia nodules and focal papillary hyperplasia lesions in NG also showed focal positive expression of CK19. CK19 has been established as an especially sensitive and specific marker for detecting malignant thyroid tumor, particularly PTC. The study by Chandrakumari et al [28] convincingly showed that CK19 was the most sensitive and specific marker for the accurate identification of malignant thyroid neoplasms, especially PTC. CK19 is a type of carcinoembryonic antigen which gets secreted by the remaining viable epithelial tumor cells. It also serves as a biomarker for identifying metastatic tumor cells present in lymph nodes, peripheral blood, and bone marrow. When the test result for CK19 is positive, it aso predicts the prognosis of the disease [29]. High CK19 expression is linked to tumor cell proliferation, invasive behavior, and metastasis. It regulates the cytoskeleton and

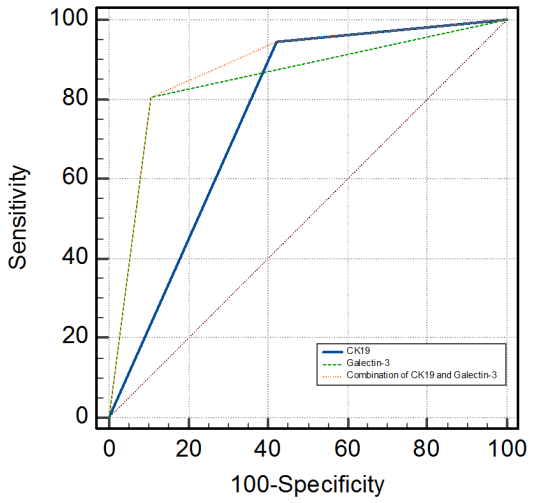

Figure 6. Receiver operating characteristics (ROC) curves for CK19, Galectin-3, and the combination of CK19 and Galectin-3 in PTC.

signaling pathways to promote cell migration. For instance, CK19-actin interaction boosts cell motility, helping tumor cells break through the basement membrane into surrounding tissues and blood vessels [27, 28], and Abouhashem et al [30] respectively observed high rates of CK19 positivity in PTC. CK19, as an intermediate filament protein, is closely associated with the cytoskeleton. It may affect cell morphology and polarity by regulating cytoskeletal reorganization and stability, which in turn indirectly affects the Wnt/β-catenin signaling pathway. For example, alterations in the cytoskeleton may affect the distribution and aggregation of cell surface receptors, thereby regulating the reception and transduction of Wnt signaling. At the same time, changes in the cytoskeleton may also affect the transport and localization of β-catenin within cells, further affecting the activity of the Wnt/β-catenin signaling pathway [29]. In support of our research findings, numerous other studies have shown that CK19 expression is of critical importance for distinguishing benign lesions, such as follicular adenoma, from malignant tumors, especially when histologic features are unclear [31].

Galectin-3 is deeply and complexly engaged in a diverse range of biological processes, encompassing cell growth, cell adhesion, inflammation, immunomodulation, and apoptosis. As a result, it is closely associated with the development and metastasis of numerous tumors, like colorectal cancer and PTC [32]. The Wnt signaling pathway is essential for processes like cell proliferation, polarity, and tissue patterning during development and in adult tissues. Galectin-3 exerts its regulatory effect on the Wnt pathway through multiple mechanisms. It can interfere with the formation of the Wnt receptor complex at the cell membrane, affecting the binding of Wnt ligands to their receptors. Furthermore, Galectin-3 has the potential to interact with intracellular proteins that are part of the Wnt signaling cascade, for instance, Dishevelled (Dvl). It is also capable of regulating the stabilization and the process of β-catenin's translocation into the nucleus. β-catenin serves as a crucial effector molecule within the Wnt pathway [33]. In addition, Galectin-3 has lately been identified as a crucial mediator within the Wnt signaling pathway. This pathway frequently undergoes mutations in various tumors. Through the action of C-Myc and the transcriptional process of the CyclinD1 gene, it gives rise to unregulated cell proliferation [34]. However, the exact mechanism by which Galectin-3 may modulate Wnt signaling and β-catenin levels remains yet to be fully elucidated. High expression of Galectin-3 promotes tumor transformation, significantly enhances tumor cell adhesion to the extracellular matrix, and actively promotes tumor metastasis [35]. In the realm of thyroid pathology, Galectin-3 has become a significant biomarker for malignant thyroid tumors. Its expression is typically higher in malignant thyroid tumors than in benign thyroid lesions [36]. The utility of Galectin-3 in intraoperative frozen section is particularly noteworthy, as it can aid in the rapid assessment of thyroid nodules during surgery. High expression of Galectin-3 in frozen sections tends to increase the likelihood of malignancy, thus influencing surgical approaches [17, 37].

Clinicians should consider using these biomarkers alone or in combination with other diagnostic techniques to improve the diagnostic accuracy of PTC. For example, when a biomarker test does not meet a definitive diagnostic threshold, another marker can be used as a supplemental diagnostic tool. In addition, both CK19 and Galectin-3 can be used independently as reliable biomarkers for the evaluation of thyroid tumors. For example, Yang et al [38] pointed out that CK19, as an independent

prognostic biomarker for esophageal squamous cell carcinoma, has the ability to assist in predicting the survival outcome of patients with this disease. At the same time, some research findings indicate that the utility of CK19 for the solitary diagnosis of PTC is restricted. CK19 can merely imply the presence of PTC when it shows a strongly positive result [39]. When facing inconclusive results from frozen section analysis, the evaluation of these two markers may improve diagnostic accuracy. According to this study, the combined detection of CK19 and Galectin-3 expression can be a more all-encompassing approach for the assessment of thyroid tumors. When comparing AUC of the combined prediction model with the single biomarker of CK19 and Galectin-3, the analysis showed that the combined detection strategy could improve the predictive power of PTC to a certain extent. These results suggest that there is a functional synergy between the two biomarkers in the predictive mechanism of PTC, and their combined application can optimize diagnostic performance through complementary effects. This strongly reinforces the necessity for more invasive surgical procedures [31, 40], such as more extensive excision or more comprehensive lymph node dissection, to ensure complete removal of the tumor and reduce the risk of recurrence. However, there are challenges to applying these markers in clinical practice. The understanding and analysis of marker expression results can be affected by a variety of factors, such as the quality of tissue samples, the skill level of the laboratory personnel, and the cut-off values used to define positive expression. To ensure reliable and reproducible results, it is essential to standardize assays and interpretation standards.

In addition, the expression profiles of these markers are capable of offering significant understanding regarding the biological characteristics and behaviors of tumors. To illustrate, tumors expressing both CK19 and Galectin-3 may exhibit more aggressive features and are more prone to metastasis. This information is critical for developing postoperative management and follow-up strategies for patients with thyroid cancer [41, 42]. In general, the findings of this research establish the groundwork for the clinical use of CK19 and Galectin-3 in the diagnosis and management of thyroid tumors. More research needs to be done to surmount these challenges and perfect the utilization of these markers in clinical situations, with the ultimate aim of improving the treatment. In the meantime, owing to the comparatively small sample size in this research, findings may not be generalizable. Following studies should aim to recruit a larger and more diverse sample population, following standard sample-size calculation methods. This will help to further validate the current findings, explore the potential interactions between CK19, Galectin-3, and other factors in a more comprehensive manner, and improve the accuracy and reliability of using these markers in terms of diagnosing and predicting the prognosis of thyroid tumors.

Conclusion

Tissue expression levels of CK19 and Galectin-3 are of great significance in thyroid tumor surgery. These markers are not only effective in differentiating benign and malignant thyroid lesions, but also provide valuable prognostic insight into tumor behavior. Evaluating these markers can improve the accuracy of pathologic diagnosis in difficult cases, and ultimately provide guidance for the operation and treatment of thyroid tumors. Monitoring changes in CK19 and Galectin-3 expression levels during treatment can help assess treatment efficacy.

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Disclosure of conflict of interest

The authors declare that this study was executed with no commercial or financial associations that could be regarded as potential conflicts of interest.

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