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Stanniocalcin-1 as a Diagnostic and Prognostic Biomarker in Papillary Thyroid Carcinoma: A Comprehensive Review

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most prevalent subtype of thyroid cancer, accounting for the majority of endocrine malignancies. Despite its generally favorable prognosis, certain PTC cases exhibit aggressive clinical behavior, underlining the importance of identifying reliable biomarkers to refine diagnosis, risk stratification, and therapeutic decision-making. Stanniocalcin-1 (STC1), a glycoprotein hormone originally described in fish, has garnered attention for its regulatory role in calcium and phosphate homeostasis and, more recently, for its involvement in tumor biology across multiple malignancies, including PTC. This comprehensive review aims to synthesize the current knowledge on STC1 as both a diagnostic and prognostic biomarker in papillary thyroid carcinoma. The review evaluates molecular and cellular mechanisms underlying STC1 expression in thyroid tissues, explores its role in PTC tumorigenesis, and discusses its clinical implications compared to other established and emerging biomarkers.

Conclusion:
The evidence indicates that aberrant expression of STC1 in PTC is associated with tumor aggressiveness, lymph node metastasis, and poor patient outcomes. Its integration into clinical practice, alongside traditional markers, could enhance diagnostic accuracy and prognostic precision. However, challenges remain regarding assay standardization and the full elucidation of STC1's mechanistic role in thyroid carcinogenesis. Future research should focus on large-scale validation studies, mechanistic exploration, and the potential utility of STC1 as a therapeutic target, which may ultimately improve the management and outcome of patients with papillary thyroid carcinoma.

Keywords: *Stanniocalcin-1, Diagnostic and Prognostic, Papillary Thyroid Carcinoma*

Introduction

Papillary thyroid carcinoma (PTC) has emerged as the most prevalent form of thyroid malignancy worldwide, representing nearly 85% of all thyroid cancer cases. While most patients enjoy a favorable prognosis following standard therapy, the rising incidence and increasing recognition of aggressive PTC subtypes underscore the necessity for improved diagnostic and prognostic strategies [1]. Traditionally, risk stratification has relied on clinical and pathological parameters, including tumor

10.48047/jocaaa.2024.33.06.100

size, lymph node involvement, and extrathyroidal extension. However, these features alone do not always adequately predict recurrence or disease progression, especially in the context of indeterminate or borderline tumors [2].

The molecular landscape of PTC is complex, involving numerous genetic alterations such as BRAF, RAS, and RET/PTC rearrangements, as well as epigenetic and microenvironmental factors. Despite these insights, the translation of molecular findings into routine clinical practice remains limited, particularly in the identification of high-risk patients who may benefit from intensified surveillance or novel therapies [3]. This unmet need has prompted the exploration of additional molecular markers with diagnostic and prognostic utility.

Stanniocalcin-1 (STC1) is a secreted glycoprotein initially identified in fish and later in mammals, including humans. It is involved in a variety of physiological processes, such as calcium and phosphate regulation, angiogenesis, and cellular metabolism [4]. Recent research has highlighted its aberrant expression in various cancers, including breast, colorectal, lung, and thyroid malignancies, implicating it in tumorigenesis, metastasis, and treatment resistance [5]. However, its clinical significance in thyroid pathology is only beginning to be understood.

The aim of this review is to provide a comprehensive analysis of current evidence regarding the role of STC1 in PTC. We will summarize the molecular biology of STC1, describe its expression patterns in thyroid tissue, discuss its functional contributions to tumorigenesis, and critically evaluate its diagnostic and prognostic significance. Furthermore, we will compare STC1 with other established and emerging PTC biomarkers, address current research limitations, and highlight future directions. By doing so, we aim to clarify the potential of STC1 as a clinically relevant biomarker and possible therapeutic target in PTC management [6–9].

A. Papillary Thyroid Carcinoma: Overview and Current Biomarkers

Papillary thyroid carcinoma (PTC) is characterized by its papillary structures, nuclear features, and a generally favorable prognosis, with a 10-year survival rate exceeding 90% for most patients. However, the disease exhibits marked clinical heterogeneity. While most cases remain indolent and confined to the thyroid gland, a significant minority present with lymph node metastasis, extrathyroidal extension, or even distant metastasis at diagnosis. Such variability complicates clinical decision-making, highlighting the need for robust risk stratification tools that can distinguish low-risk from high-risk patients and guide individualized management [10,11].

Historically, the diagnosis of PTC has relied on a combination of clinical examination, ultrasonography, and cytological assessment using fine-needle aspiration (FNA). Although FNA is highly sensitive, its specificity is limited, particularly in cases with indeterminate or suspicious cytology. The use of serum thyroglobulin as a tumor marker is standard for postoperative monitoring,

10.48047/jocaaa.2024.33.06.100

but it lacks preoperative diagnostic utility and is confounded by anti-thyroglobulin antibodies in a subset of patients. Additional imaging modalities, such as neck CT or PET scans, may be reserved for advanced cases or those with unclear findings on ultrasound [12,13].

The advent of molecular diagnostics has transformed the landscape of PTC management. Mutational analysis for BRAF V600E, RAS, and RET/PTC rearrangements is now frequently incorporated into the workup of thyroid nodules with indeterminate FNA results. The BRAF V600E mutation, present in approximately 45% of PTC cases, is associated with more aggressive clinicopathological features, including lymph node metastasis and extrathyroidal invasion. Nevertheless, the mutation is not exclusive to aggressive tumors, limiting its prognostic utility. Similarly, RAS mutations and RET/PTC rearrangements are found in various histologic subtypes and are not specific to adverse outcomes [14,15].

In addition to genetic mutations, other molecular markers—such as microRNAs, galectin-3, HBME-1, and cytokeratin-19—have been evaluated for their diagnostic and prognostic value in PTC. These markers, often assessed via immunohistochemistry or molecular panels, have improved the sensitivity and specificity of PTC diagnosis when used in combination. Yet, none have achieved universal adoption due to inter-assay variability, lack of standardization, and limited availability in routine pathology laboratories. This ongoing search for reliable biomarkers underscores the need for novel candidates such as stanniocalcin-1 (STC1), which may offer additional clinical value when integrated into current diagnostic algorithms [16–19].

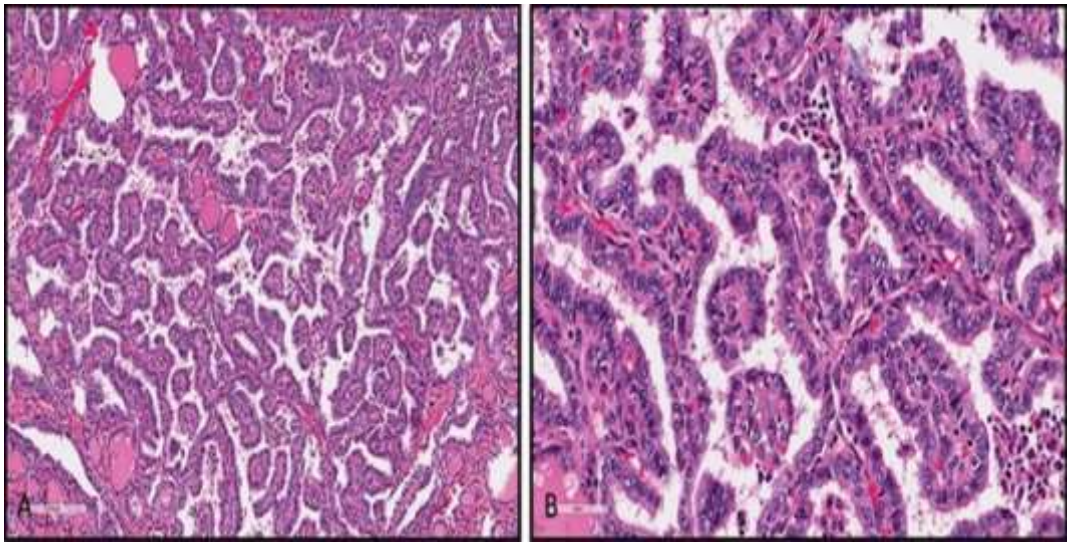

Figure (1): Classic PTC subtype showing complex papillary growth pattern (A) lined by cells with nuclear features of papillary thyroid carcioma(B) [16].

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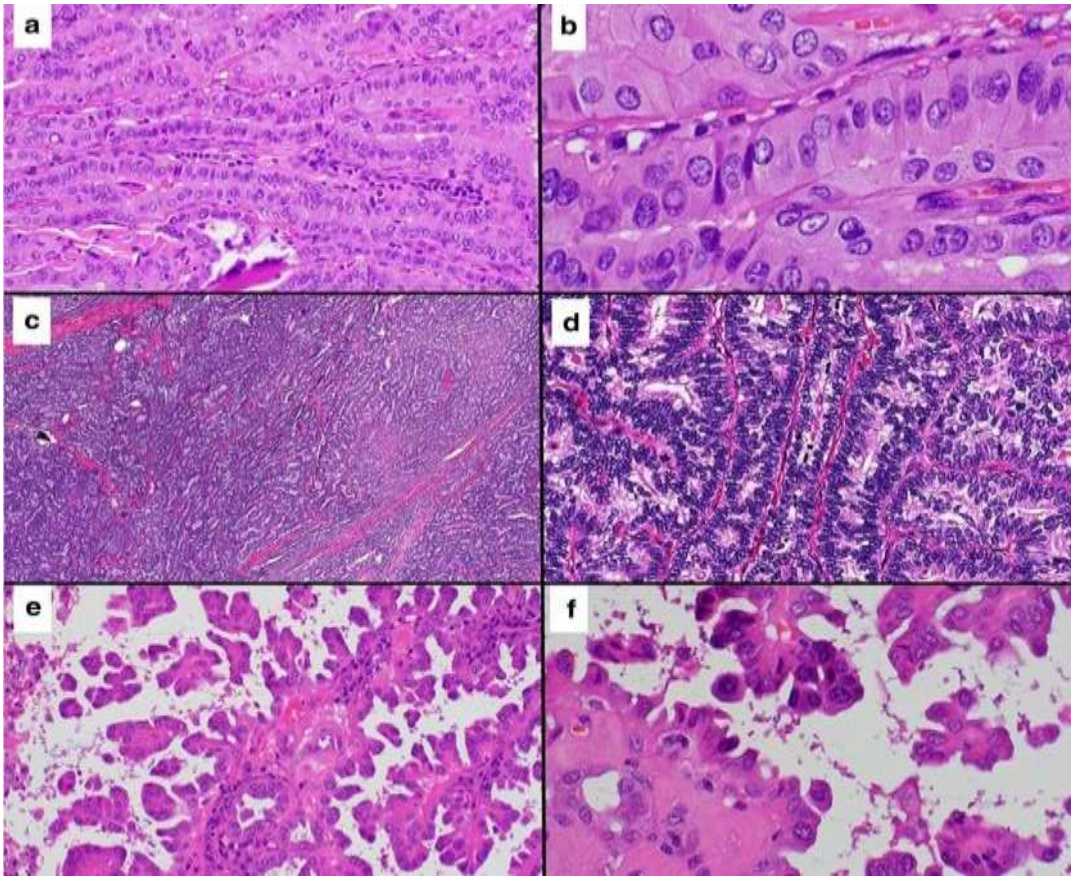

Figure 2: a Medium magnification view (20 × 10) of a TCV of PTC showing elongated follicles with parallel arrangement ("tram-track" appearance). **b** High magnification view (60 × 10) of TCV exhibiting tumor cells that are taller than wider (2:1 or 3:1 height to width ratio) with moderate to abundant light eosinophilic cytoplasm, distinct cell borders, and prominent nuclear features diagnostic of PTC. **c** Low power microscopic view (4 × 10) of CCV of PTC showing a highly cellular neoplastic proliferation. **d** High magnification view (40 × 10) of CCV exhibiting elongated tumor cells and hyperchromatic nuclei and prominent nuclear stratification, the cardinal feature of this variant. **e** Medium magnification view (20 × 10) of an HV of PTC showing complex papillary growth and micropapillary architecture. **f** High magnification view (60 × 10) of tumor cells with hobnail morphology characterized by pleomorphism, high nuclear to cytoplasmic ratio, apically or eccentrically placed nuclei, and surface bulging [16].

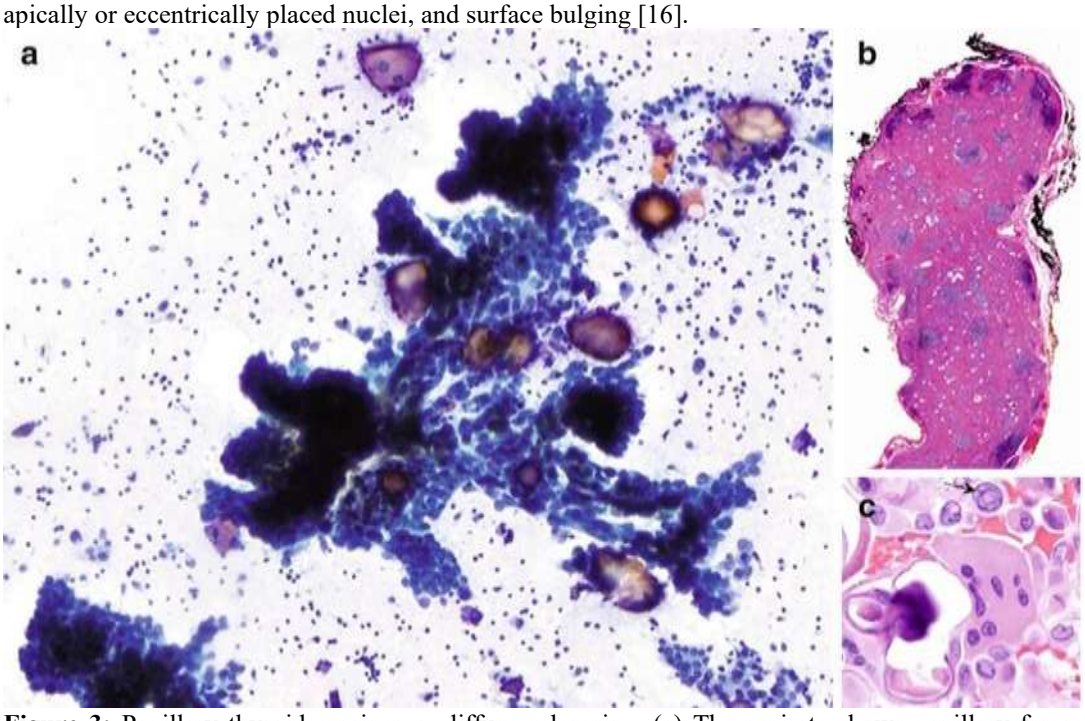

Figure 3: Papillary thyroid carcinoma, diffuse sclerosing. (a) The aspirate shows papillary fragments associated with

10.48047/jocaaa.2024.33.06.100

psammoma bodies in a lymphocytic background. The nuclear chromatin is darker than in the conventional papillary thyroid carcinoma (smear, Papanicolaou stain). (b) On histologic examination, the thyroid gland shows numerous lymphoid follicles and many small "holes." (c) The holes are from popped out psammoma bodies (b, c: hematoxylin and eosin stain). [16].

B. Stanniocalcin-1: Molecular Structure and Biological Functions

Stanniocalcin-1 (STC1) is a secreted glycoprotein hormone initially discovered in the corpuscles of Stannius in fish, where it regulates calcium and phosphate homeostasis. In mammals, STC1 is encoded by the STC1 gene located on chromosome 8p11.2 and consists of 247 amino acids with a signal peptide sequence at the N-terminus. The molecule contains multiple glycosylation sites critical for its stability, secretion, and biological activity. Structurally, STC1 forms a homodimer stabilized by disulfide bonds, a configuration essential for its endocrine and paracrine functions [20,21].

Beyond its classical role in mineral metabolism, mammalian STC1 has a wide tissue distribution, with expression detected in the thyroid, kidney, ovary, heart, and brain. STC1 exerts a multitude of physiological effects, including modulation of calcium and phosphate uptake, regulation of mitochondrial function, and protection against oxidative stress. Its involvement in processes such as angiogenesis, cellular proliferation, and apoptosis has attracted attention in the context of tissue repair, ischemia, and cancer biology. Recent studies have shown that STC1 expression can be induced by hypoxia, inflammatory cytokines, and growth factors, implicating it in cellular responses to environmental stress [22–25].

Molecularly, STC1 acts through both autocrine and paracrine mechanisms, affecting signal transduction pathways relevant to cell survival and adaptation. Notably, STC1 has been shown to interact with the PI3K/AKT and MAPK pathways, both of which are frequently dysregulated in cancers. It also influences calcium signaling and mitochondrial function, thereby impacting cell metabolism and resistance to apoptosis. In the tumor microenvironment, STC1 has been implicated in the regulation of angiogenesis by modulating vascular endothelial growth factor (VEGF) expression and hypoxia-inducible factor-1α (HIF-1α) activity. These actions suggest that STC1 serves as an integrator of stress and growth signals in both normal and neoplastic tissues [26–28].

The diverse biological roles of STC1 are supported by animal models. Mice lacking STC1 demonstrate altered calcium and phosphate homeostasis, impaired fertility, and increased susceptibility to tissue injury under ischemic conditions. In cancer models, overexpression of STC1 promotes tumor cell proliferation, invasion, and metastasis, while knockdown or pharmacologic inhibition of STC1 reduces tumorigenic potential. These findings underscore the pleiotropic and context-dependent effects of STC1 in both health and disease. As a result, STC1 has been increasingly recognized as a potential biomarker and therapeutic target, particularly in tumors such as papillary thyroid carcinoma where it

10.48047/jocaaa.2024.33.06.100

appears to play a prominent role [29–32].

C. Expression of Stanniocalcin-1 in Thyroid Tissue

Stanniocalcin-1 (STC1) is normally expressed at low levels in thyroid follicular cells, with tight regulation reflecting its role in maintaining cellular and mineral homeostasis. Early investigations utilizing in situ hybridization and immunohistochemistry established that STC1 expression in healthy thyroid tissue is sparse, limited to select follicular cells and rarely detected in the surrounding stroma or parafollicular cells [33]. This low baseline expression is consistent with STC1's physiological function and its minimal role in normal thyroid hormone synthesis or secretion [34].

In the context of thyroid pathology, mounting evidence demonstrates significant upregulation of STC1 in malignant tissues compared to benign counterparts. Several studies using tissue microarrays and quantitative PCR have shown that STC1 mRNA and protein levels are markedly increased in papillary thyroid carcinoma (PTC) samples, whereas benign nodular goiter and follicular adenoma tissues maintain only minimal expression [35,36]. This pattern of overexpression is further confirmed by immunohistochemical staining, which reveals robust cytoplasmic and sometimes nuclear STC1 localization in PTC cells, suggesting a role in tumorigenic processes distinct from its physiological function [37].

The clinical relevance of STC1 expression is highlighted by its correlation with adverse pathological features in PTC. High levels of STC1 are more frequently observed in tumors exhibiting extrathyroidal extension, lymphovascular invasion, and lymph node metastasis. Moreover, increased STC1 expression is significantly associated with higher TNM stage and larger tumor size, supporting its utility as a marker of tumor aggressiveness [38,39]. These findings have been corroborated in multiple patient cohorts, indicating the robustness and reproducibility of STC1 as a tissue biomarker in thyroid malignancy [40].

Of particular interest is the lack of significant STC1 expression in non-papillary thyroid tumors, such as medullary and anaplastic carcinoma, as well as in most benign nodules. This specificity suggests that STC1 may be preferentially involved in the pathogenesis of PTC, potentially reflecting molecular pathways unique to papillary histogenesis. Furthermore, some studies have reported that STC1 expression is higher in the classic and tall-cell variants of PTC, which are known for their aggressive clinical behavior, further emphasizing the potential diagnostic and prognostic value of STC1 in routine pathological assessment [41,42].

The localization and quantification of STC1 in thyroid tissue have important implications for both diagnosis and research. Standardized immunohistochemical scoring and mRNA quantification

10.48047/jocaaa.2024.33.06.100

methods are increasingly being integrated into tissue analysis protocols. This allows pathologists to objectively assess STC1 levels alongside established markers, improving diagnostic accuracy and informing risk stratification. Nevertheless, there is still a need for consensus regarding the optimal cutoff values and the relative significance of cytoplasmic versus nuclear STC1 staining in routine practice [43,44].

D. Mechanisms of STC1 in Tumorigenesis

Stanniocalcin-1 (STC1) has emerged as a multifaceted mediator in tumorigenesis, acting through diverse signaling pathways that collectively contribute to malignant transformation and progression. In papillary thyroid carcinoma (PTC), studies have shown that STC1 overexpression enhances cell proliferation and survival, a phenomenon attributed primarily to the activation of the PI3K/AKT and MAPK pathways—two major axes frequently dysregulated in thyroid and other solid tumors [45]. STC1 promotes phosphorylation of AKT, leading to downstream inhibition of pro-apoptotic factors such as BAD and activation of survival-promoting proteins including mTOR. This contributes to resistance against apoptotic stimuli and supports sustained tumor growth even in unfavorable microenvironments [46].

A crucial step in cancer invasion and metastasis is the epithelial-mesenchymal transition (EMT), during which tumor cells lose their epithelial characteristics and acquire a mesenchymal, migratory phenotype. Evidence indicates that STC1 induces EMT in PTC cells by upregulating mesenchymal markers like vimentin and N-cadherin while downregulating epithelial markers such as E-cadherin. These molecular changes are paralleled by enhanced migratory and invasive abilities, facilitating local invasion and dissemination through lymphatic channels—a hallmark of aggressive PTC [47]. Further, STC1-driven EMT appears to be mediated by the HIF-1α signaling pathway, linking hypoxic stress to tumor progression [48].

Beyond cell-autonomous effects, STC1 exerts significant influence on the tumor microenvironment, particularly angiogenesis. Angiogenic switch is essential for tumor expansion and metastasis, and STC1 has been shown to upregulate vascular endothelial growth factor (VEGF) both directly and through modulation of HIF-1α activity. In vitro and in vivo studies demonstrate that STC1 overexpression increases microvessel density within tumor tissues, supporting enhanced oxygen and nutrient delivery to proliferating cancer cells. This vascular remodeling is crucial for the sustenance of rapidly growing tumors and for providing pathways for metastatic spread [49,50].

In addition, STC1 is implicated in the regulation of cellular metabolism and oxidative stress response. Cancer cells typically undergo metabolic reprogramming to favor glycolysis over oxidative phosphorylation, even in the presence of oxygen—a phenomenon known as the Warburg effect. STC1 facilitates this metabolic shift by promoting glucose uptake and lactate production, while

10.48047/jocaaa.2024.33.06.100

simultaneously protecting cells from reactive oxygen species (ROS)-mediated damage. This dual action not only supports the metabolic demands of proliferation but also enhances resistance to oxidative stress, which is common in the hypoxic tumor microenvironment [51].

Mechanistically, experimental silencing of STC1 using RNA interference or CRISPR-based approaches in PTC cell lines results in decreased cell proliferation, impaired migration, reduced angiogenesis, and increased susceptibility to apoptosis. Conversely, ectopic overexpression of STC1 accelerates tumorigenic processes, underscoring its role as an oncogenic driver in PTC. Collectively, these findings highlight the complex interplay between STC1 and key oncogenic signaling networks, affirming its importance in the initiation, progression, and potential therapeutic resistance of papillary thyroid carcinoma [52,53].

E. Diagnostic Value of STC1 in Papillary Thyroid Carcinoma

The upregulation of stanniocalcin-1 (STC1) in papillary thyroid carcinoma (PTC) has significant diagnostic implications, especially given the challenges posed by indeterminate thyroid nodules. Several studies have demonstrated that STC1 immunohistochemical (IHC) staining is highly sensitive for PTC, showing strong positivity in malignant tissues compared to benign nodules and normal thyroid parenchyma. In large tissue microarray analyses, the addition of STC1 IHC to standard diagnostic panels significantly improved sensitivity and specificity for distinguishing PTC from benign and follicular lesions, supporting its potential role as an ancillary diagnostic marker [54,55].

Fine-needle aspiration (FNA) cytology remains the gold standard for initial assessment of thyroid nodules, but its diagnostic accuracy can be hampered by indeterminate or “atypia of undetermined significance” results. Recent studies have evaluated the utility of STC1 detection in FNA samples, finding that positive STC1 staining correlates strongly with the presence of papillary carcinoma. Importantly, the addition of STC1 to established cytological markers such as galectin-3 and HBME-1 increases diagnostic yield in equivocal cases, potentially reducing the need for repeat biopsies or diagnostic surgery [56,57].

The diagnostic utility of STC1 extends beyond tissue-based assays. Efforts to develop non-invasive serum biomarkers have identified elevated levels of circulating STC1 protein in patients with PTC compared to those with benign thyroid nodules and healthy controls. In one prospective study, preoperative serum STC1 levels demonstrated high sensitivity and specificity for PTC diagnosis, and levels decreased following total thyroidectomy, suggesting a potential role in both initial diagnosis and postoperative monitoring [58,59]. However, additional large-scale studies are needed to validate these findings and to determine appropriate reference ranges for clinical use.

Comparative analyses indicate that STC1 provides incremental diagnostic value when combined with other molecular and immunohistochemical markers. Molecular panels incorporating STC1, BRAF

10.48047/jocaaa.2024.33.06.100

V600E, galectin-3, and cytokeratin-19 have demonstrated superior diagnostic accuracy in distinguishing malignant from benign thyroid nodules than any single marker alone. Furthermore, the relatively high specificity of STC1 for PTC compared to other thyroid malignancies underscores its potential as a useful marker in the context of challenging or ambiguous cases [60,61].

Despite these advances, certain limitations persist. The interpretation of STC1 staining can be influenced by variability in antibody clones, staining protocols, and scoring systems. Moreover, there is still no universal cutoff for positive STC1 expression, and false positives have occasionally been reported in rare benign hyperplastic nodules. Therefore, while STC1 shows considerable promise as a diagnostic tool for PTC, its use should be contextualized within a multimodal diagnostic framework and interpreted in conjunction with clinical, radiological, and other pathological findings [62,63].

F. Prognostic Value of STC1 in Papillary Thyroid Carcinoma

Increasing evidence supports the role of stanniocalcin-1 (STC1) not only as a diagnostic biomarker but also as a significant prognostic indicator in papillary thyroid carcinoma (PTC). Numerous retrospective and prospective studies have shown that higher STC1 expression is associated with more aggressive clinicopathological features, including larger tumor size, extrathyroidal extension, lymphovascular invasion, and the presence of lymph node metastasis. These features are well-known risk factors for recurrence and poor clinical outcomes, underscoring the potential utility of STC1 as a prognostic marker in PTC [64,65].

The prognostic significance of STC1 has been validated across diverse populations. In large patient cohorts, immunohistochemical scoring of STC1 in resected PTC specimens revealed a positive correlation between high STC1 expression and advanced tumor stage, multifocality, and higher recurrence rates. Multivariate analyses indicate that STC1 expression remains an independent predictor of disease-free survival (DFS) and overall survival (OS), even after adjusting for age, gender, tumor size, and lymph node status. Thus, assessment of STC1 expression in surgical specimens may enhance existing prognostic models and support risk-adapted management strategies [66,67].

Several studies have specifically investigated the association between STC1 and disease recurrence in PTC. One meta-analysis encompassing multiple independent datasets concluded that high STC1 expression was consistently linked to a two- to threefold increased risk of local and regional recurrence. Furthermore, patients with elevated STC1 were more likely to present with persistent or recurrent disease following total thyroidectomy and radioactive iodine therapy, suggesting that STC1 could help identify individuals who may benefit from more aggressive initial treatment and closer long-term surveillance [68,69].

There is also evidence to suggest that STC1 expression may vary among histological variants of PTC, with the tall-cell and classic variants showing higher levels compared to follicular and other subtypes.

10.48047/jocaaa.2024.33.06.100

This differential expression may further refine risk stratification, as tall-cell and classic variants are typically associated with a more aggressive clinical course. STC1 may thus serve as a supplementary marker to guide therapeutic decisions, especially in cases where the traditional clinicopathological assessment is equivocal [70,71].

Serum STC1 levels have shown promise as a non-invasive biomarker for monitoring recurrence or persistent disease. In longitudinal studies, post-surgical declines in serum STC1 paralleled decreases in serum thyroglobulin, the current standard for follow-up, but with the added benefit of being unaffected by anti-thyroglobulin antibodies. This makes STC1 an attractive adjunct for post-treatment surveillance, particularly in patients at high risk for recurrence or with equivocal imaging findings [72,73].

Despite the growing body of evidence, several questions remain regarding the optimal use of STC1 as a prognostic marker. The absence of standardized thresholds for high versus low expression, variability in assay methodologies, and the need for prospective validation in larger, diverse cohorts are important considerations. Nevertheless, the integration of STC1 into prognostic algorithms, especially when combined with established molecular and pathological parameters, represents a significant advancement in the personalized management of papillary thyroid carcinoma [74,75].

G. Comparative Analysis: STC1 versus Other Biomarkers

The clinical management of papillary thyroid carcinoma (PTC) increasingly depends on the integration of molecular and immunohistochemical biomarkers for diagnosis, risk stratification, and surveillance. Among the most established molecular markers is the BRAF V600E mutation, present in approximately 45% of PTC cases. While this mutation is strongly associated with classic PTC morphology and more aggressive clinical behavior, it lacks specificity and can be found in both indolent and aggressive tumors. RAS mutations and RET/PTC rearrangements similarly contribute to diagnostic and prognostic panels, but their predictive value is limited by variable prevalence and overlapping features with other thyroid neoplasms [76,77].

Immunohistochemical markers such as galectin-3, HBME-1, and cytokeratin-19 (CK19) are frequently utilized to distinguish malignant from benign thyroid lesions. These markers, often used in combination, have improved diagnostic accuracy in fine-needle aspiration (FNA) cytology and tissue specimens. However, their specificity can be compromised by expression in benign or hyperplastic nodules, resulting in occasional false positives. The addition of STC1 to these immunohistochemical panels has been shown to increase both sensitivity and specificity for PTC, particularly in cases with indeterminate cytology, thus helping to minimize diagnostic ambiguity [78,79].

A major advantage of STC1 over many traditional biomarkers is its strong correlation with adverse pathological features and clinical outcomes. While BRAF V600E is a well-known marker for

10.48047/jocaaa.2024.33.06.100

recurrence risk, studies demonstrate that high STC1 expression more closely associates with lymph node metastasis, extrathyroidal extension, and advanced tumor stage. Moreover, multivariate analyses suggest that STC1 remains an independent prognostic factor even when controlling for the presence of BRAF or TERT promoter mutations, supporting its additive value in risk stratification algorithms [80,81].

Recent molecular panel studies have combined STC1 with other diagnostic and prognostic markers to improve overall predictive accuracy. Panels integrating STC1 with galectin-3, CK19, and BRAF V600E have shown superior performance compared to single-marker strategies, both in preoperative FNA and postoperative tissue analysis. Such multimodal approaches enable more accurate identification of high-risk patients and support more individualized management strategies, including the selection of surgical extent and adjuvant therapy [82,83].

Notably, STC1 demonstrates minimal expression in non-papillary thyroid tumors, such as medullary and anaplastic carcinomas, as well as in most benign nodules. This specificity may help reduce overtreatment in cases of indeterminate FNA, where conventional markers are less definitive. Furthermore, because STC1 is a secreted protein, its detection in serum offers a unique non-invasive diagnostic and surveillance tool not available with DNA-based markers like BRAF or RAS. However, variability in assay techniques and lack of standardized thresholds for positivity remain challenges to its universal adoption [84,85].

Overall, while no single biomarker is sufficient for all diagnostic or prognostic scenarios, the integration of STC1 into existing molecular and immunohistochemical panels has the potential to markedly improve the precision and accuracy of PTC management. Ongoing research will determine the optimal combinations and clinical settings in which STC1 provides the most benefit, and whether it may eventually serve as a therapeutic target in aggressive disease [86,87].

Conclusion

Stanniocalcin-1 (STC1) has emerged as a pivotal biomarker in the landscape of papillary thyroid carcinoma (PTC), distinguished by its notable specificity and robust association with adverse clinicopathological features. The collective evidence indicates that STC1 overexpression is not only a marker of malignant transformation but also a predictor of tumor aggressiveness, recurrence risk, and potentially diminished overall survival. This positions STC1 as a valuable adjunct to established molecular and immunohistochemical markers, especially in cases with indeterminate cytology or ambiguous histology, where traditional markers often fall short.

The diagnostic utility of STC1 is supported by its strong differential expression between benign and malignant thyroid lesions, and its inclusion in immunohistochemical or molecular panels enhances sensitivity and specificity for PTC. Equally compelling are its prognostic implications: STC1 positivity

10.48047/jocaaa.2024.33.06.100

correlates with key adverse features such as lymph node metastasis, extrathyroidal extension, and higher tumor stage, and may serve as an independent predictor of disease-free and overall survival in multivariate models. The recent development of assays for serum STC1 offers an additional, non-invasive avenue for diagnosis and postoperative surveillance, with the potential to overcome some limitations of current biomarkers such as serum thyroglobulin.

Despite these promising findings, several challenges remain before STC1 can be widely adopted in clinical practice. Variability in assay techniques, lack of standardized cutoffs, and inter-laboratory reproducibility are important considerations. Moreover, the mechanistic underpinnings of STC1's role in PTC tumorigenesis, particularly its interactions with key oncogenic pathways and the tumor microenvironment, require further elucidation through basic and translational research . The therapeutic implications of targeting STC1 are intriguing, and early preclinical studies suggest that STC1 inhibition may impair tumor growth and sensitize PTC cells to established treatments, though clinical trials are still needed.

In summary, STC1 represents a significant advance in the ongoing effort to individualize the management of papillary thyroid carcinoma. Its integration into diagnostic and prognostic algorithms, either alone or in combination with other markers, could refine risk stratification, guide therapeutic decision-making, and ultimately improve patient outcomes. Ongoing research aimed at standardizing testing methods, validating clinical utility across diverse populations, and exploring targeted therapeutic strategies will be crucial to realizing the full potential of STC1 in PTC care.

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