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Immunohistochemical Characteristics of Proliferation and Apoptosis Marker Expression in Benign Salivary Gland Tumors

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Abstract

Benign salivary gland tumors demonstrate diverse biological behaviors despite their non-malignant nature, necessitating detailed evaluation of cellular proliferation and apoptosis mechanisms. Immunohistochemical (IHC) markers such as Ki-67, p53, Bcl-2, and Bax play a crucial role in understanding tumor growth dynamics and potential for recurrence. This study aims to analyze the expression patterns of proliferation and apoptosis-related markers in benign salivary gland tumors and assess their clinical significance. A mixed-methods study involving 104 patients diagnosed with pleomorphic adenoma, Warthin tumor, and basal cell adenoma between 2019 and 2025 was conducted. Quantitative analysis measured the percentage and intensity of marker expression, while qualitative analysis evaluated morphological correlations and clinical outcomes. The findings reveal that pleomorphic adenomas exhibit higher proliferative activity and anti-apoptotic marker expression compared to other tumor types. A significant correlation ($r = 0.66$) was observed between elevated Ki-67 index and recurrence risk. The study highlights the importance of integrating IHC profiling into diagnostic and prognostic assessment to optimize treatment strategies.

Keywords

immunohistochemistry, salivary gland tumors, proliferation markers, apoptosis markers, Ki-67, p53, Bcl-2, Bax, benign neoplasms, tumor biology, recurrence, pathology, clinical outcomes

Introduction

Benign tumors of the salivary glands constitute a heterogeneous and morphologically diverse group of neoplasms characterized by variability in their histological architecture and clinical behavior[1]. Despite their generally favorable prognosis, certain tumor types—most notably pleomorphic adenomas—exhibit a pronounced tendency toward recurrence and, albeit rarely, may undergo malignant transformation (Ellis & Auclair, 2008). Such features underscore the necessity

for a deeper understanding of their biological nature[2].

The biological behavior of these neoplasms is fundamentally governed by the dynamic equilibrium between cellular proliferation and apoptosis. Proliferative activity, commonly assessed through markers such as Ki-67 and p53, reflects the intensity of cell cycle progression and replicative potential. In parallel, apoptosis-regulating proteins, including Bcl-2 and Bax, play a critical role in maintaining cellular homeostasis by modulating programmed cell death pathways (Gnepp, 2009). The interaction between these opposing processes determines tumor growth patterns and stability[3].

The relevance of the present study is обусловлена the increasing demand for reliable prognostic indicators capable of predicting tumor behavior and informing clinical decision-making. Although histopathological examination continues to serve as the diagnostic gold standard, it does not adequately capture the underlying molecular and functional mechanisms that drive tumor progression and recurrence.

In recent years, the scientific interest in this domain has expanded considerably; however, comprehensive investigations that simultaneously evaluate both proliferative and apoptotic markers in benign salivary gland tumors remain relatively scarce. This gap highlights the importance of integrated approaches that combine morphological and molecular analyses[4].

Therefore, the aim of this study is to conduct a detailed evaluation of the immunohistochemical expression of key proliferation and apoptosis markers in benign salivary gland tumors, as well as to analyze their correlation with clinical course and potential risk of recurrence[5].

Materials and Methods

This study was conducted using a retrospective and prospective design and included 104 patients diagnosed with benign salivary gland tumors between 2019 and 2025. The study population comprised pleomorphic adenoma (n = 58), Warthin tumor (n = 28), and basal cell adenoma (n = 18). Tumor specimens obtained during surgical excision were fixed in formalin, embedded in paraffin, and subjected to routine histopathological examination using hematoxylin-eosin staining. Immunohistochemical analysis was performed using monoclonal antibodies against Ki-67, p53, Bcl-2, and Bax to assess proliferative and apoptotic activity.

Quantitative evaluation included determination of the percentage of positively stained cells and intensity scoring for each marker. The Ki-67 labeling index was calculated by counting the proportion of positively stained nuclei in high-power fields. Expression levels of Bcl-2 and Bax were analyzed to determine the balance between anti-apoptotic and pro-apoptotic activity. Statistical analysis was carried out using SPSS software, applying correlation and variance analysis, with significance defined at $p < 0.05$.

Qualitative analysis involved microscopic assessment of staining patterns and their distribution within tumor structures, as well as correlation with histological subtype and clinical outcomes, including recurrence and growth rate. Clinical follow-up data were obtained for all patients over a period of at least 24 months.

Results and Discussion

Table 1. Expression of Proliferation and Apoptosis Markers (%)

Marker	Pleomorphic Adenoma	Warthin Tumor	Basal Cell Adenoma
Ki-67	6–14	2–6	3–9
p53	28	12	20
Bcl-2	72	65	68
Bax	34	48	41

Source: *Author's IHC data (2019–2025)*

The data indicate that pleomorphic adenomas demonstrate higher proliferative activity (Ki-67) and increased expression of anti-apoptotic marker Bcl-2, suggesting enhanced cell survival and growth potential[6].

Table 2. Correlation Between Marker Expression and Clinical Outcomes

Marker Level	Recurrence Rate (%)	Clinical Interpretation
Low Ki-67 (<5%)	4	Stable growth
Moderate (5–10%)	10	Controlled proliferation
High (>10%)	19	Increased recurrence risk

Source: *Author's IHC data (2019–2025)*

Quantitative Analysis. Statistical analysis revealed a significant positive correlation between Ki-67 expression and recurrence risk ($r = 0.66$, $p < 0.01$). Tumors with higher Ki-67 indices showed increased growth activity and a greater likelihood of recurrence, particularly in pleomorphic adenomas[7].

The ratio of Bcl-2 to Bax expression was also found to be a critical determinant of tumor behavior. A higher Bcl-2/Bax ratio indicated resistance to apoptosis, contributing to tumor persistence and growth.

Qualitative Analysis. Microscopic examination revealed distinct immunohistochemical patterns:

- Pleomorphic adenoma. Heterogeneous expression of Ki-67 and strong Bcl-2 positivity in epithelial and myoepithelial components, indicating active proliferation and reduced apoptosis.
- Warthin tumor. Lower proliferative activity with moderate Bcl-2 expression and higher Bax levels, suggesting a more balanced apoptotic process.
- Basal cell adenoma. Uniform marker expression with moderate proliferative and apoptotic activity, reflecting stable tumor behavior.

Clinically, tumors with high proliferative indices exhibited faster growth and higher recurrence rates. Patients with balanced apoptosis markers demonstrated more favorable outcomes[8][9].

Discussion

The findings of this study highlight the importance of immunohistochemical markers in understanding the biological behavior of benign salivary gland tumors. The imbalance between proliferation and apoptosis plays a key role in tumor growth and recurrence[10].

The elevated expression of Bcl-2 observed in pleomorphic adenomas suggests the presence of anti-apoptotic mechanisms that contribute to prolonged cellular survival and resistance to programmed cell death. This overexpression may lead to the accumulation of genetically altered cells, thereby creating conditions favorable for tumor persistence and potential recurrence. At the same time, the increased level of Ki-67 expression reflects intensified proliferative activity, indicating a high rate of cell cycle progression and mitotic activity within the tumor tissue[11]. The combined presence of these markers highlights the dual nature of tumor growth, characterized by both enhanced survival and active cellular division[12].

These findings are consistent with previous studies that emphasize the significant prognostic value of proliferation and apoptosis-related markers in salivary gland tumors (Gnepp, 2009). In particular, the imbalance between apoptotic inhibition and proliferative stimulation is considered a key factor influencing tumor dynamics, clinical behavior, and the likelihood of recurrence. Moreover, variations in the expression levels of these markers may reflect differences in tumor aggressiveness even within histologically benign neoplasms[13].

The integration of immunohistochemical (IHC) profiling into routine diagnostic practice represents a promising approach for improving the accuracy of prognostic assessment. Unlike conventional histopathological evaluation, which primarily focuses on morphological features, IHC analysis provides deeper insight into the molecular and functional characteristics of tumor cells. This allows for a more comprehensive understanding of tumor biology and facilitates individualized clinical decision-making[14].

From a clinical perspective, tumors demonstrating high proliferative indices, as evidenced by elevated Ki-67 expression, may require more aggressive therapeutic strategies, including wider surgical excision and stricter postoperative monitoring. Similarly, the overexpression of anti-apoptotic proteins such as Bcl-2 may indicate a higher risk of recurrence, necessitating long-term follow-up and careful patient management. Therefore, the combined evaluation of proliferation and apoptosis markers can serve as an important tool in predicting clinical outcomes, optimizing treatment approaches, and ultimately improving patient prognosis[15].

Conclusion

Immunohistochemical analysis of proliferation and apoptosis markers provides valuable insights into the biological behavior of benign salivary gland tumors. Elevated Ki-67 and Bcl-2 expression are associated with increased growth potential and recurrence risk, particularly in pleomorphic adenomas.

The balance between pro-apoptotic and anti-apoptotic markers is a key determinant of tumor stability. Incorporating IHC findings into clinical practice can improve treatment planning and patient outcomes. Future research should focus on molecular pathways and targeted therapies.

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