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Salivary Gland Adenoid Cystic Carcinoma: A Systematic Review

[1]Dr Susmita Choudhary (Corresponding author), [2]Dr Anindita Talukdar, [3]Dr Naveen Balaji G V,

[4] Dr. Karthi Kumar Murari, [5] Dr.Priyanka Sawadkar, [6]Dr. Karthik Shunmugavelu

[1]Associate Professor, Department of Orthodontics and Dentofacial Orthopaedics , Narsinhbhai Patel Dental College and Hospital, Visnagar, Gujarat India

[2]Assistant Professor, Department of Pedodontics and Preventive Dentistry, Regional Dental College, Guwahati, Assam India

[3]MBBS, Tutor , Department of forensic medicine, Sree Balaji Medical College and Hospital India

[4]MDS in Prosthodontics , Lecturer, University of science and technology, Fujairah

[5]M.D.S. Oral & Maxillofacial Surgery , Lecturer , Department of Oral & Maxillofacial Surgery, Tatyasaheb Kore Dental College and Research Center, New Pargaon, Maharashtra, India

[6]BDS, MDS OMFP, MSC London, Mfdsrcs England, Mfdsrcps Glasgow, Faculty Affiliate RCS Ireland, Affiliate RCS Edinburgh, MCIP, FIBMS Usa, Masid Australia

[6]Assistant Professor, Department of Dentistry, PSP medical college hospital and research institute Tambaram Kanchipuram main road Oragadam Panruti Kanchipuram district Tamilnadu 631604 India

https://orcid.org/0000-0001-7562-8802, drkarthiks1981@gmail.com

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Abstract: Background: Adenoid cystic carcinoma (ACC) of the salivary glands is a slow-growing, aggressive malignancy with perineural invasion and late metastasis. Although it has an indolent course, ACC poses a formidable clinical problem due to diagnostic difficulties and limited treatment options.

Materials and Methods: This systematic review was conducted according to PRISMA guidelines. Electronic searches were conducted on PubMed, Scopus, and Web of Science databases, incorporating literature between 2005 and 2025. Included studies varied across clinical, molecular, imaging, and computational studies investigating salivary gland ACC. Selected articles were evaluated based on study type, sample size, diagnostic markers, treatment protocols, and prognostic outcomes.

Results: The final review included six relevant studies. ACC mostly occurs in patients aged between their fifth to seventh decade of life and is more common in females. Tumors most frequently develop in parotid and submandibular glands and show cribriform, tubular, or solid histologic patterns. Molecular studies identified recurrent MYB-NFIB and MYBL1-NFIB gene fusions and NOTCH pathway mutations. Immunohistochemical analysis showed prevalence M2 macrophage invasion and increased angiogenesis. Imaging technologies, especially machine learning-based models of ultrasound, greatly enhanced the diagnostic rate. High survival rates and low recurrence were observed with surgical resection and radiotherapy. MicroRNA profiling also indicated tumor aggressiveness-related miRNAs.

Conclusion: ACC of the salivary glands is a biologically complex neoplasm with unpredictable clinical behavior. Integration of molecular genetics, immunopathology, radiologic innovation, and artificial intelligence maximizes diagnostic accuracy and may dictate future therapeutic directions. Despite promising findings, long-term multicenter trials are essential to validate new strategies.

Keywords: Adenoid cystic carcinoma, salivary gland tumor, MYB-NFIB fusion, perineural invasion, radiotherapy, immunohistochemistry, machine learning, microRNA, ultrasound imaging.

INTRODUCTION

Salivary gland neoplasms are a diverse group of tumors with disparate biological behavior, clinical presentation, and prognosis. Of these, adenoid cystic carcinoma (ACC) is unique in its paradoxical nature of having indolent growth but displaying aggressive histological characteristics and a strong tendency for perineural invasion.[1] ACC is found to account for about 10% of all salivary gland malignancies and up to 30% of minor salivary gland tumors. While uncommon, its clinical importance is highlighted by its multifaceted pathobiology and propense to metastasize hematogenously to the distant organs, most importantly the lungs and bones, many years following initial therapy.[2] The disease occurs most commonly in patients in their fifth to seventh decades of life with a slight female predominance.[3]

Clinically, ACC typically appears as a painless, slowly growing mass and can be asymptomatic until it has caused neurological deficits from perineural spread. The disease's insidious nature explains the late diagnosis, and its biology makes long-term control very difficult. Even with extensive surgical resection and adjuvant radiotherapy, local or distant recurrence is common. This is largely attributed to the subclinical extension of the tumor within nerve sheaths and vascular routes, which undermines the effectiveness of standard local therapy.[4]

In addition, the rarity and histological heterogeneity of ACC have precluded the conduct of large-scale, randomized clinical trials. Thus, there is a continuous need to discover molecular biomarkers and to devise new diagnostic and therapeutic approaches. The development in next-generation sequencing has clarified seminal genetic changes, including MYB-NFIB and MYBL1-NFIB gene fusions and NOTCH pathway mutations, with potential to target therapy.[5] Also, new developments in immunohistochemistry, radiologic evaluation, and computational imaging—most importantly the application of machine learning algorithms—are transforming the diagnostic scenario.

In this context, the present systematic review aims to provide a comprehensive synthesis of the current understanding of salivary gland ACC, drawing upon clinical, molecular, immunological, and imaging perspectives. By evaluating the latest evidence, this review seeks to support clinicians and researchers in optimizing diagnostic accuracy and informing evidence-based therapeutic decision-making.

MATERIALS AND METHODS

This systematic review was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[6] (Figure 1). Comprehensive literature search was conducted on PubMed, Scopus, and Web of Science databases from January 2005 to March 2025.

Search Strategy: The search utilized keywords and Boolean operators, including: “adenoid cystic carcinoma,” “salivary gland cancer,” “MYB-NFIB fusion,” “radiotherapy,” “perineural invasion,” “machine learning,” and “microRNA.”

Inclusion Criteria:

- Original studies published in English
- Clinical or preclinical investigations on salivary gland ACC

- Studies evaluating histology, molecular markers, treatment, imaging, or computational diagnostics
- Studies with clear methodological and outcome data

Exclusion Criteria:

- Narrative reviews, case reports, editorials, or commentaries
- Studies not specific to salivary gland ACC

A total of six studies met the eligibility criteria after full-text assessment and were included in the qualitative synthesis.

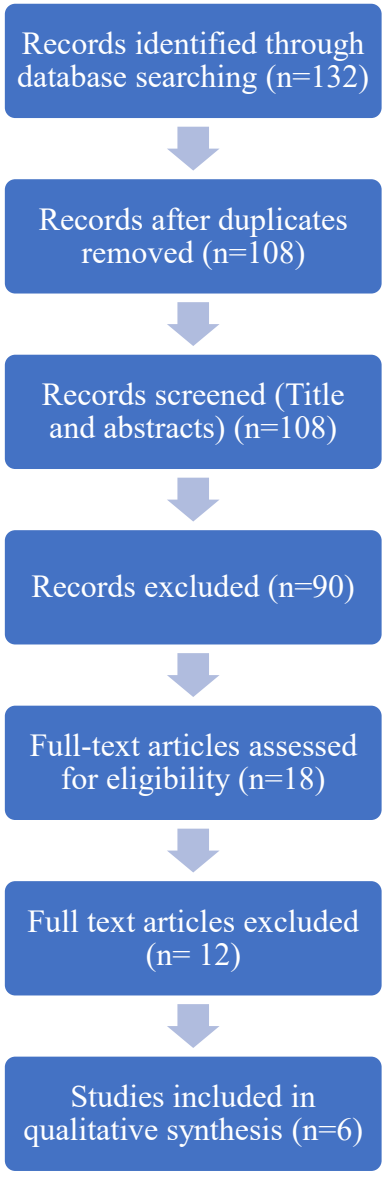

Figure 1: PRISMA Flowchart

RESULTS

Table 1: Summary of Included Studies

Author	Study	Focus Area	Study Type	Key Findings
Su et al. (2025)[7]	Machine learning model for diagnosing salivary gland adenoid cystic carcinoma based on clinical and ultrasound features.	Imaging & AI	ML-based diagnostic model	SVM model achieved >90% AUC in distinguishing ACC vs. non-ACC
Michaelides et al. (2023)[8]	Adenoid cystic carcinoma of the salivary glands: a pilot study of potential therapeutic targets and characterization of the immunological tumor environment and angiogenesis.	Immunopathology	Immunohistochemistry	M2 macrophage dominance, high angiogenesis, absent PD-L1
Zanon et al. (2023)[9]	Identification of MicroRNA Expression Profiles Related to the Aggressiveness of Salivary Gland Adenoid Cystic Carcinomas.	Molecular biology	miRNA expression	Identified miRNAs associated with perineural invasion and aggressive subtypes
Bin Liu et al. (2017)[10]	Spatio-Temporal Genomic Heterogeneity,	Genomics	Whole-genome sequencing	Identified MYB/MYBL1 fusions, NOTCH

	Phylogeny, and Metastatic Evolution in Salivary Adenoid Cystic Carcinoma.			mutations, and subclonal heterogeneity
Sumida et al. (2016)[11]	Estrogen Enhances Malignant Phenotypes in Human Salivary Adenoid Cystic Carcinoma Cells.	Hormonal regulation	Cell line study	Estrogen receptor expression promoted proliferation in engineered ACC cells
Gurney et al. (2005)[12]	Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation.	Treatment outcomes	Retrospective	Surgery + radiotherapy gave 85% 5-year survival, 69% at 10 years

DISCUSSION

The multifactorial etiology of ACC makes it difficult to diagnose and treat. Histologically, solid architecture tumors have a worse prognosis than cribriform or tubular variants. This was confirmed by Zanon et al. (2023)[9], who identified upregulated miRNA profiles in solid variants, with a corresponding more aggressive clinical behavior and perineural invasion. Concurrently, Bin Liu et al. (2017)[10] exhibited the genomic complexity of ACC and highlighted that solid variants tended to show more spatial and temporal heterogeneity in MYB-related fusions, postulating a molecular basis for the reported clinical aggressiveness.

In terms of etiopathogenesis, ACC is primarily driven by genetic alterations, most notably the MYB-NFIB and MYBL1-NFIB fusion genes, which result from chromosomal translocations such as t(6;9)(q23;p23). These fusions result in overexpression of the MYB or MYBL1 oncogenes that code for transcription factors controlling genes that are important for cell cycle progression, resistance to apoptosis, angiogenesis, and invasion. Zanon et al. (2023)[9] have demonstrated that the truncated MYB proteins generated by these fusions are able to evade regulation by microRNA binding as a consequence of deletion of the 3′-UTR, enhancing oncogenic signaling. In addition, NOTCH pathway mutations, particularly in NOTCH1, correlate with ACC aggressiveness and poor prognosis, especially for solid histological pattern tumors. They promote tumor survival and growth by determining cell fate. Hormonal pathways have also been suggested, as per Sumida et al. (2016)[11], where the expression of estrogen

receptors promoted the proliferation of ACC cells, with another added complexity to its etiopathogenesis. In general, these results suggest a complex interplay of genetic, epigenetic, and hormonal elements in the pathogenesis and progression of ACC.

Molecular studies also converged to identify key oncogenic drivers. Bin Liu et al.[10] and Zanon et al.[9] both indicated the importance of MYB/MYBL1 fusions but while Liu[10] emphasized mutational burden and clonal heterogeneity, Zanon[9] provided depth by identifying post-transcriptional regulators such as microRNAs that govern oncogenic pathways. Taken together, these studies indicate a requirement for multi-layered molecular diagnostics to address genomic as well as epigenomic complexity.

From an immunologic point of view, Michaelides et al. (2023)[8] identified the tumor microenvironment to be immunosuppressive, with a preponderance of M2 macrophage invasion and with very low PD-L1 expression. Such low immunogenicity is consistent with that reported by Liu et al.[10], with minimal T-cell invasion reported in high-grade types. Collectively, these studies caution against the sole reliance on checkpoint inhibitors and instead imply a necessity for methods to modulate the immune microenvironment or to combine immunotherapy with other forms of therapy. Of special note, the immune microenvironment observed in Michaelides et al.[8] study aligns with that described by Zupancic et al. (2024)[13], who also identified concordant macrophage infiltration and vascular proliferation patterns and emphasized the key role of tumor-associated macrophages in ACC pathoegenesis.

Su et al. (2025)[7] made diagnostic contributions through machine learning. Their support vector machine model was able to differentiate ACC from other salivary tumors with AUCs > 0.90. Compared to conventional histopathology or IHC studies such as those by Michaelides et al.[8], Su et al's. computational method provides a reproducible, non-invasive diagnostic adjunct. Additionally, the imaging features employed—such as rat tail sign and polar vessels—could be associated with perineural invasion patterns observed in Zanon's[9] molecular and histological analysis, acting as a bridge between imaging phenotypes and molecular pathology.

On the treatment side, Gurney et al. (2005)[12] reported good survival with surgery and radiotherapy, in accord with contemporary clinical practice. They did not consider molecular heterogeneity or immune profiling—shortcomings remedied in subsequent research. For example, Sumida et al. (2016)[11] supplemented potential endocrine therapies by showing that estrogen receptor-positive ACC cells are responsive to hormonal stimulation with increased proliferation. Although their results are preclinical, they reveal a novel therapeutic window for biomarker-based treatments in ER-positive ACC subgroups. In addition, evidence by Tomoki Sumida et al. (2016)[11] supports the estrogen receptor function of upregulating cell cycle and motility genes, lending mechanistic evidence to observations from previous molecular studies.

In addition, Maicon Zanon et al. (2023)[9] correlated certain miRNAs (e.g., miR-21, miR-29c, and miR-195) with aggressive tumor phenotypes, proposing potential markers for prognosis. These results complement Bin Liu et al.'s[10] discovery of MYB fusion-positive subtypes correlated with upregulated miRNA expression, together indicating integrated gene–miRNA–phenotype axes. Significantly, the coincidence of clinical aggressiveness, perineural invasion, and solid histology in both studies reinforces the suggested miRNA-based risk stratification models.

Collectively, these studies document an increasing consensus that ACC management needs to incorporate surgical, radiologic, molecular, and computational knowledge. They also identify complementary strengths: Liu et al.[10] and Zanon et al.[9] investigate genetic and post-genetic drivers, Michaelides et al.[8] and Sumida et al.[11] provide immune and hormonal background, Su et al.[7] contributes diagnostic innovation, and Gurney et al.[12] grounds these advances in clinical outcome standards. However, variability in methodologies, small cohort sizes, and uneven follow-up periods continue to be major limitations. In order to progress, there will need to be standardized multicenter protocols combining molecular diagnostics, radiomics, and immunoprofiling.

CONCLUSION

Salivary gland adenoid cystic carcinoma is still a rare but formidable cancer. Though conventional management with surgery and radiotherapy results in reasonable survival results, new genomic, immunologic, and radiologic discoveries offer hopeful hopes for targeted therapies in salivary gland cancer. The convergence of molecular diagnostics, artificial intelligence, and targeted therapeutics has the potential to enhance prognostic discriminability and therapeutic efficacy. It is essential that future multicenter, prospective studies are necessary to confirm these methods and optimize evidence-based treatment protocols.

REFERENCES

[1] Cantù G. Adenoid cystic carcinoma. An indolent but aggressive tumour. Part A: from aetiopathogenesis to diagnosis. Acta Otorhinolaryngol Ital. 2021 Jun;41(3):206-214. doi: 10.14639/0392-100X-N1379. PMID: 34264913; PMCID: PMC8283400.

[2] Saleh E, Ukwas A. Adenoid Cystic Carcinoma of Salivary Glands: A Ten-Year Review and an Assessment of the Current Management, Surgery, Radiotherapy, and Chemotherapy. Int J Otolaryngol. 2023 Apr 29;2023:7401458. doi: 10.1155/2023/7401458. PMID: 37159817; PMCID: PMC10163974.

[3] Sofi, Mushtaq Ahmad; Mir, Mohmad Hussain; Fatima, Kaneez; Andleeb, Asifa; Siraj, Farhana; Dar, Nazir Ahmad. Clinicoepidemiological Profile of Adenoid Cystic Carcinoma: Experience from a Tertiary Care Oncology Center in Kashmir, India. Journal of Radiation and Cancer Research 13(1):p 19-22, Jan–Mar 2022. | DOI: 10.4103/jrcr.jrcr_36_21

[4] Moreira MCS, Dos Santos AC, Cintra MB. Perineural spread of malignant head and neck tumors: review of the literature and analysis of cases treated at a teaching hospital. Radiol Bras. 2017 Sep-Oct;50(5):323-327. doi: 10.1590/0100-3984.2015.0215. PMID: 29085166; PMCID: PMC5656073.

[5] Chu, Ying-Hsia & Xu, Bin & Sukhadia, Purvil & Mohanty, Abhinita & DiNapoli, Sara & Ho, Alan & Katabi, Nora & Dogan, Snjezana. (2024). Targeted RNA Sequencing of Head and Neck Adenoid Cystic Carcinoma Reveals SEC16A::NOTCH1 Fusion and MET Exon 14 Skipping as Potentially Actionable Alterations. Head and Neck Pathology. 18. 10.1007/s12105-024-01694-7.

[6] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA,

Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.

[7] Su HZ, Li ZY, Hong LC, Wu YH, Zhang F, Zhang ZB, Zhang XD. Machine learning model for diagnosing salivary gland adenoid cystic carcinoma based on clinical and ultrasound features. Insights Imaging. 2025 May 8;16(1):96. doi: 10.1186/s13244-025-01974-y. PMID: 40342001; PMCID: PMC12061827.

[8] Michaelides I, Künzel J, Ettl T, Beckhove P, Bohr C, Brochhausen C, Mamilos A. Adenoid cystic carcinoma of the salivary glands: a pilot study of potential therapeutic targets and characterization of the immunological tumor environment and angiogenesis. Eur Arch Otorhinolaryngol. 2023 Jun;280(6):2937-2944. doi: 10.1007/s00405-023-07884-3. Epub 2023 Mar 1. PMID: 36856809; PMCID: PMC10175421.

[9] Zanon MF, Scapulatempo-Neto C, Gama RR, Marques MMC, Reis RM, Evangelista AF. Identification of MicroRNA Expression Profiles Related to the Aggressiveness of Salivary Gland Adenoid Cystic Carcinomas. Genes (Basel). 2023 Jun 2;14(6):1220. doi: 10.3390/genes14061220. PMID: 37372400; PMCID: PMC10298384.

[10] Liu B, Mitani Y, Rao X, Zafereo M, Zhang J, Zhang J, Futreal PA, Lozano G, El-Naggar AK. Spatio-Temporal Genomic Heterogeneity, Phylogeny, and Metastatic Evolution in Salivary Adenoid Cystic Carcinoma. J Natl Cancer Inst. 2017 Oct 1;109(10):djx033. doi: 10.1093/jnci/djx033. PMID: 29117356; PMCID: PMC6059240.

[11] Sumida T, Ishikawa A, Kamata YU, Nakano H, Yamada T, Mori Y. Estrogen Enhances Malignant Phenotypes in Human Salivary Adenoid Cystic Carcinoma Cells. Anticancer Res. 2016 Jun;36(6):2793-8. PMID: 27272790.

[12] Gurney TA, Eisele DW, Weinberg V, Shin E, Lee N. Adenoid cystic carcinoma of the major salivary glands treated with surgery and radiation. Laryngoscope. 2005 Jul;115(7):1278-82. doi: 10.1097/01.MLG.0000165381.64157.AD. PMID: 15995521.

[13] Zupancic M, Näsman A, Friesland S, Dalianis T. Adenoid Cystic Carcinoma, Clinical Presentation, Current Treatment and Approaches Towards Novel Therapies. Anticancer Res. 2024 Apr;44(4):1325-1334. doi: 10.21873/anticanres.16929. PMID: 38537991.