Gingivobuccal Squamous Cell Carcinoma
A Different Genomic Entity

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KEYWORDS

• Gingivobuccal squamous cell carcinoma • Genomic alterations • Transcriptomics • Epigenetics • Tumor microenvironment • Immune evasion

KEY POINTS

- Gingivobuccal mucosal squamous cell carcinoma is clinically distinct from other head and neck squamous cell carcinoma because of areca nut–driven carcinogenesis and its strong association with oral submucous fibrosis.
- The tumor harbors recurrent genomic alterations including TP53, FAT family genes, CASP8, and PIK3CA, alongside arachidonic acid metabolism pathway mutations.
- Copy number changes (eg, 11q22 amplification, 9p21 loss) and transcriptomic programs involving extracellular matrix remodeling and epithelial-mesenchymal transition drive invasion and progression.
- The tumor microenvironment is characterized by exhausted T cells, macrophage polarization, and cancer-associated fibroblasts, promoting early immune evasion.
- Multiomics insights support subsite-specific strategies for early detection, prognostication, immunotherapy, and targeted clinical interventions.

INTRODUCTION

Gingivobuccal mucosal squamous cell carcinoma (GBMSCC) is a clinically distinct entity of head and neck squamous cell carcinomas (HNSCCs). It has a unique geographic predilection in the south-east Asian countries and strongly correlated with consumption of areca nut and chewing of tobacco products. Other HNSCC are associated with smoking of tobacco, alcohol, and human papilloma virus (HPV) infection. With the exposure to local risk factors, more than 80% of GBMSCC are preceded by either oral leukoplakia or oral submucous fibrosis (OSMF), which is less common in other HNSCC. The GBMSCCs are locally invasive carcinoma with less nodal and distant metastasis. These differences in the risk habits and clinicopathologic behavior are endowed by unique genomic landscape. Understanding these

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Abbreviations

AAM	arachidonic acid metabolism
CNA	copy number alteration
CNV	copy number variation
ECM	extracellular matrix
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
GBMSCC	gingivobuccal mucosal squamous cell carcinoma
HNSCC	head and neck squamous cell carcinoma
lncRNAs	long noncoding RNAs
MMP	matrix metalloproteinase
OSMF	oral submucous fibrosis
TME	tumor microenvironment

molecular mechanisms may help to develop better strategies for detection and treatment of GBMSCC.

In this article, the genomic landscape of GBMSCC will be outlined along with translational applications of this knowledge to improve clinical outcome.

Gingivobuccal Mucosal Squamous Cell Carcinoma Carcinogenesis

The primary risk habit for GBMSCC is smokeless tobacco and areca nut in the form of beetle quid chewing. Majority of these cancers are preceded by development of OSMF. The tobacco-induced oral squamous cell carcinomas have high mutational burden, particularly in TP53 with point mutations (G:C > T:A, G:C > C:G transversions), which are clustered in exon 5 to 8. Associated p53 protein over expression is observed. TP53 mutation leads to chromosomal instability with common somatic copy number variations (CNVs) seen are gains in 8q, 9q, 11q, 17q, and 20q, and loss in 3p (including genes like FHIT, RARb, and VHL), 9p21, and 18q. The primary oncogenic pathways affected are rat sarcoma oncogene (RAS), epidermal growth factor receptor (EGFR), cyclin-dependent kinase inhibitor-2A (CDKN2A), cyclin D1, and c-myc in addition to TP53.[1,2]

Areca nut alkaloids (arecoline, arecaidine) are the primary risk factor for OSMF, which precedes the development of GBMSCC. It generates reactive oxygen species and upregulation of inflammatory cytokines such as ineterleukin-6 (IL-6). Increased collagen production through Lysyl oxidase activation (via high copper), proinflammatory cytokines, and tissue inhibitor of metalloproteinases (TIMP) up regulation creates fibrotic milieu leading to the development of submucous fibrosis. In addition, areca nut exposure leads to M2-macrophage polarization with elevated VCAM-1/p-CREB signaling, promoting epithelial-mesenchymal transition (EMT) and migration. It induces EMT via upregulation of Slug, Twist, ZEB1, Snail, and downregulation of E-cadherin; concurrently increase matrix metalloproteinases (MMPs)-2/9 activity creating a milieu for malignant transformation.[3]

The malignant transformation of OSMF is heralded by upregulation of hypoxia-inducing factor, reactive oxygen species in fibroblast cells, and VEGF expression promoting angiogenesis and metastasis. Other factors and pathways enhancing this multistep process include[4] increased cell motility via MMPs, p38 mitogen-activated protein kinase upregulation, and[5] EMT via PI3/AKT pathway. Areca nut–induced oral cancers have lower TP53 mutation rate. In Indian, Taiwanese, and Sri Lankan population with oral cancers caused by Areca nut, TP53 mutations are nearly absent.[6] However, as tobacco smoking habits coexists, the prevalence is about 22% to 43%. However, epigenetic and DNA repair alterations are common. Frequent p16 (CDKN2A) promoter hypermethylation (about 54%) contributes to tumor suppression beyond genomic mutations.[7] Arecoline exposure triggers γ-H2AX phosphorylation, activates ataxia telangiectasia mutated (ATM) signaling, causes G_2/M arrest, suppresses DNA repair, and impairs p53 transactivation. The driver mutations for GBMSCC are quite different from the ones affecting other head and neck site, making it unique and unequivocally important to study the genomic variations (**Fig. 1**, **Table 1**).

GENOMIC ALTERATIONS IN GINGIVOBUCCAL MUCOSAL SQUAMOUS CELL CARCINOMA

Somatic Mutation Landscape in Gingivobuccal Mucosal Squamous Cell Carcinoma

An alteration in the genomic DNA is one of the key factors driving the initiation and progression of cancer. In GBMSCC, these aberrations often reflect the region-specific exposure to tobacco carcinogens, particularly from smokeless forms such as gutka, khaini, and betel quid, which are prevalent in the Indian subcontinent. The molecular landscape of GBMSCC is shaped by cumulative DNA damage leading to single-nucleotide substitutions, insertions, deletions, and chromosomal instability that disrupt cellular regulatory pathways leading to carcinogenesis. Advances in next-generation sequencing over the past decade have facilitated a deeper understanding of these genomic events, revealing both shared and unique features of GBMSCC compared to other HNSCC subtypes.

Comprehensive genomic profiling of GBMSCC has consistently identified recurrent mutations in

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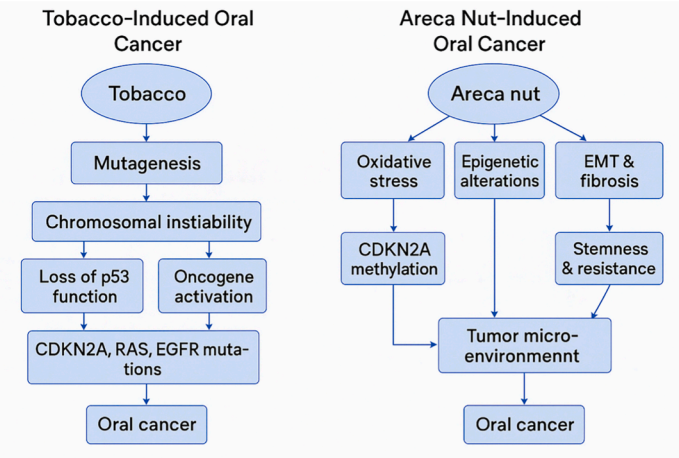

Fig. 1. Comparison of tobacco and areca nut–induced oral carcinogenesis.

well-established driver genes, including TP53, FAT1, CASP8, HRAS, NOTCH1, and PIK3CA, underscoring their pivotal role in tumor development.[8] Furthermore, studies have also highlighted additional novel mutations in genes such as USP9X, MLL4, ARID2, UNC13C, and TRPM3, reflecting the molecular heterogeneity of GBMSCC compared to other HNSCC subsites.[8,9] While FAT1 mutations are commonly observed across HNSCC, recurrent alterations in other FAT family members, including FAT3 and FAT4, were observed in up to 12% and 8% of GBMSCC cases, respectively. The invasive and metastatic behavior of this tumor type may be influenced by these genes, which are involved in cell adhesion and polarity.[8] As tobacco consumption co-exists with areca nut mutational signatures associated with tobacco-induced DNA damage are also observed in GBMSCC. Several studies have reported high frequencies of C>T transitions, consistent with COSMIC Signature SBS5, commonly linked to tobacco carcinogenesis.[10–12] This mutational pattern is further enriched by apolipoprotein B mRNA editing enzyme, catalytic polypetide (APOBEC)-mediated cytidine deamination events, corresponding to SBS2, especially in tumor tissues whereby APOBEC3A and APOBEC3B are upregulated.[11,13] The contribution of APOBEC activity suggests that in addition to tobacco-induced DNA damage, endogenous mutagenic processes play a major role in shaping the GBMSCC genome. Adding to this complexity, early events in

Table 1
Difference in molecular basis of oral cancers developed by tobacco and areca nut

Feature	Tobacco-Induced OSCC	Areca Nut–Induced OSCC (Betel Quid)
TP53 mutations	High incidence (∼>50%), classic transversions	Relatively low; stronger impact via methylation or indirect suppression
Chromosomal CNVs	Frequent gains (8q,17q), losses (3p,9p)	Less well-defined; more epigenetic/genotoxic effects
DNA repair genes	Mutations in CDKN2A, RAS, EGFR, and so forth.	Methylation (p16), *ERCC1* altered expression
Oxidative DNA damage	Present via tobacco carcinogens	Prominent via ROS from arecoline and nitrosamines
EMT & invasion	RAS/MAPK pathways	Strong EMT transcription program (Snail, Twist), MMPs up
Fibrosis	Absent	OSF leading to malignant niche
Genetic polymorphisms	TP53 codon hotspots	Polymorphisms in CYP2E1, GST, BRCA1/2, IL8, IGF1R

Abbreviations: MAPK, mitogen-activated protein kinase; OSCC, oral squamous cell carcinoma, OSF, oral submucous fibrosis; ROS, reactive oxygen species.

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GBMSCC tumorigenesis have been mapped through the analysis of premalignant lesions such as leukoplakia.[13] The study has shown that CASP8 mutations identified in both leukoplakia and invasive tumors, may serve as early drivers of malignant transformation. These mutations often co-occur with alterations in TP53, NOTCH1, FAT1, HRAS, and FBXW7, indicating a cooperative role in disease progression. The tumor mutation burden in GBMSCC seems to increase progressively, with leukoplakia samples exhibiting a lower tumor mutation burden than invasive tumors. This pattern supports the idea of stepwise accumulation of genetic alterations during the transition from precancerous to malignant stages (**Fig. 2**).

The impact of somatic mutations in GBMSCC extends beyond hallmark oncogenic signaling pathways. Notably, alterations in the arachidonic acid metabolism (AAM) pathway have emerged as prognostically relevant in GBMSCC. Around 18% of patients harbored mutations in AAM pathway-related genes, including PLA2G3, PLA2G4E, PLA2G4F, PLA2G6, PTGIS, TBXAS1, GGT7, CYP2C19, and CYP2U1. This study highlighted that loss-of-function mutations in AAM pathway genes lead to the downregulation of PI3K-Akt signaling pathway cascade resulting in slower progression and prolonged survival. Patients with AAM pathway genes mutation experienced slower disease progression and significant higher disease-free survival.[9] Complementing these observations, patient-derived GBMSCC cell lines have provided valuable experimental models that recapitulate the genomic alterations reported in primary tumors. Whole-exome sequencing of these cell lines confirmed the presence of key driver mutations, such as TP53 and NOTCH1, and also revealed smokeless tobacco-associated mutations in genes like PCLO, FAT3, and SYNE2.[10] These findings reinforce the idea that smokeless tobacco exposure leaves a distinct mutational imprint in GBMSCC, setting it apart from the patterns typically seen in smoking-related head and neck cancers.

Beyond the nuclear genome, mitochondrial DNA has also been implicated in GBMSCC pathogenesis. High-depth mitochondrial sequencing has uncovered recurrent somatic mutations in the mitochondrial genome, predominantly C>T and T>C transitions. Nonsynonymous mutations affecting complexes III, IV, and V were associated with an increased risk of lymph node metastasis, suggesting that mitochondrial dysfunction may contribute to aggressive behavior in GBMSCC.[12] Recent integrative analyses have shed new light on how specific genomic alterations may contribute to disease relapse and therapy resistance. By combining machine learning-based patient stratification with somatic mutation profiling, Kumar and colleagues,[11] found that relapsed tumors carry distinct mutations linked to cancer stemness and treatment failure. One of the key findings was a novel MAPKAP1 (p.T215A) missense mutation, identified uniquely in relapsed cases. This mutation affects the SIN1 domain of the mTORC2 complex, likely impairing AKT phosphorylation and disrupting the mTORC2–AKT–CREBBP–TP53–CD44 signaling cascade. Dysregulation of this cascade may promote a stem cell-like phenotype that contributes to therapy resistance and recurrence.

Copy Number Alterations in Gingivobuccal Squamous Cell Carcinoma

Similar to other oral cancers, GBMSCC is characterized by widespread somatic copy number alterations (CNAs), reflecting a high degree of chromosomal instability. Genomic imbalances, including amplifications and deletions across various chromosomal arms, play a central role in both tumor initiation and progression. Studies over the years have consistently reported

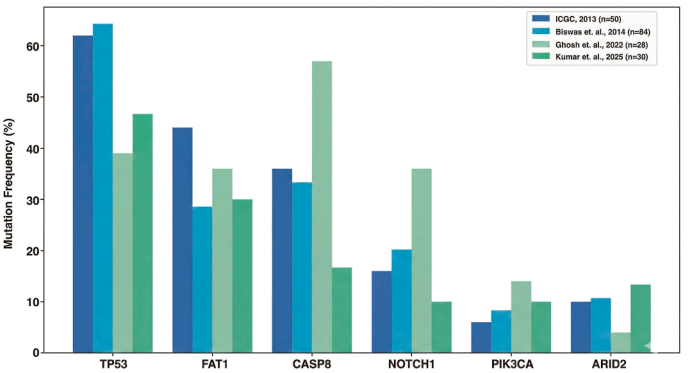

Fig. 2. Comparison of mutation frequencies of key genes across GBMSCC studies. The grouped bar chart shows the mutation frequencies (%) of six recurrently mutated genes (TP53, NOTCH1, FAT1, CASP8, PIK3CA, and ARID2) reported in GBMSCC across 4 independent cohorts.

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recurrent CNAs in GBMSCC, many of which overlap with patterns reported in HNSCC, but several alterations appear to be uniquely enriched in the gingivobuccal subsite.

One of the most frequently observed events in GBMSCC is the deletion of chromosomal arms 3p and 8p, which are also common across other oral cancers. These deletions often involve tumor suppressor genes, contributing to the loss of regulatory control over cell growth and adhesion. Alongside these losses, arm-level gains are frequently observed in regions such as 7p, 8q, 10p, 19p, and 20q, reflecting the widespread genomic imbalance that drives tumor proliferation and progression.[13] A landmark integrative study combining gene expression data with copy number profiles Ambatipudi and colleagues mapped several CNA hotspots in GBMSCC. Their findings highlighted gains at 11q22.1–q22.2, 11q13.2–q13.3, 8q24.3, and 20p11.21, along with losses at 9p21.3 and 11q23.3–q25.[14] These regions harbor genes that play critical roles in tumor progression, immune evasion, and metastasis. For example, amplification of 11q22.1–q22.2 affects genes such as BIRC2, BIRC3, YAP1, MMP7, and MMP10, which collectively promote survival, invasion, and resistance to apoptosis. In particular BIRC3 overexpression is associated with poor clinical outcomes, likely through its role in inhibiting apoptosis.[14–16] Similarly, 11q13.2–q13.3 amplification enriches for oncogenes like ORAOV1, FADD, FGF3, and PPFIA1, which are linked to aggressive tumor behavior and poor survival. The study also reported gain at 8q24.3, whereby LY6K was consistently overexpressed in tumor tissues. Recurrent loss of 9p21.3, which includes the CDKN2A and CDKN2B tumor suppressor genes, may contribute to cellular proliferation in GBMSCC.[14] Expanding on these findings, Indian Cancer Genome Consortium, which profiled 50 GBMSCC tumors identified several recurrent CNAs. Amplifications of CCND1 (22%) and TP63 (8%) were prominent, both of which play central roles in squamous epithelial maintenance and cell cycle regulation. Interestingly, amplifications were also observed in genes not typically associated with HNSCC CNA profiles, including drosha ribonuclease III (DROSHA) (12%), MDS1 and EV11 complex locus (MECOM) (10%), NFIB (10%), and a MMP gene cluster that encompasses YAP1 (10%). These findings point toward additional layers of genomic complexity that may be unique to GBMSCC.[8] Homozygous loss of GSTT1 and DDX3X occurred in 14% and 10% of patients, whereas CDKN2A and CDH19 showed heterozygous deletions in 10% of cases.

The transition from premalignant lesions to GBMSCC seems to involve a stepwise accumulation of CNAs. Studies comparing leukoplakia with matched tumor samples have shown that certain alterations occur early in the disease course and become more frequent in invasive cancer. Bhosale and colleagues showed that amplifications in 8q24.3 and 1p36.33 were already present in leukoplakia and became more frequent as lesions progressed to GBMSCC, suggesting their role in tumorigenesis. Further gains in 3q26.31 (EIF5A2 and ECT2), 12q13.2 (HOXC9 and HOXC13), and 11q22.1 (BIRC2 and BIRC3) were associated with aggressive disease and poor survival. Meanwhile, deletions in 3p26.3, 3p14.2, and 8p23.2 impacted tumor suppressor genes such as CHL1 and CSMD1, further promoting invasion and metastasis.[17] These genomic changes also appear to play a role in immune evasion. Amplification of 9p24.1, which includes the PD-L1 (CD274) gene, could enable tumor cells to suppress immune responses, potentially limiting the effectiveness of immunotherapies.[17] The accumulation of CNAs from precancerous to invasive tumors has been further validated in longitudinal studies. Kil and colleagues compared oral leukoplakia samples that eventually progressed to cancer with those that did not, finding that progressing lesions harbored significantly more CNAs. Common alterations in 3p, 9p, and 13q were seen in progressing dysplasia, with 3p14 and 9p21 deletions appearing in 50% of cases that later developed into GBMSCC. In contrast, nonprogressing lesions exhibited minimal chromosomal changes, primarily involving isolated CNAs in 3p. Progressing lesions also showed a higher frequency of multiple CNA events affecting regions such as 11q13, 8p21, 17p13, and 18q21, supporting the idea that cumulative genomic instability drives malignant transformation.[18] As GBMSCC advances, the CNA profile becomes increasingly complex. Late-stage tumors frequently acquire EGFR amplifications and deletions in DNA repair genes, features that are typically absent in leukoplakia. These alterations not only mark the transition to malignancy but may also contribute to therapy resistance and disease recurrence.[13] Together, these findings indicate that CNA in GBMSCC accumulate progressively, starting in precancerous lesions and becoming more complex as the tumor advances.

Transcriptomic Signature in Gingivobuccal Mucosal Squamous Cell Carcinoma

The transcriptomic landscape of GBMSCC has revealed complex molecular alterations that drive tumor initiation, progression, immune evasion, and metastasis. Unlike other head and neck

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subsites, GBMSCC shows distinct gene expression patterns, many of which are shaped by environmental factors such as smokeless tobacco contributing to its unique clinical behavior. A key finding across multiple transcriptomic studies in GBMSCC is the enrichment of extracellular matrix (ECM) remodeling and immune modulation pathways, driven by the dysregulation of related genes. These changes are observed even in precancerous stages and become more prominent as the tumor progresses. Large-scale RNA sequencing of 72 GBMSCC patients has identified more than 1700 dysregulated genes in GBMSCC tumors compared to adjacent normal tissues.[19,20] These alterations include upregulation of ECM-related genes such as MMP1, MMP13, MFAP2, COL4A1, COL4A2, and LAMC2, reflecting increased tissue remodeling, invasion, and metastatic potential. Genes such as COL4A1, COL4A2, LAMC2, and TLR2 consistently show increased expression during the transition from normal tissue to leukoplakia and further into tumor, implicating pathways like ECM-receptor interaction, PI3K-Akt signaling, and cytokine–cytokine receptor interactions in early disease development. A recent single-cell transcriptomic profiling more than 28,000 cells from 12 GBMSCC patients also supported the upregulation of ECM-receptor interaction and focal adhesion pathways, promoting invasion and metastasis in GBMSCC.[21] Notably, in tumors arising from OSMF, a separate transcriptional program involving genes like FOS, ATP1A1, and DUSP1 was identified, suggesting a unique pathogenic route for tumor progression in fibrotic backgrounds.[21] Immune checkpoint activation is another early feature widely observed in GBMSCC. Several studies have consistently reported upregulation of PD-L1 (CD274), CD80, and IDO1, not only in tumor tissues but also in leukoplakia samples, highlighting the presence of an immunosuppressive tumor microenvironment (TME) even in the precancerous stages of GBMSCC.[13,20] The amplification of 9p24.1, a locus that includes PD-L1, further supports this, indicating that both genomic and transcriptomic events together promote immune escape.[17] This early and sustained immune suppression suggests potential beneficial effect of PD-1:PD-L1 blockade.

Similar gene expression patterns have been reported by Bhosale and colleagues, who observed consistent upregulation of ECM and immune-related genes during the progression from leukoplakia to GBMSCC. Genes such as HOXC9, HOXC13, MFAP5, NELL2, EIF5A2, and ECT2 were found to be overexpressed in both precancerous and malignant stages, linking cell proliferation and invasion to early disease development.[17] Importantly, integrative analysis of CNAs and gene expression highlighted regions like 3q26.31 (EIF5A2, ECT2) and 12q13.2 (HOXC9, HOXC13), whereby genomic alterations directly influenced the transcriptional overactivation. A study by Prasad and colleagues, focused on smokeless tobacco-associated GBMSCC, identified more than 600 differentially expressed genes involved in inflammation, immune modulation, and invasion. Key findings included the upregulation of MMP9 and FZD2, both linked to metastasis, and the downregulation of CADM1, a molecule involved in immune surveillance. The study also highlighted increased levels of chemokines like CCL5, CXCL8, CXCL10, and IL1B, contributing to a proinflammatory and immune-evasive TME. Moreover, the upregulation of P-cadherin and downregulation of E-cadherin suggest an EMT-like state, further promoting aggressive tumor behavior.[22] Further, genes involved in the AAM pathway, previously identified as mutated in GBMSCC, also shows transcriptional downregulation in GBMSCC-derived cell lines. Genes such as PLA2G3, PLA2G4E, PLA2G4F, PTGIS, TBXAS1, CYP2U1, CYP2C19, and GPX7 were consistently downregulated, underpinning the complex cross-talk between somatic mutations and gene expression.[10]

Epigenetic Alterations and Gene Dysregulation in Gingivobuccal Mucosal Squamous Cell Carcinoma

The epigenetic regulation plays an intricate role in GBMSCC transcriptomic landscape. Das and colleagues (2019)[19] revealed that many of the downregulated genes, especially transcription factors like ZNF132, ZNF626, ZSCAN18, and ZNF844, are silenced through promoter hypermethylation. In contrast, immune evasion genes such as PD-L1 and CD80 are upregulated via promoter hypomethylation, reinforcing the tumor's capacity to evade immune detection. Beyond protein-coding genes, recent work has uncovered the role of long noncoding RNAs (lncRNAs) in GBMSCC. Haldar and Singh identified 1201 previously unannotated dysregulated lncRNAs.[23] Among these, CTA-384D8.35 emerged as a potential prognostic biomarker, whereby lower expression was linked to poor disease-free survival. Other dysregulated lncRNAs, including DUXAP8, SNHG1, AGAP2-AS1, PART1, LINC01116, and PCAT1 overlapped with known oncogenic lncRNAs in other cancers, suggesting shared mechanisms of tumor progression. The clinical relevance of these transcriptomic alterations was highlighted by a study by

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Chatterjee and colleagues,[24] who analyzed the expression profiles of 2039 immune-related genes and identified two distinct patient clusters: a good prognosis cluster and a bad prognosis cluster. The bad prognosis cluster group exhibited higher expression of CD73 (NT5E) and ITGA6, both associated with poor survival, deeper tumor invasion, and higher recurrence rates. CD73 is known to regulate extracellular adenosine production, whereas ITGA6 promotes EMT. Gene set enrichment analyses confirmed that the ECM-receptor interaction and focal adhesion pathways were significantly activated in this poor prognosis group, further linking the ECM signature to disease aggressiveness.

Overall, these findings suggest that GBMSCC is not driven by a single pathway but by a combination of changes in the tumor environment, immune system, and cellular functions. The progressive nature of these changes from leukoplakia to invasive carcinoma reflects a complex interplay of genetic, environmental, and immunologic factors. Furthermore, the discovery of lncRNA signatures and prognostic molecular subtypes provides new avenues for early detection, prognosis, and targeted therapy development tailored to GBMSCC.

MOLECULAR PATHWAYS

The development and progression of GBMSCC involves a complex interplay between the molecular pathways that regulate cellular growth, immunologic response, and tissue homeostasis. Molecular pathways including any genetic alterations, transcriptional, epigenetic, or immune-related changes are usually disrupted during carcinogenesis. Understanding these molecular dysregulations provides crucial insights into early detection, prognosis, and therapeutic interventions. Multiomics studies have revealed key alterations during the transition from normal mucosa to leukoplakia and ultimately to GBMSCC. Integrative genome-wide analysis of leukoplakia and GBMSCC by Bhosale and colleagues demonstrated that premalignant lesions exhibit chromosomal aberrations similar to late stages of OSCC. The study reported amplifications at 8q24.3 and deletions at 8p23.2, alongside dysregulation in genes including DERL3, EIF5A2, HOXC9, HOXC13, and NELL2. Importantly, these chromosomal alterations were not only involved in early stages but also appeared to predict metastatic potential, as evidenced by differences in copy number profiles between node-negative and node-positive tumors. Novel regions such as 1p36.33 (MXRA8) and 9p24.1 (CD274) emerged as potential prognostic indicators, reflecting the clinical relevance of these alterations in disease progression.[17] Large-scale epigenomic and transcriptomic profiling revealed significant involvement of epigenomic alterations in GBMSCC. The promoter hypomethylation–induced upregulation of immunoregulatory genes such as CD274 (PD-L1) and CD80 indicating the involvement of mechanisms of immune evasion. In addition, key epigenetic regulators such as DNMT3B and TET1 were found to be dysregulated, supporting the hypothesis that widespread methylation imbalances are a hallmark of GBMSCC. This study further reported the alterations in pathways including PPAR signaling, B cell receptor signaling, and AAM, linking epigenomic changes to metabolic reprogramming and immune modulation.[19] In addition, methylation study by Inchanalkar and colleagues, reported 846 differentially methylated promoters in leukoplakia and 5000 in GBMSCC. Integration with transcriptomic and genomic data revealed potential biomarkers such as FAT1 (hypomethylated), GLDC, and HOXB13 (both hypermethylated), which were significantly associated with patient survival.[25] These findings highlight the dynamic methylation status that evolves during carcinogenesis, which contributes to both tumor initiation and progression. The transcriptional analysis of leukoplakia identified key pathways that were increasingly dysregulated as the disease progressed, including ECM-receptor interactions, PI3K-Akt signaling, cytokine-cytokine receptor interactions, focal adhesion, and cell cycle regulation. Moreover, genes such as CD274, CD80, and IDO1, which are involved in immune escape, were also upregulated in precancerous lesions, suggesting the immune modulation may begin well before the malignant transformation. The genomic characterization of novel GBMSCC cell lines from patients with areca nut exposure also revealed oncogenic PIK3CA mutation. In addition, reported alterations in PCLO, FAT3, and SYNE2 are consistent with ICGC-GB dataset.[10] The transcriptomic analysis of the cell lines further identified significant dysregulation of Notch and p53 signaling, AAM, mitogen-activated protein kinase, chemokine, focal adhesion, ECM receptor interaction, cell-cycle, and DNA replication pathways.[10] The single-cell RNA sequencing of GBMSCC samples identified partial EMT and fetal cell-type reprogramming as two dominant pathways. These programs were associated with immune pathway gene expression, indicating active interaction with the TME. Furthermore, the analysis revealed diversity in T cell subsets and macrophage polarization, highlighting the immunologic complexity of the

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tumor ecosystem and the challenges it poses for therapy.[21] The integration of computational methods was explored by Singh and colleagues, who applied machine learning techniques to gene expression datasets in OSCC. Their analysis identified features within chromosome segregation, DNA damage response, and Notch signaling pathways as critical for prognosis.[26] This work illustrates the growing potential of artificial intelligence to complement molecular profiling and guide personalized treatment planning.

THE TUMOR MICROENVIRONMENT OF GINGIVOBUCCAL MUCOSAL SQUAMOUS CELL CARCINOMA

The TME of GBMSCC is dynamic, heterogenous, and immunologically active, comprising diverse immune and stromal components that interact closely with tumor cells. Recent single-cell and bulk profiling studies have provided critical insights into the cellular composition and immune landscape of GBMSCC, highlighting features that distinguish it from other head and neck cancer subsites.

T cells, which are the one of the most prominent immune players, account for nearly one-third of the tumor-infiltrating immune cells in GBMSCC. Single-cell RNA sequencing study have revealed a rich diversity of T cell subtypes, including cytotoxic $CD8^+$ T cells, exhausted T cells, and an unusual population of double-negative ($CD4-$/$CD8-$) PLCG2 + T cells. Interestingly, these double-negative T cells appear to be more abundant in GBMSCC compared to other head and neck cancer subsites, suggesting that GBMSCC may harbor a distinct T cell composition.[21] Adding to this, bulk immune profiling studies have shown a high abundance of $CD4^+$ memory-activated T cells in GBMSCC tumor tissues compared to normal mucosa.[13] $CD8^+$ cytotoxic T cells, which normally play a critical role in eliminating tumor cells, are progressively depleted during the transition from normal tissue to leukoplakia and eventually to GBMSCC. In tumors, the remaining $CD8^+$ T cells exhibit a functionally exhausted state, co-expressing immune checkpoint molecules like PD-1, CTLA4, and LAG3, which further weakens the cytotoxic T cell–mediated defense and allows the tumor to evade immune surveillance.[13,21]

Beyond the T cell compartment, the myeloid cell population, particularly macrophages, plays a significant role in shaping the GBMSCC microenvironment. Macrophages constitute about 14% of the tumor-infiltrating-immune-cells and displayed a hybrid phenotype, expressing markers of both proinflammatory M1 and immunosuppressive M2 states.[21] This plasticity likely contributes to immune modulation, simultaneously supporting inflammation and tumor progression. Complementary studies have also reported an increased infiltration of M1 macrophages in tumor tissues compared to normal tissues, suggesting an inflammatory microenvironment that may promote carcinogenesis in this tumor type.[13,20] Single cell RNA sequencing study identified two major fibroblast populations in GBMSCC. Cancer-associated fibroblasts (CAFs) that are enriched in genes related to ECM remodeling, such as FAP, PDPN, and various MMPs might be involved in stromal modification and tumor invasion. Another subset, myofibroblasts, expressed contractile proteins like ACTA2 and MYLK, contributing to the mechanical reshaping of the tumor stroma and facilitating cancer cell dissemination. Mast cells were less abundant than T cells or macrophages in this study dataset.[21] However, bulk immune profiling suggests that activated mast cells are significantly elevated in tumor tissues compared to leukoplakia and normal samples, implying a role in chronic inflammation and possibly facilitating tumor progression through stromal remodeling.[13,20] Dendritic cells, which are essential for antigen presentation and initiating immune responses, are gradually lost during the progression from normal mucosa to leukoplakia and tumor. This decline affects the recognition capacity of the immune system, further enabling immune escape.[13] B-cells are relatively less abundant in the GBMSCC TME compared to other major immune cells like T cells and macrophages. Their numbers further decline in tumors compared to normal tissues, suggesting a loss of humoral immune surveillance as the disease progresses.[20,21]

These findings highlight the complex mutational landscape and TME of GBMSCC and emphasize the need to understand these multifaceted alterations to develop subsite-specific biomarkers, prognostic tools, and personalized treatment strategies (**Fig. 3**).

TRANSLATIONAL AND CLINICAL IMPLICATIONS

Understanding the genomic landscape, immune profile, and TME has paved the way for the development of various targeted therapies. These advances have enabled progress in several areas, including cancer screening and surveillance, whereby circulating tumor DNA, DNA methylation markers, and protein markers are being explored for early detection and monitoring. Efforts in chemoprevention are also underway, particularly for managing oral potentially malignant lesions and

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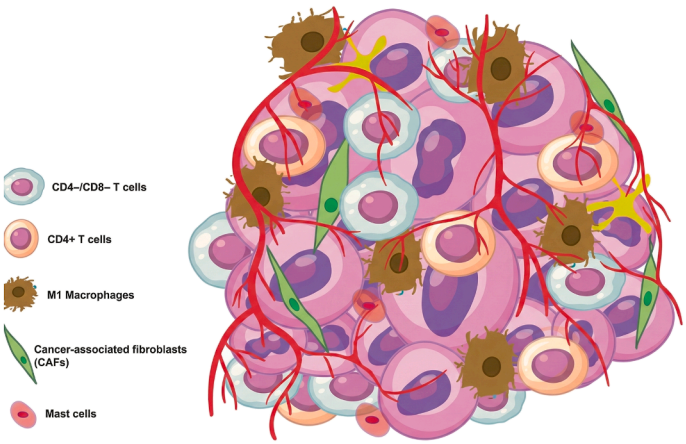

Fig. 3. Schematic representation of tumor microenvironment in GBMSCC. The TME is composed of complex network of malignant cells, immune cells such as CD4-/CD8- T cells, $CD4^{+}$ T cells, mast cells, M1 macrophages, and CAFs. TME, tumor microenvironment.

preventing second primary tumors. In addition, targeted therapies such as EGFR inhibitors have shown promise in treating specific subsets of HNSCC patients.

Targeted Therapies

EGFR is a transmembrane glycoprotein of the ErbB/HER family that is overexpressed in about 90% squamous cell carcinomas, including GBMSCC cancers. Cetuximab is a chimeric mouse-human monoclonal IgG1 antibody against the extracellular domain of EGFR that can induce cancer cell death via antibody-dependent NK cell–mediated cytotoxicity. Nimotuzumab is fully humanized monoclonal antibody against EGFR. Gefitinib is an orally administered selective inhibitor of EGFR. It reversibly inhibits the kinase activity of EGFR preventing the auto phosphorylation of tyrosine residues associated with the receptor, thereby inhibiting further downstream signaling and blocking EGFR-dependent proliferation (Table 2).

Immunotherapy

Apart from tyrosine kinase inhibitor–based targeted therapies, immune checkpoint inhibitors have emerged as a transformative approach in the treatment of HNSCC. Immune checkpoint inhibitors work by blocking the binding of check point proteins to their partner proteins, thereby switching *off* the signaling allowing the T cells to mount a response against the cancer cells. These drugs are particularly used in advanced or recurrent settings. Pembrolizumab is a monoclonal antibody

Table 2
Clinical trials involving epidermal growth factor receptor inhibitors in head and neck squamous cell carcinomas (inclusive of oral cavity)

Trials	Year	Setting	Intervention	Result	Conclusion
Vermokren et al,[27] 2008	2008	Recurrent/ metastatic	CT CT + cetuximab	OS - 7.4 10.1	Improved OS
Hitt et al,[28] 2012	2012	Recurrent/ metastatic	Paclitaxel Paclitaxel + cetuximab	PFS - 4.2 OS - 8.1	Active and well tolerated
DAHANCA 19[29]	2014	Concurrent	CT + RT CT + RT + zalutumumab	LRC - 79% −78%	No significant improvement
GORTEC 2007–01[30]	2017	Concurrent	RT + CT RT + cetuximab + CT	PFS - 40 53	Improved PFS + LRC
RTOG 0920[31]	2023	Adjuvant	RT RT + cetuximab	DFS - 63.6 71.7	Improved DFS No increase in long term toxicity

Abbreviations: CT, chemotherapy; DFS, disease free survival; LRC, locoregional control; OS, overall survival; PFS, progression-free survival.

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Table 3
Clinical trials with immune checkpoint inhibitors in head and neck squamous cell carcinoma

Trials	Year	Setting	Intervention	Results	Conclusion
Keynote 048[32]	2019	Recurrent/ metastatic	Pem Pem + CT Cet + CT	OS - 13 −10.7	Pem + CT as first line regimen
Keynote 689[33]	2025	Neoadjuvant	S + RT ± CT Conventional + Pem	EFS - 45.9% 59.8%	Potential standard of care
Patil et al,[34] 2023	2022	Palliative	CT CT + low dose Nivo	OS - 6.7 10.1 PFS - 4.6 6.6	Alternative standard of care

Abbreviations: Cet, cetuximab; CT, chemotherapy; Nivo, nivolumab; Pem, pembrolizumab; RT, radiotherapy.

that blocks the interaction between PD-1 and its ligands (PD-L1 and PD-L2) that would otherwise lead to inhibition of immune activation and reduced T cell cytotoxic activity. These ligands are expressed on the surface of activated T cell. Nivolumab, another monoclonal antibody works with a similar mechanism of action. However, it differs in safety profile and clinical efficacy (**Table 3**).

Treatment of oral precancer lesions by chemoprevention is also being explored to reduce disease burden and intercept cancer development at earlier stages. A wide range of agents have been used in the past including retinoids, carotenoids, natural agents such as green tea and curcumin. Of these curcumin is found to be most effective.[35] Second Primary Trial is a phase IIb/III ongoing trial in India, determining the efficacy of curcumin and metformin in reducing the incidence of second primary tumors in patients with a history of HNSCC.[36] However, long-term studies assessing the efficacy are lacking with other drawbacks such as inconsistency, toxicity and heterogeneity of OPMDs in several chemopreventive trials.[37]

On the contrary, the cutting-edge approach for the early detection of oral cancers is gaining popularity. Because of the physical/direct contact of saliva with the tumor, the circulating tumor DNA and other biomarkers may be used to our benefit with increased concentrations of tumor-derived DNA as opposed to regular blood tests.[38] Studies have shown that this simple, noninvasive modality may be used for early detection and as a surveillance tool in oral patients with cancer.[39] Presence of common cancer-driving mutations such as TP53, PIK3CA, HRAS, EGFR, and FAT1 may indicate malignancy even before the presence of a visible lesion. This can be used in monitoring treatment response, in predicting recurrence and so on. Similarly, DNA methylation markers are detectable in saliva from patients with OPMDs and early-stage OSCC.

SUMMARY

GBMSCC is clinically and biologically different from rest of HNSCC. This is attributed because of areca nut as the primary risk factor leading to a distinct carcinogenesis mechanism. Because of the proximity to bone and muscles of mastication the lesion tends to present with advanced stage, especially because of submucous fibrosis–related trismus limiting mouth opening and clinical examination.

Understanding the genomic landscape has helped to develop targeted therapy and immune modulation, which is showing improvement in disease outcome. In addition, these genomic and protein markers may be identified in saliva to improve early detection and posttreatment surveillance.

CLINICS CARE POINTS

- Clinical behaviour of GBSCC is related to its unique genomic profile.
- Genomic and immune profile of GBSCC are different, hence the response to immonotherapy and targetted therapy will be different.

DISCLOSURE

None.

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