

Oral Cancer Through A Maxillofacial Lens: A Systematic Review Of Molecular And Surgical Perspectives

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) remains a significant global health burden and a major concern in maxillofacial surgical practice. Beyond resection and reconstruction, understanding the molecular mechanisms driving tumour progression has become essential in improving prognostic accuracy and therapeutic outcomes. Key biomarkers such as estrogen receptor (ER), progesterone receptor (PR), Ki-67, and p53 have shown prognostic potential in other epithelial malignancies, suggesting their possible role in oral cancer biology. **Objective:** This systematic review aims to integrate current evidence on the molecular pathology and surgical dimensions of OSCC, emphasizing the correlation between biomarker expression and clinical outcomes relevant to maxillofacial surgery. **Methods:** A PRISMA-compliant search was conducted across PubMed, Scopus, and Cochrane databases for studies published between 2010 and 2025. Eligible articles included those evaluating molecular markers, surgical management, functional outcomes, or perioperative complications in OSCC. Data were extracted and analyzed to identify overlapping trends between molecular alterations and surgical prognostic indicators. **Results:** Molecular marker expression patterns, particularly high Ki-67 and mutant p53, were associated with poor differentiation and reduced survival. Surgical factors such as airway management, TMJ function, and perioperative complications emerged as key determinants of quality of life and recovery. **Conclusion:** An integrated molecular-surgical framework enhances understanding of OSCC prognosis and management. Combining molecular profiling with maxillofacial surgical planning could improve precision, functional outcomes, and patient survival.

Keywords: Oral cancer; Maxillofacial surgery; Ki-67; p53; Estrogen receptor; Airway management; Smoking; Alcohol.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) remains one of the most challenging neoplasms encountered in maxillofacial surgical practice. Globally, it constitutes a substantial proportion of head and neck malignancies and is associated with significant mortality and morbidity owing to its propensity for local invasion, nodal metastasis, and functional impairment. [1] Surgical resection remains the cornerstone of management, often complemented by adjuvant therapies, reconstruction, and rehabilitation. [2] Despite advances in technique, five-year survival rates have improved only modestly over recent decades, underscoring the need for improved prognostic stratification and integrative treatment planning.

From a maxillofacial surgery perspective, the complexity of OSCC involves multiple dimensions: the oncologic margin, reconstruction of bony and soft tissues, preservation or restoration of airway and swallowing functions, temporomandibular joint (TMJ) considerations, and the management of comorbidities such as obstructive sleep apnea or analgesic hypersensitivity. These functional and perioperative factors can significantly influence patient outcomes beyond the attainment of oncologic control.

Concurrently, the molecular pathology of OSCC is evolving. Biomarkers such as Ki-67 (a proliferative index) and p53 (a tumour suppressor protein) have been extensively studied in OSCC, though with variable prognostic impact. [3] Recent reviews indicate that while p53 and Ki-67 are among the most

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frequently evaluated markers in oral tongue SCC, their individual prognostic validity remains limited. [4] In parallel, hormone receptors and other molecular pathways well characterised in other epithelial cancers such as endometrial carcinoma may offer translational insights for OSCC, yet remain under-explored.

Given this scenario, there is a compelling rationale to integrate molecular marker analysis with the practical surgical and functional challenges faced in maxillofacial oncology. The aim of the present systematic review is to synthesise evidence that links molecular pathology (including ER, PR, Ki-67, p53) with maxillofacial surgical, airway, TMJ and perioperative considerations in OSCC, thereby offering a comprehensive perspective that may guide surgical planning, reconstructive strategy and research direction.

METHODS

Study Design

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [5]. The protocol was designed a priori to identify and synthesize existing literature addressing both molecular and surgical aspects of oral squamous cell carcinoma (OSCC), with particular focus on maxillofacial surgical relevance and molecular marker expression patterns.

Search Strategy

A comprehensive electronic search was performed in PubMed, Scopus, and the Cochrane Library for articles published between January 2010 and May 2025. The following search terms and Boolean operators were used:

("oral squamous cell carcinoma" OR "oral cancer") AND ("maxillofacial surgery" OR "oral and maxillofacial surgery") AND ("Ki-67" OR "p53" OR "estrogen receptor" OR "progesterone receptor" OR "ER" OR "PR") AND ("surgical outcomes" OR "airway management" OR "temporomandibular joint" OR "TMJ" OR "reconstruction").

Additionally, the reference lists of retrieved articles were manually screened to identify studies missed by

the initial search. No restrictions were placed on study design, but only English-language publications were included.

Inclusion and Exclusion Criteria

Inclusion criteria:

1. Studies involving human subjects with histologically confirmed OSCC.
2. Studies evaluating at least one molecular biomarker (ER, PR, Ki-67, or p53).
3. Articles addressing surgical, functional, or perioperative considerations relevant to maxillofacial oncology.
4. Randomized controlled trials, cohort studies, case-control studies, and systematic reviews.

Exclusion criteria:

1. Non-English articles or animal studies.
2. Studies focusing exclusively on non-oral head and neck malignancies (laryngeal, nasopharyngeal, thyroid).
3. Case reports without measurable outcome data.

Study Selection and Data Extraction

Two independent reviewers screened the retrieved titles and abstracts using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Disagreements were resolved by consensus. Full texts of eligible studies were reviewed, and the following data were extracted:

1. Study characteristics: author, year, country, study type, sample size.
2. Molecular markers: ER, PR, Ki-67, p53 positivity rates, and correlation with clinical parameters.
3. Surgical/functional outcomes: airway management approach, TMJ function, reconstructive technique, postoperative complications.

4. Prognostic outcomes: recurrence, disease-free survival (DFS), and overall survival (OS).

Quality Assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality of observational studies [6], while systematic reviews were evaluated using the AMSTAR 2 checklist [7]. Only studies of moderate-to-high quality were included in the final synthesis.

Data Synthesis

A narrative synthesis was undertaken due to heterogeneity in study design and outcome reporting. Results were grouped thematically into:

1. Molecular biomarker expression patterns in OSCC.
2. Comparative insights from other epithelial malignancies (notably endometrial carcinoma).
3. Surgical and functional outcomes in maxillofacial oncology practice.

Where available, quantitative data were summarized using descriptive statistics, and overlapping trends were discussed qualitatively.

RESULTS

1. Molecular Markers in Oral Squamous Cell Carcinoma (OSCC)

Among the 78 studies initially identified, 41 met the inclusion criteria for molecular analysis. Expression of Ki-67 and p53 was the most frequently studied, with positivity rates ranging from 45% to 85% across OSCC specimens. Overexpression of Ki-67 was consistently correlated with higher tumour grade, deeper invasion, and reduced disease-free survival [8,9]. Similarly, p53 mutations were significantly associated with increased recurrence risk and poor differentiation, although some studies found no independent prognostic impact after multivariate adjustment [10,11].

Emerging evidence also highlights the potential role of hormone receptors in oral epithelial malignancies.

Immunohistochemical detection of estrogen (ER) and progesterone receptors (PR) in OSCC remains variable, with most studies reporting low-to-moderate positivity (<25%), suggesting a possible hormonal influence in a subset of cases [12,13]. However, standardized testing protocols are lacking, limiting clinical translation.

2. Comparative Insights from Endometrial Carcinoma

Parallel analysis of epithelial malignancies such as endometrial carcinoma provides a useful model for understanding the biological behavior of OSCC. Studies of endometrial neoplasia have demonstrated a clear transition from hyperplasia to carcinoma characterized by declining ER/PR expression and increased Ki-67 and p53 activity [14]. These findings suggest that a similar molecular shift may underpin oral epithelial dysplasia and carcinoma progression. Translating this paradigm to OSCC highlights potential opportunities for molecular cross-validation and prognostic biomarker development.

In the comparative context, Acharya *et al.*'s institutional study demonstrated a strong correlation between ER/PR loss and elevated Ki-67/p53 index across endometrial carcinoma grades [15]. These patterns mirror the proliferative and apoptotic dysregulation observed in aggressive OSCC, reinforcing the translational value of hormonal and proliferative markers for oral cancer research.

3. Surgical and Functional Implications in Maxillofacial Oncology

From a maxillofacial perspective, several key functional and perioperative factors influence OSCC management. Airway management, particularly in patients with obstructive sleep apnea (OSA) or complex resections, is critical for perioperative safety. Evidence-based protocols emphasize preoperative OSA screening and intraoperative airway protection to minimize aspiration and hypoxia [16].

Temporomandibular joint (TMJ) function and occlusal stability also require careful attention in reconstructive surgery. Long-term TMJ dysfunction and malocclusion are associated with reduced postoperative quality of life [17].

Pharmacologic considerations, such as NSAID hypersensitivity or diclofenac allergy, although rare, can pose significant intraoperative challenges. Proper drug history documentation and allergy testing are recommended for patients undergoing maxillofacial oncologic procedures [18].

Finally, perioperative techniques like pharyngeal packing commonly used to prevent blood aspiration carry potential risks of airway trauma or retained gauze, warranting strict adherence to surgical safety checklists [19].

Collectively, these findings emphasize the importance of integrating molecular profiling with surgical and functional planning to achieve optimal oncologic, functional, and aesthetic outcomes in oral cancer care.

The key molecular, environmental, and surgical correlations identified across included studies are summarized in **Table 1**, providing an integrated overview of biomarkers, functional factors, and their clinical implications in oral squamous cell carcinoma.

DISCUSSION

The present systematic review demonstrates that oral squamous cell carcinoma (OSCC) embodies a complex interplay between molecular pathogenesis and maxillofacial surgical outcomes. Integration of molecular biomarkers such as Ki-67, p53, ER, and PR with surgical and functional parameters provides a more holistic framework for personalized management.

1. Molecular Insights and Translational Implications

In OSCC, Ki-67 expression reflects tumour proliferative activity and correlates with aggressiveness, recurrence, and poor prognosis [8,9]. Similarly, p53 mutations represent one of the earliest genetic events in oral carcinogenesis and are frequently linked to treatment resistance and reduced survival [10,11]. However, heterogeneity in immunohistochemical protocols and scoring methods limits the reproducibility of these biomarkers across centers [20].

In contrast, studies of endometrial carcinoma where ER, PR, Ki-67, and p53 are well-validated demonstrate predictable marker transitions across the hyperplasia-carcinoma sequence [14,15]. This

molecular pattern suggests that loss of hormonal receptor control and uncontrolled proliferation, measured via Ki-67, may similarly drive oral epithelial dysplasia toward carcinoma. Establishing standardized immunohistochemical assessment in OSCC could therefore enhance prognostic precision and therapeutic planning.

Emerging research supports the notion that ER and PR receptors may influence oral mucosal homeostasis and tumour differentiation through estrogen-dependent pathways [12,13,21]. Their role in modulating inflammation, cell cycle progression, and angiogenesis in oral tissues warrants further exploration, particularly in postmenopausal or hormonally influenced patient populations.

2. Surgical and Functional Integration

Maxillofacial oncologic surgery requires balancing oncologic clearance with preservation of function and aesthetics. The integration of molecular markers into preoperative planning could potentially refine resection margins and tailor adjuvant therapy. For instance, high Ki-67 or p53 positivity may justify more aggressive surgical margins or intensified follow-up schedules [22].

Airway management remains a critical perioperative consideration, especially in patients with pre-existing obstructive sleep apnea (OSA) or after extensive mandibular resections. Evidence-based protocols emphasize multidisciplinary preoperative screening and intraoperative airway protection, both of which significantly reduce postoperative complications [16,23].

TMJ integrity and occlusal balance are equally vital for long-term function. Post-reconstruction TMJ derangement contributes to trismus, malocclusion, and reduced quality of life. Comprehensive rehabilitation protocols, as detailed in advanced orthodontic-maxillofacial literature, are essential to minimize these sequelae [17].

Pharmacological vigilance, particularly regarding NSAID or diclofenac allergy, is crucial in postoperative pain management. Even rare hypersensitivity reactions can provoke airway edema or anaphylaxis, complicating recovery in oncologic cases [18,24].

3. Broader Clinical and Ethical Perspectives

While this review centers on molecular and surgical domains, it is important to acknowledge that the practice of maxillofacial oncology inherently intersects with ethical and medico-legal responsibilities. Documentation of consent for major resections, airway risks, and drug allergies forms a critical component of safe surgical practice. Adherence to institutional protocols and surgical safety checklists especially regarding airway protection and pharyngeal packing helps mitigate both clinical and legal complications [19,25].

4. Experimental Insights into Lifestyle-Related Risk Factors

An *in vitro* study evaluated the effects of smoking and alcohol on oral squamous cell carcinoma (SCC-25) cell proliferation. Ethanol (10%) increased proliferation by 25% at 48 hours, while nicotine (20 μ M) produced a 30% rise at 72 hours. The combination of both agents caused a synergistic 50% increase ($P < 0.01$), accompanied by marked cellular spreading and clumping suggestive of aggressive behavior [26]. These findings confirm that alcohol and nicotine individually and together stimulate tumour cell growth, reinforcing the need for preventive measures and further molecular investigation of these risk factors[26].

5. Additional Clinical and Translational Perspectives

Oral cancer management requires consideration of both disease biology and site-specific clinical characteristics. In the Indian context, tobacco exposure and the implementation of tobacco-control measures remain important components of oral cancer prevention. Evidence from Odisha highlights the continuing challenges associated with tobacco-control legislation and its implications for oral cancer prevention, emphasizing the importance of integrating preventive strategies with clinical management [27].

In addition to conventional tissue-based biomarkers, minimally invasive molecular approaches may provide complementary information for oral cancer assessment. Salivary oxidative-stress markers have demonstrated differential patterns between oral

precancer and oral cancer, suggesting potential utility as adjunctive biomarkers for disease detection and risk stratification [28]. Such approaches may complement established tissue biomarkers including Ki-67, p53, ER, and PR, although their clinical application requires further validation.

Site-specific clinical factors are also relevant to maxillofacial oncology. Buccal mucosal carcinoma represents an important clinical presentation of oral cancer and may involve distinct considerations related to local disease extent, surgical management, and functional rehabilitation [29]. Incorporating anatomical site and functional considerations alongside molecular characteristics may therefore provide a more comprehensive framework for individualized treatment planning.

Airway considerations represent another important component of maxillofacial surgical care. Evidence from orthognathic surgical practice highlights the relationship between maxillofacial anatomy, airway function, and sleep-disordered breathing, providing additional context for perioperative airway assessment in patients undergoing complex maxillofacial procedures [30]. In patients with OSCC, these considerations may be particularly relevant when extensive resections, reconstruction, or pre-existing airway-related conditions are present.

6. Limitations and Future Directions

This review's main limitation lies in the heterogeneity of included studies, particularly in biomarker methodology and outcome reporting. Few studies provide integrative data linking molecular expression with surgical parameters, reflecting a persistent gap in translational oncology. Future multicentric studies employing standardized immunohistochemistry, digital pathology, and molecular assays could clarify these associations.

Additionally, developing a molecular-surgical prognostic index combining Ki-67/p53 expression with clinical factors such as margin status, TMJ preservation, and airway complexity may offer a more precise model for survival prediction and personalized therapy.

Molecular Marker / Factor	Biological Role	Findings in OSCC	Clinical / Surgical Implications	Key References (Author, Year)
Ki-67	Proliferation index	Overexpression correlates with higher tumour grade and recurrence	Indicates tumour aggressiveness; may guide margin determination	Motta R et al., 2015; Monteiro L et al., 2013; Hu Z et al., 2021
p53	Tumour suppressor gene	Mutation linked to poor differentiation and resistance to therapy	Predicts recurrence and need for close postoperative monitoring	Cruz I et al., 2014; Medeiros D et al., 2022
ER / PR	Hormonal receptors	Variable expression; often reduced in advanced OSCC	Suggests hormonal modulation potential; translational value from endometrial models	Grimm M et al., 2016; Marocchio L et al., 2013; Acharya L et al., 2025
Smoking & Alcohol	Environmental cofactors	Combined exposure increases SCC-25 proliferation by $\approx 50\%$ <i>in vitro</i>	Supports preventive focus; highlights synergistic cellular aggression	Panda A et al., 2025
TMJ Function	Biomechanical / functional	Reconstruction and occlusal stability affect long-term quality of life	Essential for postoperative rehabilitation and occlusal harmony	Nayak SC et al., 2025
Airway Management	Surgical safety	OSA and extensive resections elevate perioperative risk	Requires multidisciplinary airway planning and protection	Nayak SC et al., 2025; Sato FRL et al., 2016

Table 1. Summary of key molecular, functional, and environmental correlates influencing oral squamous cell carcinoma outcomes from a maxillofacial perspective.

CONCLUSION

Oral squamous cell carcinoma (OSCC) remains a multifactorial disease that demands a comprehensive, interdisciplinary approach. This systematic review highlights the importance of integrating molecular pathology specifically biomarkers such as Ki-67, p53, estrogen receptor (ER), and progesterone receptor (PR) with maxillofacial surgical principles to optimize prognostic assessment and therapeutic outcomes.

The reviewed evidence indicates that elevated Ki-67 and aberrant p53 expression correlate with increased

tumour aggressiveness, recurrence, and poor survival. Although ER/PR expression in OSCC is variable, parallels with endometrial carcinoma suggest a possible hormonal influence that warrants deeper exploration. On the surgical front, airway management, TMJ preservation, and perioperative pharmacologic vigilance are key determinants of postoperative quality of life.

Future research should focus on multicentric, molecular-surgical correlation studies to establish standardized biomarker panels and develop predictive models linking molecular profiles with maxillofacial functional outcomes. The evolution of such

integrative frameworks represents a significant step toward precision maxillofacial oncology, ultimately improving survival and life quality in oral cancer patients.

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