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Chapter 1

The clinical landscape of head and neck cancer

Surabhi Halder [1], Rajesh Kumar.S [2]

[1] *Department of Prosthodontics crown and Bridge, Priyadarshini Dental College and Hospital, Chennai, Tamil Nadu, India*
[2] *Nanobiomedicine lab, Centre for global health and Research, Saveetha Institute of Medical and Technical Siences, Chennai, India*

[1] surabhihalder7@gmail.com

1 Introduction

Although they have somewhat different beginnings, tumors and carcinomas are two related things. While not every tumor turns into a carcinoma, every carcinoma starts as a tumor. Tumors are among the world's most prevalent diseases, accounting for 14 millions of new instances each year, According to the World Health Organization's (WHO) 2014 World Cancer Report, it causes 8.2 million deaths yearly. The majority of head and neck squamous cell carcinomas are oral squamous cell carcinomas (OSCC), the most prevalent cancer of the oral cavity. According to a recent estimate, there were 145 000 cancer-related fatalities and 3,00 000 new instances of oral cancer reported globally in 2012.Approximately 3% of all malignancies are oral squamous cell carcinomas (OSCCs), which impact over 300,000 people annually and rank as the eighth most common malignant neoplasm globally.

Originating in the anterior two-thirds of the tongue, oral tongue squamous cell carcinoma (TSCC) has been on the rise and is now the most often diagnosed cancer in the oral cavity, accounting for 25–40% of all oral carcinomas. OSCC is the third most common cause of cancer-related deaths among males and is responsible for 40% of cancer-related fatalities in various Asian countries.Every year, around 48,000 patients pass away from the illness, and about 70,000 new cases are identified.

According to the data, 20% to 40% of cases of oral mobile tongue squamous cell carcinoma are already detected at an early stage. 6. The goal is to identify a subset of patients with a high probability of a negative outcome at an early stage of mobile tongue cancer who will require aggressive treatment planning, such as multimodality therapy, in

contrast to another fraction who have a higher chance of a positive outcome. Compared to malignancies of other oral sites, tongue squamous cell carcinoma (TSCC), the most prevalent cancer of the oral cavity, has an especially high risk of spreading to the neck.

The use of alcohol and tobacco by people in the western world are the two primary aetiological causes for OSCC. The most prevalent aetiological variables among Indians include chewing areca nut and sniffing. The 5-year survival rate for OSCC patients is comparatively poor. These patients experience more recurrences and poorer outcomes. Finding cases that are likely to reoccur is still difficult.

The area of research focus is the invasive tumor front, where the cancer cells act aggressively in relation to the tumor mass. Furthermore, the epithelial-mesenchymal transition, a crucial stage in the development of tumor metastasis, may occur in cancer cells at the IF (Amaral et al., 2022; Anderson et al., 2021; Bhat et al., 2021; Dou et al., 2021; Farah, 2021).

When evaluating a novel marker for clinical use, simplicity, reproducibility, and affordability are the three most crucial factors. According to reports, the OSCC and other malignancies displayed each of these traits. Additionally, the tumor microenvironment is supported by the neoplastic cells and related stroma, which promotes tumor growth.Tumor-related stroma may therefore offer fresh and different approaches to biological intervention in the management of cancerous malignancies.

In 1960, Williams Coley's research revealed a novel strategy for fighting cancers. In order to trigger an immunological response, he introduced streptococcal bacteria into the tumor cells that were irreparable. It may be possible to fight tumor cells with these immune responses that cancer cells have produced. When his research was first published, it was shown that the immune system could identify malignancies (Muzaffar et al., 2021; Nakano, 2021; Noji et al., 2022; Ohmoto et al., 2021; Plath et al., 2021).

The selection of patients with various malignancies is the first and most crucial phase. There is now more focus on personalized treatment and focused therapy. Prior to putting immunotherapy into practice, it is also crucial to identify the predictive indicators that could aid in forecasting the antitumor effect and survival advantages (Feng & Hess, 2021; Gu et al., 2022; Huang et al., 2022; Lauer & Beil, 2022; Marret et al., 2021).

The histologic risk assessment score (HRS) model was presented by Brandwein-Gensler et al. (figure 1(a)). For the same reasons, several comparable models have also been proposed.

2 Clinicopathological features to be reviewed

The Potential Parameters in Early Stage OSCC are (figure 1(a) & figure 1(b)) :

1.Grade

a. Well differentiated

b. Moderately differentiated

c. Poorly differentiated

2.Tumor budding

a. Low

b. High

3.Tumor thickness

a. <= 4

b. 5-10

c. >10

4.Tumor depth

a. Low (< 4 mm)

b. High (> = 4 mm)

5.Depth of Invasion

a. < = 4

b. > = 5

6.Shape of tumor nest

a. Type A

b. Type B

7.Lymphoid response

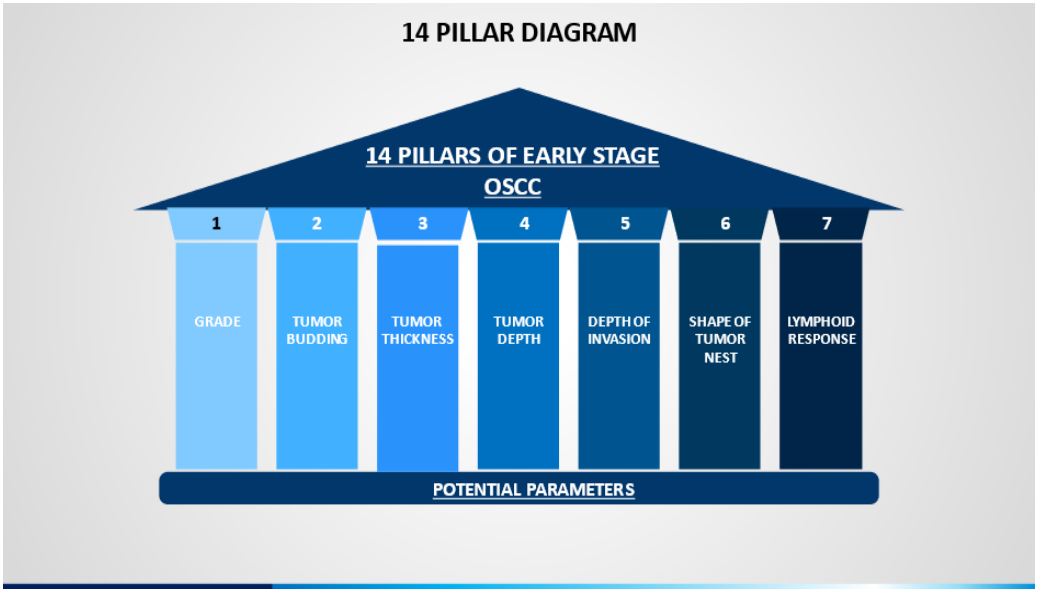

Figure 1 (a)

a.Pattern 1

b. Pattern 2

c. Pattern 3

8.Pattern of Invasion

a. Type 1

b. Type 2

c. Type 3

d. Type 4

9.Eosinophil infiltration

a. Yes

b. No

10.Foreign body giant cell interaction

a. Yes

b. No

11.Lymphovascular invasion

a. Yes

b. No

12.Perineural invasion

a. Absent

b. Small nerve involvement

c. Large nerve involvement

13.Histologic risk assessment score

a. Low (< 3)

b. High (> =3)[22]

14.CAF score

a. Low (0-1)

b. Medium (2-3)

c. High (4)

Tumor grade is characterized as follows (Figure 2):

- Well differentiated consists of abundant keratin and keratin pearls.
- Poorly differentiated consists of minimal keratinization,atypia,mitosis.
    - Moderately differentiated lies in between first two category.

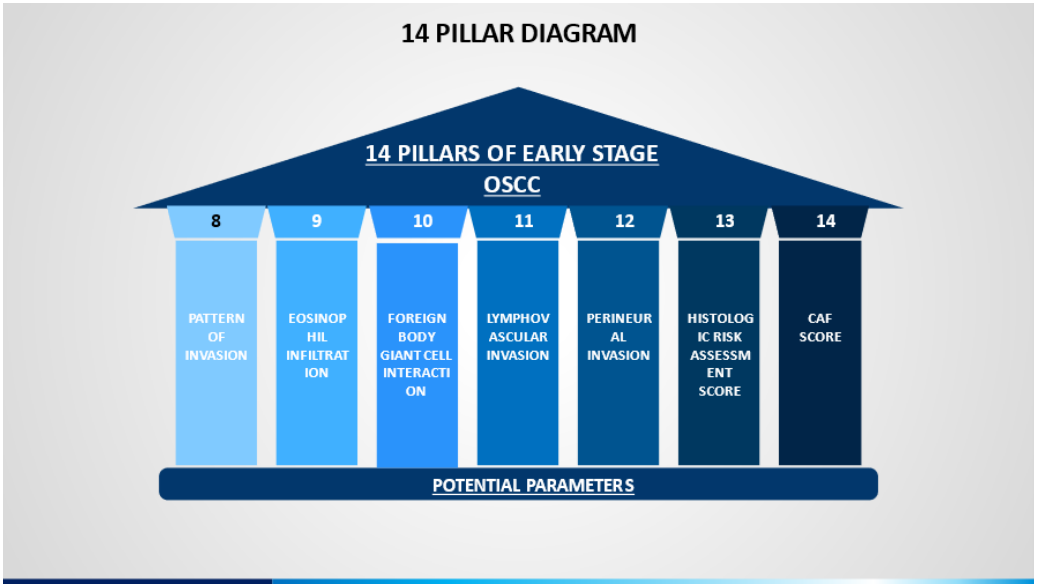

Figure 1 (b)

Tumor budding refers to isolated tumor cells or small clusters containing fewer than five cells located within the stroma at the invasive front. The presence of fewer than five tumor buds within a single 20x magnification field (0.785 mm^2) qualifies as low budding, whereas five or more buds indicate high tumor budding.

Tumor thickness is measured as the vertical distance from the top surface of the tumor (excluding non-cellular keratin layers) to its deepest point of penetration, taken perpendicularly (Yun et al., 2022; Zaryouh et al., 2022).

The invasion depth was determined based on the configuration of the tumor nest and classified into two types: Type A, consisting of tumors with more than 80% of nests being oval-shaped or sheet-like with smooth edges, and Type B, where over 20% of the nests are small, scattered, or have irregular margins.

The lymphoid response at the tumor-host boundary was categorized into three patterns:

Pattern 1: A continuous, dense rim of lymphoid tissue at the interface.

Pattern 2: Dense lymphoid patches at the interface, though the inflammation was not continuous.

Pattern 3: A minimal response that either lacked lymphoid patches or showed no lymphoid response.

Patterns of Invasion are described as follows:

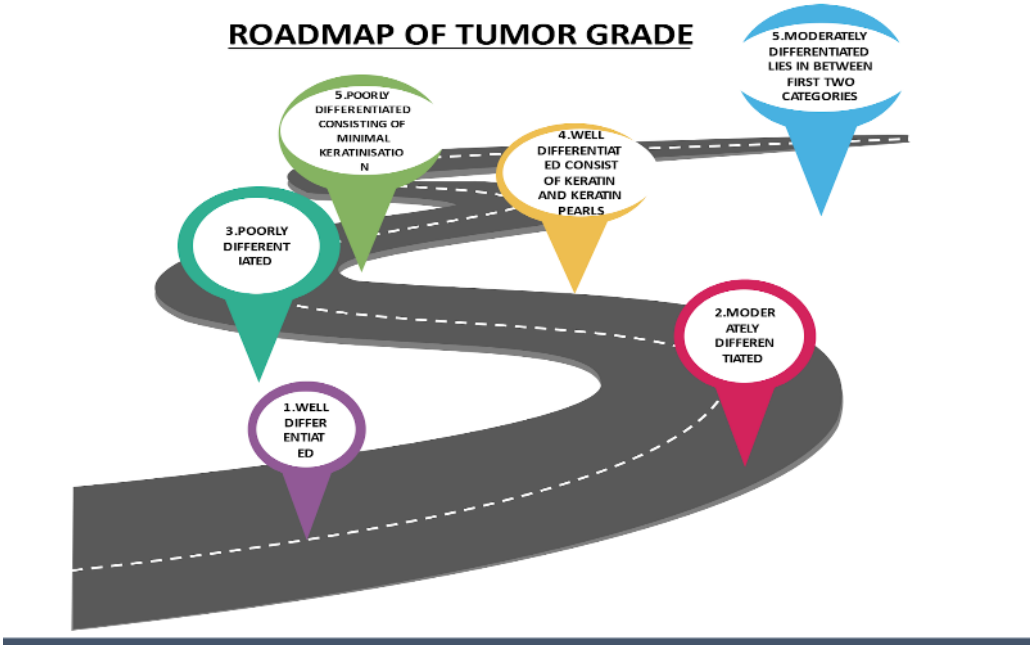

Figure 2

Type 1: Tumor invades in a broad, pushing manner with a smooth contour.

Type 2: Tumor invasion characterized by broad pushing fingers or separate large tumor islands with a stellate configuration.

Type 3: Invasive islands of the tumor containing more than 15 cells per island.

Type 4: Invasive tumor islands comprising fewer than 15 cells per island, including formations resembling cords and single cells.

2 Tumour Budding

Tumor budding is influenced by two critical factors: the loss of cellular adhesion and active invasive behavior. This phenomenon at the tumor's invasive front signifies the separation of invasive cancer cells from the primary tumor bulk. Tumor budding has been recognized as a valuable prognostic indicator, particularly due to its strong association

with the presence of lymph node metastasis, marking it as a key discovery. It represents an initial step toward metastasis and stands as an independent prognostic factor with thresholds at five and ten buds. In cases of oral squamous cell carcinomas (OSCCs) with high-grade tumor budding, there is a significant risk of adverse outcomes. Even in the early stages of the disease, tumor budding holds considerable prognostic significance for OSCC.

Key characteristics of Tumor Budding (Figure 3):

Simple, dependable.

Assessment of tumor budding can aid in the tailored management of OSCC.

Breakdown of cellular cohesion.

Proactive invasive activity.

Figure 3 Techniques for Identifying Tumor Budding:

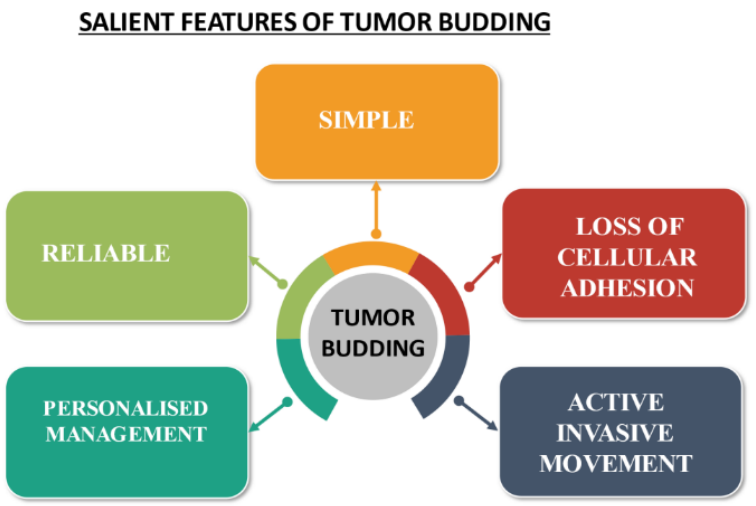

Figure 3

H-E Staining.

Immunohistochemical staining using a pan-cytokeratin antibody to detect cytokeratins. However, there is no standardized optimal method yet, and results vary based on the type of tumor using these methods.

Evaluating DOI and Tumor Budding: In brief, the depth of invasion (DOI) is measured from the level of the basement membrane of the nearest normal mucosa to the deepest part of the invading tumor across all surgical specimens. When tumor buds are present and detached from the main tumor mass, the distance to these buds from the basement membrane of the nearest normal mucosa is measured.

In the process of evaluating tumor budding, the entire tumor region is initially examined at a lower magnification (40x) to identify areas with the most significant budding. Subsequently, budding is counted at a higher magnification (200x), with the highest count per sample determining the tumor budding score. In cases where DOI assessment and tumor budding evaluations differ among observers, a collaborative review is conducted to reach a consensus. Table 1 shows the clinical landscape of head and neck cancer.

DOI range (0.1-10.0)

Tumor budding score (0-40)

Table 1 The clinical landscape of head and neck cancer

Sr No.	**Type of Cancer**	**Common Causes**	**Symptoms**	**Diagnostic Methods**	**Treatment Options**	**Survival Rates**
1	Oral Cavity Cancer	Tobacco use, alcohol, HPV	Sores, lumps in the mouth, pain	Biopsy, Imaging (CT, MRI)	Surgery, Radiation, Chemotherapy	50-60% (5-year)
2	Oropharyngeal Cancer	HPV, smoking, alcohol	Sore throat, pain/swelling in neck	HPV testing, Biopsy, Imaging	Radiation, Surgery, Chemotherapy	65% (5-year)
3	Laryngeal Cancer	Smoking, alcohol, exposure to toxins	Hoarseness, breathing difficulty	Laryngoscopy, Biopsy, Imaging	Radiation, Surgery, Chemotherapy	60-70% (5-year)
4	Hypopharyngeal Cancer	Tobacco, alcohol	Lump in neck, change in voice	Endoscopy, Biopsy, Imaging	Chemotherapy, Radiation, Surgery	30-35% (5-year)
5	Nasopharyngeal Cancer	Epstein-Barr virus, genetic predisposition	Nasal blockages, nosebleeds, hearing loss	Biopsy, MRI, EBV DNA test	Radiation, Chemotherapy	70-80% (5-year)

6	Salivary Gland Cancer	Radiation exposure, family history	Swelling near jaw, difficulty swallowing	Fine needle aspiration, Imaging	Surgery, Radiation, Targeted therapy	90% (5-year) for low-grade tumors
7	Paranasal Sinus Cancer	Smoking, industrial chemicals, wood dust	Sinus congestion, decreased sense of smell	Imaging (CT, MRI), Biopsy	Surgery, Radiation, Chemotherapy	50-70% (5-year)
8	Cutaneous Head and Neck Cancer	Prolonged sun exposure, immunosuppression	Skin lesions, ulcers on head and neck	Biopsy, Dermoscopy	Surgery, Radiation, Chemotherapy	Highly variable based on stage
9	Thyroid Cancer	Radiation exposure, genetic factors	Lump in the neck, voice changes	Ultrasound, Biopsy, Blood tests	Surgery, Radiation, Hormone therapy	98% (5-year) for most types
10	Esophageal Cancer	Smoking, alcohol, hot liquids, acid reflux	Difficulty swallowing, chest pain	Endoscopy, Biopsy, Barium swallow	Surgery, Radiation, Chemotherapy	20% (5-year)
11	Soft Tissue Sarcomas of the Head and Neck	Genetic disorders, radiation exposure	Mass or swelling in the affected area	MRI, Biopsy	Surgery, Radiation, Chemotherapy	50-70% (5-year) depending on stage and location
12	Metastatic Skin Cancers	Prolonged sun exposure, previous skin cancer	Nodules or ulcers in the skin, lymph node swelling	Biopsy, Imaging (CT, PET)	Surgery, Radiation, Chemotherapy	Variable, based on primary cancer and stage

3 Grading Proposal of Head and Neck squamous cell carcinoma

Tumor budding activity / 10 HPF

No budding

< 15 budding foci

>= 15 budding foci

Smallest cell nest size within the tumor core region

>15 cells

5-15 cells

2-4 cells

Single cell invasion

Tumor grading implies the same well differentiated, moderately differentiated and poorly differentiated. The current WHO grade incorporates keratinization, nuclear pleomorphism, mitotic activity with P 16 expression whether negative or positive. According to WHO classification,8.9 % OSCCs were classified as WHO G1,G2,G3. The majority displayed keratinization, non-keratinisation and basaloid cells

also the extent of keratinization was strong, intermediate, weak.

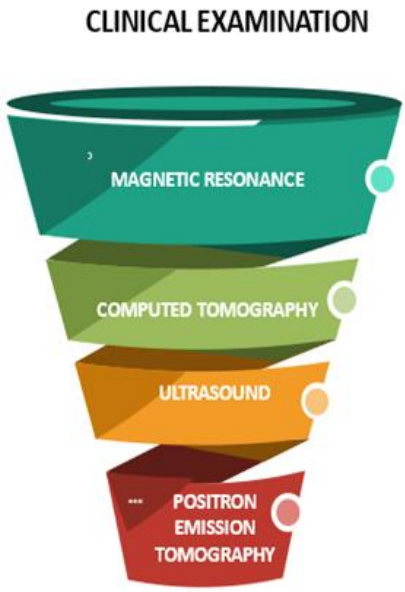

Figure 4

4 Diagnostic Features

It entails recognizing an issue and naming it. Examine the lips, gingiva, hard and soft palate, tonsillar regions, buccal mucosa, and floor of the mouth simply (Figure 4) for the following:
Color and texture changes
Multiple genetic alterations can result in biomarkers, including overexpression of telomerase, epidermal growth factor (EGFR), survival, and suppression or inactivation of tumor suppressor genes such FHIT P53.a number of other biomarkers, such as chromosome polysomy and DNA content, loss of heterozygosity, proliferative markers, elevated EGFR, and reduced expression.Variations in microsatellite motifs and patterns of DNA and RNA expression.

5 Diagnostic Features

It involves making educated guesses about how the treatment will turn out. The prognosis and grading alone do not correlate well. These parameters have no predictive value in terms of outcome because nodal metastasis or survival cannot be linked to the dedterioration and differentiation grade. As a result, these things are not very useful for treatment planning.Since the invasion pattern in the differentiation grade of the resection material in tiny OSCC is likely an independent risk factor for nodal metastasis, it may raise the prognostic value. In conclusion, tumor budding can be incorporated into the traditional WHO grading system to increase its prognostic relevance in early OTSCC.

Amr elseragy et al.'s study, which shown a strong prognostic value for early OTSCC, aimed to incorporate tumor budding into the WHO grading system. Notably, a noncohesive pattern of invasion is linked to a poor prognosis for OSCC, according to the most recent WHO classification of head and neck malignancies.

Tumor budding's clinical significance has been proven by recent research, and a recent meta-analysis reaffirmed its importance for OTSCC. Crucially, tumor budding was only included as a predictive marker for colorectal cancer in the Union for International Cancer Control's TNM classification. Numerous malignancies have been successfully evaluated for tumor budding using standard HE-stained sections. According to Jiayuan et al.'s study, the tumor-stroma ratio may be a helpful tool for predicting the prognosis and results of solid tumors. Tumor budding is the dependent prognosis factor for subjects with OSCC, while tumor-stroma ratio, occult neck metastasis, and depth of invasion are independent prognostic factors for patients with tongue squamous cell carcinoma in some studies.

Based on seven immunological characteristics of OSCC, Zhou et al. has developed a unique prognostic classifier called 7IFBPS, which has good performance, sensitivity, and specificity. In addition to improving or enhancing the predictive value of standard clinicopathological criteria, this integrative immune classifier may accurately predict patient survival.

The author posited that this immune prognostic score could aid in patient consultations, tailored treatment decisions, and planning follow-up appointments. It remains an intriguing and unresolved issue to integrate such an immune-feature-based classifier into the traditional prognostic framework to evaluate patient outcomes and the risk of disease progression. In a separate study, the i B D score was proposed as an innovative prognostic model for SCC. This model exhibited a strong correlation with T classification, lymph node metastasis, clinical stage, and recurrence, and effectively differentiated between scores of 0, 1, and 2. This scoring system has a significant association with lymph node metastasis and recurrence in TSCC and shows promise as a survival predictor for patients with TSCC.

6 Multimodality Therapy of Oral Squamous Cell

Combining surgery, radiotherapy, and chemotherapy is commonly recommended for treating certain head and neck cancers. Prosthodontic rehabilitation in these patients is intricate due to the challenges in creating prostheses, the need for frequent adjustments or replacements, and handling the psychological effects on the patient. The treatment strategy involved using an interim obturator as a radiation stent, delivering a total of 63 Gy across 30 sessions, with an initial survival period of six weeks. With advancements leading to higher survival rates, there is now an increased emphasis on enhancing the quality of life for these cancer survivors. These patients encounter numerous obstacles during and after the ablative cancer treatments, particularly with the long-term adverse effects of the treatments. According to a clinical report by Varun and Mark, a patient experienced multiple challenges during and following the multimodality therapy for squamous cell carcinoma affecting the maxillary and paranasal sinus. Lifelong prosthodontic care is essential for these patients to maintain the functionality and aesthetic quality of their prostheses. Another study found that implant-supported prostheses significantly enhance the quality of life compared to adhesive methods in managing various oral cancers, including oral squamous cell carcinoma. Table 2 shows aspects of multimodality therapy for Oral Squamous Cell Carcinoma (OSCC).

Table 2 Aspects of multimodality therapy for Oral Squamous Cell Carcinoma (OSCC)

Sr No.	Treatment Type	Indications	Common Combinations	Expected Outcomes	Potential Side Effects
1	Surgery	Localized tumors, operable cases	Followed by radiation or chemotherapy	Removal of tumor, potential cure	Pain, infection, speech and eating difficulties
2	Radiation Therapy	Inoperable tumors, adjuvant to surgery	Concurrent with chemotherapy	Tumor shrinkage, control of local spread	Dry mouth, sore throat, skin changes
3	Chemotherapy	Advanced disease, adjuvant to radiation	Combined with radiation therapy	Disease control, symptom relief	Nausea, hair loss, immune suppression
4	Targeted Therapy	Recurrent/metastatic cases	Alongside chemotherapy or radiation	Improved prognosis in specific cases	Mild compared to chemotherapy
5	Immunotherapy	Selected advanced cases	Can be combined with other treatments	Potential for durable response	Immune-related adverse effects
6	Rehabilitation	Post-treatment recovery	N/A	Restore function, quality of life	Depends on specific rehabilitation needed
7	Nutritional Support	All stages	Concurrent with all treatments	Support overall health and recovery	N/A
8	Psychological Support	All stages	Concurrent with all treatments	Improve mental health and coping	N/A
9	Palliative Care	Advanced, non-curable cases	Alongside any active treatment	Symptom management, comfort	N/A
10	Hormonal Therapy	Cases with hormonal receptor positivity	Combined with radiation	Adjunctive treatment to	Hormone-related side effects

			or chemotherapy	reduce recurrence	
11	Photodynamic Therapy	Early-stage or superficial tumors	Used as an alternative to surgery	Non-invasive treatment, localized control	Sensitivity to light, skin reactions
12	Gene Therapy	Experimental, specific genetic alterations	Research stage or clinical trials	Targeted genetic treatment possibilities	Potential for unknown genetic effects
13	Cryotherapy	Superficial lesions, early stage	As an adjunct to surgery	Tissue destruction, minimally invasive	Local pain, swelling
14	Laser Therapy	Early-stage, small, accessible tumors	As an alternative to traditional surgery	High precision tumor removal	Localized pain, minimal bleeding
15	Social Support Programs	All stages, especially during long treatments	Concurrent with all treatments	Enhanced coping mechanisms, community support	N/A

Conclusion

The most prevalent type of head and neck cancer, oral squamous cell carcinoma, has numerous invasive side effects. The current article reviews a wide range of histopathological features.When compared to other histopathological findings, tumor budding appears to be one of the most promising and has a high predictive value. Tumor budding is also the primary characteristic included in the head and neck cancer grading proposal. Tumor budding turns out to be the most significant of the four unique prognostic characteristics. Therapy entails frequent visits to minimize problems, other recurrences, and risk factors because multimodality therapy alternatives appear to provide difficulties for the patient.

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