REVIEW

The Clinical Landscape in Head and Neck Cancer-A Review

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Abstract

This paper reviews the various clinical and histopathological features of head and neck cancer. The paper also revises the various diagnostic features according to WHO classification. It also introduces a new Broder's classification of WHO classification. Head and Neck cancer is the third most cancer to be detected in the world. Among the head and neck cancers, oral squamous cell carcinoma is the most commonly detected cancer worldwide. In this paper, various emerging hallmarks are also described along with methods of detection of each clinicopathology features pertaining to oral squamous cell carcinoma. This paper also highlights both early and late prognostic features and concludes which prognostic feature plays an important role in the recurrences risk of the cancer.

Keywords: clinical, features, diagnostic, cancer, detection, clinicopathology, prognostic, hallmarks, recurrences risk.

Introduction

Tumor and carcinomas are two similar entities but there is a slight difference in their origins. Not all tumors develop into carcinoma but all carcinomas arise from the tumor[1]. One of the most common diseases in the world are tumors causing deaths with 14 million new cases diagnosed annually, causing 8.2 million deaths annually as World Health Organization (WHO) reported in the World Cancer Report 2014[2]. Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and constitutes the majority of head and neck squamous cell carcinomas. According to a recent report, 3,00 000 new cases of oral cancer were diagnosed worldwide in 2012, and with a consequent 145 000 cancer-related deaths[3]. Oral squamous cell carcinoma (OSCC) is the eighth most frequent malignant neoplasm worldwide, affecting more than 300,000 individuals each year and accounting for approximately 3% of all malignancies. Oral tongue squamous cell carcinoma (TSCC), arising at the anterior two-thirds of the tongue, has been rapidly increasing in incidence and become the most common malignancy diagnosed in the oral cavity comprising 25-40% of oral carcinomas[4].

OSCC is among the 3 most common cancers and accounts for about 40% of total cancer-related deaths in some regions of Asia, including India, where it is the commonest cancer in male individuals. About 70,000 new cases are diagnosed each year, and >48,000 patients succumb to the disease yearly[5].

Detection of oral (mobile) tongue squamous cell carcinoma (SCC) at an early-stage (T1/T2N0M0) does not always portend good prognosis as evidence shows that 20% to 40% already have occult metastasis at presentation[6]. At an early stage of mobile tongue cancer, its purpose is to identify a subset of patients having high risk of adverse outcome and will need aggressive treatment planning, such as multimodality therapy, in contrast with another subset who have increased chances of a favorable outcome[7]. Tongue squamous cell carcinoma (TSCC) is the most common cancer of the oral cavity, and has a particularly higher risk of neck metastasis compared with tumors of other oral sites[8].

The two main aetiological factors for OSCC are tobacco and alcohol consumption found in the population of western world. In the Indian population chewing of areca nuts and sniff are the most common aetiological factors. The patients with OSCC have relatively low survival rate (5 years). These patients have poor outcomes with more recurrences. Identi-

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fying cases at risk for recurrence remains challenging[9].

In the recent decades the invasive tumor front of OSCC is the area of research interest. In the tumor mass when compared with the cells surrounding the central and the superficial area, the cancer cells behave aggressively. In addition, cancer cells at the IF may undergo epithelial– mesenchymal transition, which is an important step in progression of tumour metastasis[10].

The three most important characteristics when considering a new marker for clinical application are simplicity, reproducibility and low cost. The OSCC and other cancers had reportedly showed all these characteristics.[11,12,13]

In the "seed and soil"concept, cancer cells, called "seeds", survive in a highly complex microenvironment of the surrounding stroma, called "soil." In fact, the stroma surrounding the cancer cells is not passive, as it plays an active role in supporting and nourishing tumor parenchyma. The neoplastic cells and associated stroma furthermore supports the tumor microenvironment leading to tumor progression.[14] Furthermore, aggressive tumor cells exploit the tumor microenvironment by residing in the stroma, transforming the surrounding tissue, and modifying the metabolism of the resident cells. Thus, tumor-related stroma could provide novel and alternative strategies for biological intervention in the treatment of malignant tumors[15].

Williams Coley's work in 1960 demonstrated a new approach to combat tumors. He induced streptococcal bacteria into the inoperable tumor cells that could induce immune response[16]. These immune responses developed by cancer cells could be used to combat tumor cells. His work was firstly published and tumors were discovered to be recognized by the immune system[17].

The first and most important step is the selection of patient with different tumors. More emphasis on targeted therapy and personalised medicine has been laid down. Identifying the predictive markers which may help us to predict the antitumor effect and survival benefits are also very necessary before implementing the immunotherapy[17].

CLINICOPATHOLOGICAL FEATURES TO BE REVIEWED

Brandwein–Gensler et al[18] proposed a multiparametric histologic risk assessment score (HRS) model that was reported to predict the survival of patients with T1 to T4 oral SCC and capable of differentiating high-risk and low-risk patients (figure1(a)). Other similar models, such as those of Jakobsson et al[19], Anneroth et al[20], Bryne et al[21], and Martınez–Gimeno et al[22], have also been suggested for the same purposes.

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
   Pattern 1
   Pattern 2
   Pattern 3

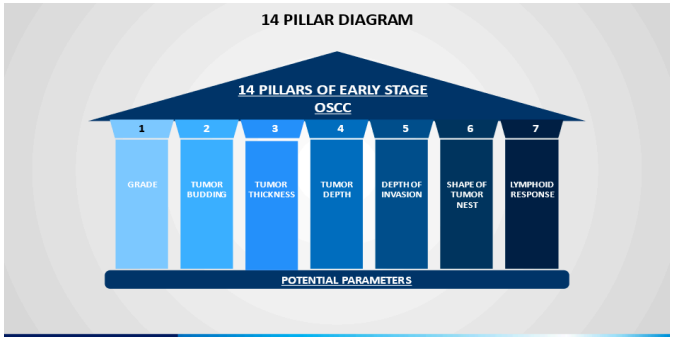

Figure 1 (a)

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)

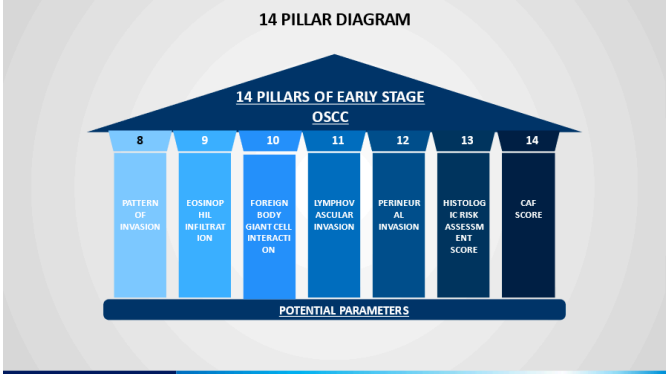

Figure 1 (b)

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[23].

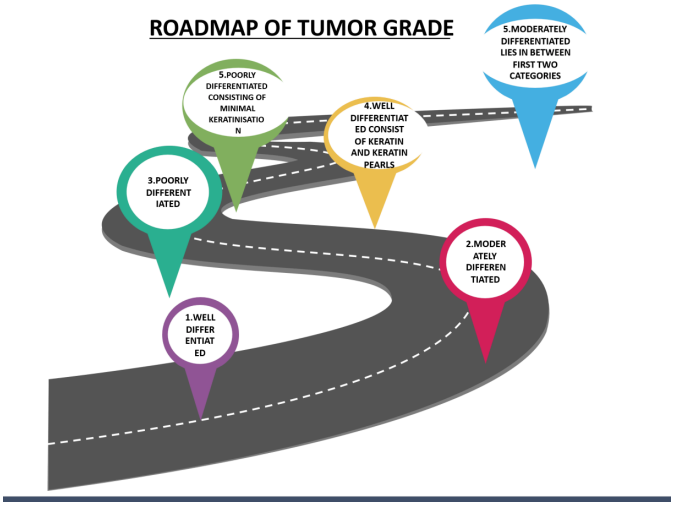

Figure 2

Tumor budding consist of single tumor cell and the tumor cell in clusters less than 5 cells in stroma at the invasive front. Tumor budding was characterized as low if less than 5 tumor buds were found in single 20 * field (0.785 mm2) and high if > = 5 buds were seen[24].

Tumor thickness was taken as the vertical, extent of tumor from its surface (excluding the acellular keratin) to the deepest point of invasion measured perpendicularly[25].

Depth of invasion was measured as the invasive part of the tumor extending below the basement membrane of the adjoining unremarkable mucosa to the deepest point of invasion. The shape of the tumor nest was classified as type A and type B. The type A category comprised of tumors having > 80% oval shaped or sheet like nests with smooth borders, whereas type B comprised of tumors showing > 20% scattered small tumor nests or tumor nests with irregular margins[26].

Lymphoid response at the tumor host interface was divided into three categories :

Pattern 1 – continuous and dense rim of lymphoid tissue was present at the interface.
Pattern 2 – was assigned when patches of dense lymphoid infiltrate were present at interface but inflammation was discontinuous.
Pattern 3 – limited response that did not form lymphoid patches or for no lymphoid response.

Pattern of Invasion :

Type 1 – Represents tumor invasion in a broad pushing manner with a smooth outline.
Type 2 – Represents tumor invasion with broad pushing fingers or separate large tumor islands with a stellate appearance.
Type 3 – Represents invasive islands of the tumor > 15 cells per island.
Type 4 – Represent invasive tumor islands < 15 cells per island. The includes cord-like and single cell invasion[27].

TUMOR BUDDING

Tumor budding depends upon 2 properties—that is, loss of cellular cohesion and active invasive movement.[28] Tumor budding at the invasive front indicates the dissociation of invasive cancer cells from the main tumor mass. It has been noted as a promising prognostic marker[29]. A significant correlation between high tumor budding count and the presence of lymph node metastasis is one of the most important findings. Tumor budding is an early step en-route to metastasis. It is also an independent prognostic marker with 5 bud cut off point and 10 bud cut off point[30]. OSCCs with high grade tumor budding are at high risk of poor prognosis. Tumor budding has prominent prognostic power for OSCC even at early stages of disease[31].

Salient features of Tumor budding (Figure 3) :

1. Simple, Reliable.
2. Evaluate of tumor budding could facilitate personalized management of OSCC.
3. Loss of cellular cohesion.
4. Active invasive movement[32].

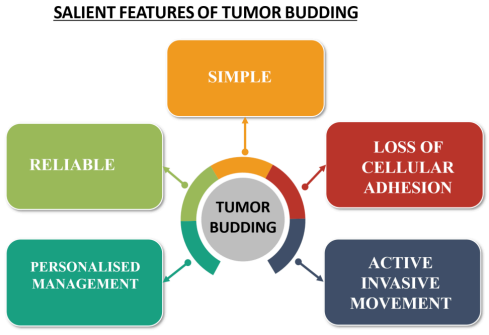

Figure 3

Methods of detecting Tumor budding :

H-E Staining.

Immunohistochemical staining for cytokeratin using pan-cytokeratin antibody.

However the optimal method has not been standardized and results using these techniques have been inconsistent depending upon tumor type[33].

Assessment of DOI and tumor budding :

Briefly, DOI is measured from the level of the basement membrane of the closest adjacent normal mucosa to the deepest part of the invaded tumor in all resected specimens[34]. When tumor bud existed separated from the main tumor mass, the distance from the level of the basement membrane of the closest adjacent normal mucosa to the tumor buds are measured[35].

During the scoring of tumor budding the whole tumor area was scanned at low magnification (40x) to select areas with the highest tumor budding. Next budding was counted at higher magnification (200x) and the highest count per sample was used as the tumor budding score. When the DOI assessment and tumor budding differed between the observers, a joint evaluation was performed to arrive at a consensus.

DOI range (0.1-10.0)

Tumor budding score (0-40)[36].

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[37]

Tumor grading implies the same well differentiated, moderately differentiated and poorly differentiated. The current WHO grade incorporates keratinization, nuclear pleomorphism, mitotic activity with P16 expression whether negative or positive[38]. 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[39].

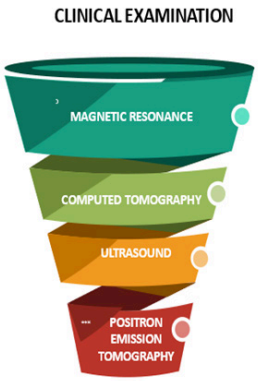

Figure 4

DIAGNOSTIC FEATURES

It includes identifying a problem and giving it a name. Simple examination (Figure 4) of lips, gingiva, hard and soft palate, tonsillar areas, buccal mucosa and floor of mouth for the following –

Changes in color and texture[40].

Biomarkers resulting from multiple genetic mutations such as overexpression of epidermal growth factor (EGFR), telomerase, surviving and suppression or inactivation of tumor suppressor genes such as FHIT P53. Various other biomarkers like DNA content and chromosome polysomy, loss of heterozygosity, proliferation markers, increased EGFR and decreased expression. Difference in DNA and RNA expression pattern and microsatellite motifs[41].

PROGNOSTIC FEATURES

It includes guessing so as to the outcome of the treatment. Grading alone does not correlate well with prognosis[42]. The presence of nodal metastasis or survival could not be corelated with the dedterioration and differentiation grade, hence these criterias do not have any prognostic value concerning outcome. Consequently, these items are of little value for treatment planning[43]. The pattern of invasion in differentiation grade of resection specimen in small OSCC could increase the prognostic value probably because it is, apart from differentiation grade, an independent risk factor for nodal metastasis. In conclusion, the conventional WHO grading system has low prognostic utility in early OTSCC but can be improved by incorporation of tumor budding[44].

In the study conducted by Amr elseragy et al[45], proposal to introduce tumor budding into the WHO grading system was attempted which showed a high prognostic value for early OTSCC. Of note, the recent WHO classification of head and neck tumors indicates that a noncohesive pattern of invasion is associated with poor prognosis of OSCC. Recent studies[2,32,46]

have validated the clinical significance of tumor budding, and recent meta-analysis[2] confirmed this as significance for OTSCC. Importantly, tumor budding was recently listed by the Union for International Cancer Control's TNM classification as a prognostic marker for colorectal cancer. The assessment of tumor budding using routine HE-stained sections has been successfully reported in many cancers[47]. In the study conducted by Jiayuan et al[48], Tumor-stroma ratio could be a useful tool for the prediction of prognosis and outcomes of solid tumors. In certain studies[49,50], tumor-stroma ratio, occult neck metastasis, depth of invasion are all independent prognostic factor for patient with tongue squamous cell carcinoma whereas tumor budding is the dependent prognostic factor for subjects with OSCC.

Recently, Zhou et al[51] constructed a novel prognostic classifier 7IFBPS, based on seven immune features of OSCC with satisfactory performance, sensitivity and specificity. This integrative immune classifier can effectively predict patient survival, and improve or complement the prognostic power of routine clinicopathological parameters. Thus, the author believed that this immune prognostic score might facilitate patient counseling, decision-making regarding individualized treatment and follow-up scheduling. It remains an open and interesting question to incorporate such immune-feature-based classifier into conventional prognostic regime to assess patient outcome and risk of disease progression. In another study[52], i B D score was suggested as a novel prognostic model for SCC. This novel model was strongly correlated with T classification, lymph node metastasis, clinical stage and recurrence and showed clear distinction of score 0,1,2.i B D scoring model is strongly associated with lymph node metastasis and recurrence in TSCC and could be a promising survival predictor for TSCC patients.

MULTIMODALITY THERAPY OF ORAL SQUAMOUS CELL CARCINOMA

Multimodality therapy that includes surgical resection, radiation therapy, and/or chemotherapy is often indicated to manage certain patients with head and neck cancer. Prosthodontic rehabilitation of this patient population is complex, owing to the technical challenges involved in the fabrication of a prosthesis, frequent prosthetic adjustments or remakes and the management of the subsequent psychological implications of the patient[5]. Using the interim obturator as radiation stent with a total of 63 Gy in 30 fractions was the prescribed treatment plan along with the survival of 6 weeks. Recently, with better survival rates, the focus has broadened to paying greater attention to improving the quality of life for cancer survivors. Patients face multiple challenges as they undergo ablative cancer treatment and substantial difficulties afterward due to the late side effects of cancer therapy. In a clinical report presented by Varun and Mark[54], there were many challenges faced by a patient during and after multimodality treatment of the patient with squamous cell carcinoma of maxillary and paranasal sinus involvement. These patients require lifelong prosthodontic care to ensure continued success with the function and esthetics of the prosthesis. In another study[55,56,57,58], it was concluded that implant-retained prosthesis showed better and improved quality of life when compared to adhesive techniques in the prosthodontic management of many oral cancers including oral squamous cell carcinoma[59, 60,61].

Conclusion

Oral squamous cell carcinoma being the most common among the head and neck cancer has many complications in the invasive front. There are many histopathological features reviewed in the present article. Among the various histopathological features, tumor budding seems to be a very promising feature with high prognostic value compared to other histopathological features. Grading proposal of head and neck cancer also includes tumor budding as the main feature. Of the other novel prognostic features, tumor budding proves out to be the most important factor. Since multimodality treatment options seems to present challenges to the patient, the treatment involves frequent visits to reduce the complications, other recurrences and risk factors.

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