Case Report

Does a Well-Differentiated Oral Squamous Cell Carcinoma Always Behave Well? A Case Series

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Abstract

Oral squamous cell carcinoma is the sixth most common human cancer and is usually preceded by a premalignant lesion. The patient usually presents it to the clinician at an advanced stage where there are limited treatment options available with declining survival rates. Cancer-deteriorated human lives have prepared the clinicians to take a significant step toward the better survival of patients. Hence, here, we report a case series of oral cancer using some prognostic factors that served in reaching out to conclusion and might favor a diagnostic help to clinicians and pathologists. The final diagnosis for every case was given as well-differentiated squamous cell carcinoma, yet they all exhibited poor prognostic parameters. Predictive markers of oral carcinoma in clinical, surgical, and histopathological fields contribute to their improved status of living. Such parameters, evaluated here in this case series, might lend a helping hand in determining the patient vulnerability toward poor survival and be provided with best treatment interventions.

Keywords: Invasion, oral squamous cell carcinoma, prognostic markers, survival, tumor invasive front

Introduction

Oral squamous cell carcinoma (OSCC) makes up the bulk of cancers found in oral cavity.[1] It forms the major mortality concern, accounting for 16%–40% of all head-and-neck cancer.[2] Clinically, primary tumor, regional lymph node [LN] metastasis, and distant metastasis (TNM) staging supports the treatment plan and prognosis, lacking biological distinction.[3] Surgery, radiation, targeted therapy, and chemotherapy are the most frequent treatment modalities available.[4] Being a tumor of high invasiveness, metastasis, and poor survival with heterogeneous assemblage at the clinical, biological, and histopathological levels,[2] collective approach is essential.

Histopathological grading systems alone are less constructive for prognosis. For that reason, certain essential aids are put into diagnostic process. These parameters have a potential to predict the patient outcome both at clinical and histopathological levels.

The present case series forms the first of its kind to depict well-differentiated squamous cell carcinomas (WDSCCs) with various important prognostic parameters being evaluated in all the three cases which have helped the pathologists and surgeons in viewing the survival status of the patients. None of the studies have analyzed all these predictive factors in WDSCC.

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Case Reports

Case 1

A 45-year-old male reported an unhealed ulcer in the left posterior mandibular region for 6 months which was gradually growing with associated pain and burning sensation. Deleterious habits included bidi smoking (8–10 years), smokeless tobacco (4–5 years), and pan and betel nut chewing (2–3 years). Extraorally, diffuse facial swelling was present with solitary enlarged left submandibular LN. Intraorally, an ulceroproliferative growth extended from the left buccal mucosa and vestibule till retromolar trigone [Figure 1a]. Radiological imaging demonstrated soft

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tissue thickening in the mandibular arch and well-defined hypodense, necrotic area in the center of lesion. Based on clinico-radiological evidence, the provisional diagnosis of malignancy with lower left buccal vestibule, mucosa, and retromolar area was established. Segmented mandibulectomy with partial maxillectomy [Figure 1b] was attempted along with LN (level I–V) excision and followed by pectoralis major myocutaneous flap reconstruction. In addition, combined chemo- and radiotherapy was recommended. Histopathologically, hematoxylin and eosin (H and E)-stained sections showed surface epithelium infiltrating into underlying fibrocellular connective tissue stroma in the form of nests, islands, cords, and sheets [Figure 1c]. Tumor islands revealed anaplastic features, prominent vesiculated nuclei and nucleoli, pleomorphism, and increased nucleo-cytoplasmic ratio. Individual cell keratinization, large keratin pearls, and atypical mitoses were detected.

Various parameters were studied histopathologically [Table 1], depth of invasion,[5] tumor thickness (TT),[5] tumor invasiveness[6,7] and migration in the form of deeper structures involvement, metastases with LN involvement, and inflammatory response. This was followed by immunohistochemical analysis using specific prognostic markers for cellular proliferation or angiogenesis. Finally, histopathological grading (STNMP) was established for rating the patient prognosis. It was done for the other two cases as well. The patient was called in after a week to check the healing and followed up for 1 month. No recurrence was seen at follow-up.

Case 2

A 25-year-old male reported the nonhealing ulcer on the left lateral border of the tongue for the last 1 year [Figure 1d]. Initially, he was asymptomatic but later experienced multiple ulcers gradually increasing in size, painful, associated with burning sensation and dysphagia. Clinical inspection revealed papillary-shaped ulcer with white keratotic rough surface on the left lateral border of the tongue and anterior faucial pillar. It was diffuse, patchy shaped, firm in consistency with ill-defined margins, and tender on palpation. No LN involvement was evident. Clinically, provisional diagnosis was given as carcinoma tongue. Surgical intervention included site of lesion along with neck dissection. H and E-stained section revealed overlying surface epithelium proliferating deep into the underlying connective tissue stroma in the form of tumor islands, cords, sheets, droplets, and nests. Superficial focal ulceration was evident. Bulbous rete ridges with pushing borders were seen [Figure 1e]. Features of anaplasia were evident with several mitotic figures. Underlying connective tissue showed numerous areas of keratin formation with dense inflammatory response and hemorrhagic areas. The parameters were evaluated [Table 1] in this case also, similar to case 1. The patient was followed up for 1 month with no recurrence and uneventful healing.

Case 3

A 64-year-old male reported an ulcer on the right lateral border of the tongue for the past 3–4 months. It was insidious in onset and associated with mild pain on food consumption. Deleterious habits included bidi smoking (2–3 bundles/day, 30–35 years), tobacco chewing (5–6 times/day, 15 years), and alcohol consumption (90 ml/day, 20 years). Extraoral examination revealed palpable, tender, and firm right submandibular LN. Clinical examination revealed a reddish ulcerative lesion with whitish-gray plaque-like area [Figure 1f], irregularly shaped, circumscribed with rolled out margins, and smooth and

Table 1: Prognostic factors studied in cases

Parameters evaluated	Case number		
	Case 1	Case 2	Case 3
DOI	8.41 mm [Figure 2a]	6.50 mm [Figure 2b]	6.25 mm [Figure 2c]
TT	5.86 mm [Figure 2a]	6.90 mm [Figure 2b]	6.22 mm [Figure 2c]
POI	Type 3 (small groups/cords of infiltrating cells, *n* <15) and Type 4 (marked and widespread cellular dissociation in small groups and/or isolated cells, *n* <15) with TB at TIF [Figure 2d]	Type 1 (droplets), type 2 (elongating) and type 4 (reticular) at TIF [Figure 2e]	NA
Deeper connective tissue structures involvement	Nerves (PNI) [Figure 2f], blood vessels (PVI), muscles, salivary glands [Figure 2g], adipocytes	Muscular involvement [Figure 2h]	Muscle bundle architecture obscured by tumor cells
LN involvement	ECS involving levels I, II, and III with irregular cords and stands of neoplastic cells [Figure 2i]	Level IV LN [Figure 2j]	NA
Inflammatory response	Diffuse lymphocytes and eosinophils at TIF [Figure 3a]	Intense lymphocytic cell infiltration	Intense mixed inflammatory reaction of lymphocytes, eosinophils, and plasma cells [Figure 3b]
IHC	PCNA and GLUT-1 intense labeling (>50% positive cells) [Figure 3c and d]	EGFR, p53, PCNA, and VEGF (>50% positive cells) [Figure 3e-h]	p53 intense labeling (>50% positive cells) [Figure 3i]
STNMP	S4T4N2M0P3b (Stage III)	S3T4N2M0P3b (Stage IV)	S3T2N2M0P3b (Stage II)

POI: Pattern of invasion/invasiveness, TT: Tumor thickness, DOI: Depth of invasion, TB: Tumor budding, TIF: Tumor invasive front, LN: Lymph node, IHC: Immunohistochemistry, PCNA: Proliferating cell nuclear antigen, GLUT-1: Glucose transporter-1, EGFR: Epidermal growth factor receptor, VEGF: Vascular endothelial growth factor, S: Site, T: Tumor, N: Nodal involvement, M: Metastasis, P: Pathology, NA: Not applicable, PNI: Perineural invasion, PVI: Perivascular invasion, ECS: Extracapsular spread, NA: Not available, STNMP: Site Tumor Node Metastases Pathology

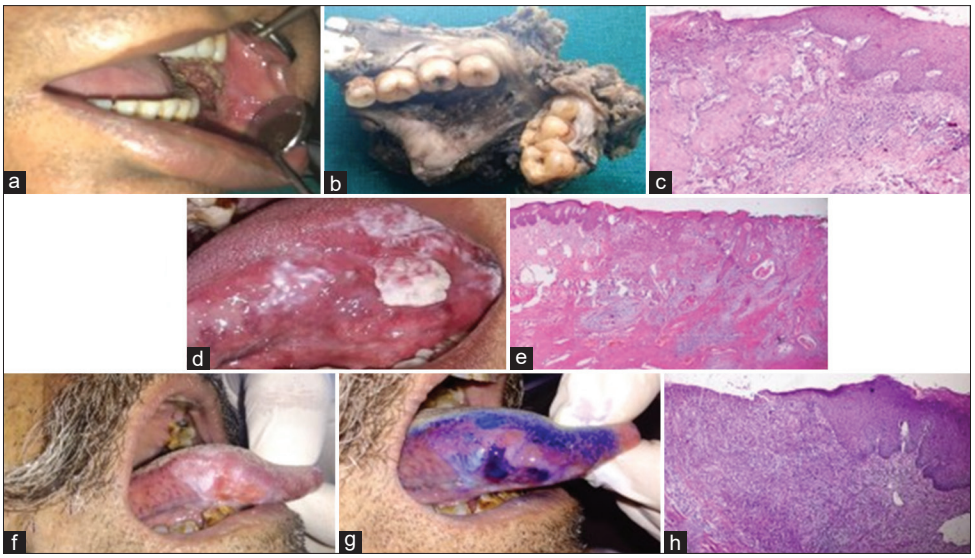

Figure 1: Clinical and histopathological characteristics of cases. (a) Case 1 showing red and white ulceroproliferative lesion, (b) Biopsy specimen (segmented mandible and partial maxilla), (c) Tumor cells exhibiting anaplastic features (H and E, ×400), (d) Case 2 showing white keratotic lesion, (e) Tumor proliferation with anaplastic features (H and E, ×100), (f) Case 3 showing reddish ulcerative lesion with whitish-gray plaque-like area, (g) Vital staining, (h) Hyperplastic epithelium with epithelial denudation, and pushing borders (H and E, ×100)

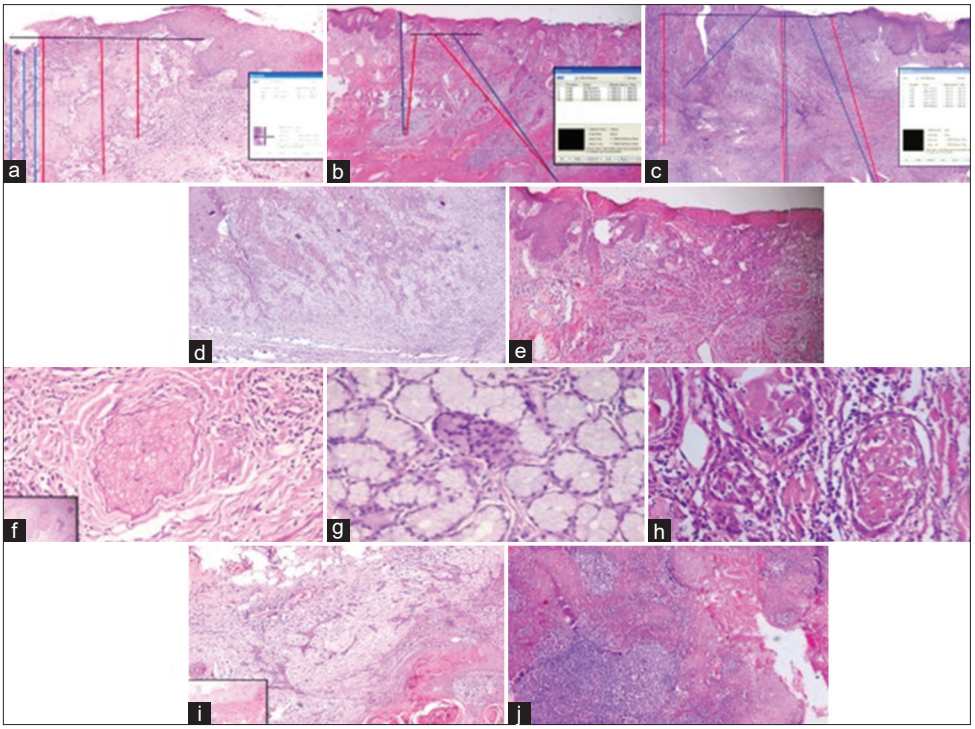

Figure 2: DOI, TT, patterns of invasion, and deeper structures studied for cases. (a) Case 1 showing DOI > TT, (b) Case 2 showing TT > DOI, (c) Case 3 showing DOI > TT, (d) Type 3 and 4 pattern with tumor budding in case 1 (H and E, ×400), (e) Type 2, 3, and 4 invasive patterns in case 2 (H and E, ×100), (f) PNI in Case 1 (H and E, ×400), inset (H and E, ×40), (g) Salivary gland infiltration in Case 1 (H and E, ×400), (h) Muscular involvement in Case 2 (H and E, ×400), (i) ECS of lymph node in Case 1 (H and E, ×100), inset (H and E, ×40), (j) Lymph node invasion in Case 2 (H and E, ×400). TT: Tumor thickness, DOI: Depth of invasion, PNI: Perineural invasion

nonscrapable texture. Bilateral buccal mucosa blanching with palpable circumoral and vertical bands was appreciated (mouth opening = 34 mm). Vital staining by Toluidine blue highlighted the most dysplastic area [Figure 1g]. Provisional diagnosis of carcinoma tongue was made clinically. Histopathologically, H and E-stained section showed hyperplastic epithelium with chevron-like surface proliferations and broad, bulbous rete ridges. Focal ulcerative area with epithelial denudation was evident [Figure 1h]. Epithelium proliferated into the underlying stroma in the form of long cords, nests, sheets, and strands of

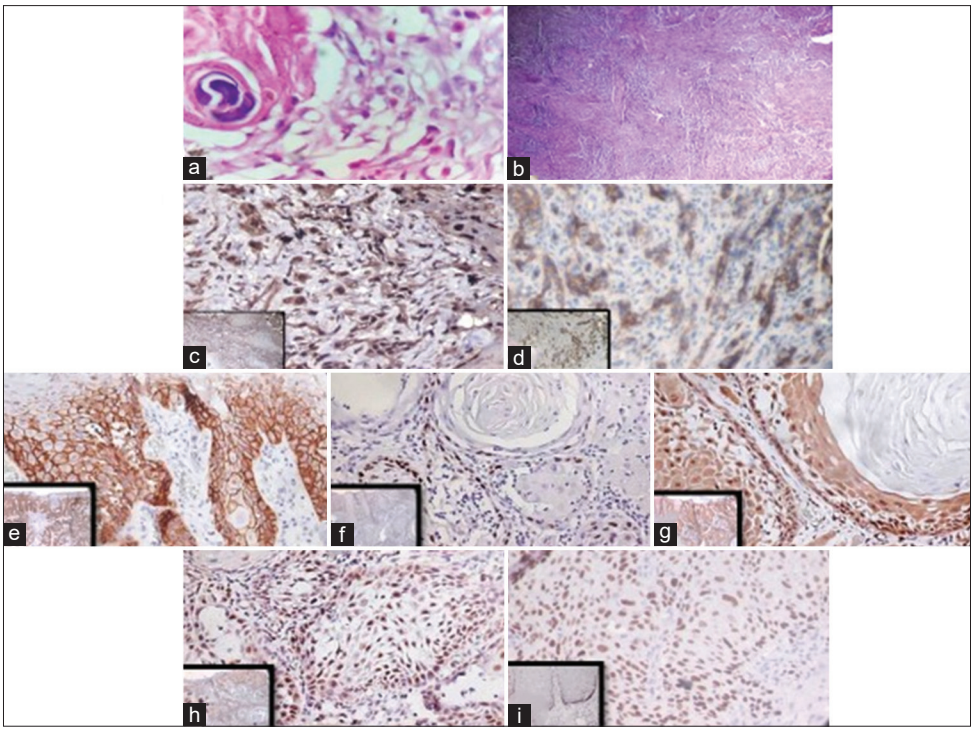

Figure 3: Inflammatory response and immunohistochemical analysis for cases. (a) Eosinophilic infiltration at TIF in Case 1 (H and E, ×400), (b) Diffuse immune response in Case 3 (H and E, ×400), (c) PCNA (IHC, ×400) labeling in Case 1, inset (IHC, ×40), (d) GLUT-1 (IHC, ×400) immunoexpression in Case 1, inset (IHC, ×40), (e) EGFR (IHC, ×400) expression in Case 2, inset (IHC, ×40), (f) p53 (IHC, ×400) labeling in Case 2, inset (IHC, ×40), (g) PCNA (IHC, ×400) immunoreaction in Case 2, inset (IHC, ×40), (h) VEGF (IHC, ×400) overexpression in case 2, inset (IHC, ×40), (i) p53 (IHC, ×400) labeling in Case 3, inset (IHC, ×40). TIF: Tumor invasive front, PCNA: Proliferating cell nuclear antigen, IHC: Immunohistochemistry, GLUT-1: Glucose transporter 1, EGFR: Epidermal growth factor receptor, VEGF: Vascular endothelial growth factor

tumor cells. Features of anaplasia were seen with numerous keratin pearls and individual cell keratinization. Mitoses were evident. Intense mixed inflammatory reaction was present. The parameters studied here were similar to as stated in case 1 [Table 1] but differing in results. The patient could not be followed up since he left the town.

Discussion

OSCC classically presents tumor differentiation, anaplasia, heterogeneity, polyclonality, and aggressive behavior. Surgical intervention forms the mainstay of the treatment option for OSCC with improvements in patient survival, whereas advanced disease stage along with poor histopathological grading may degrade the overall survival of the patient.[8]

Tumor invasive front (TIF) represents the most progressive part comprising highly active malignant cells impending toward invasion and migration, thus declining the survival. The present case series depicts the tumor activity at TIF in its grave form. Mere histological grading has no effect on prognosis, unless DOI is measured pathologically, stratifying the patients as low-risk and high-risk groups.[9] TT more than 4 mm implicates the worst prognosis.[10] DOI is measured from the adjacent normal basement membrane to the deepest point the tumor invades (millimeters), whereas TT is measured from the highest point of the surface of tumor to the deepest point of the tumor invasion (millimeters).[11] For an exophytic lesion, TT > DOI, whereas for ulcerative lesion, TT < DOI.[12] In the present case series, both Cases 1 and 3 showed DOI > TT. Though Lee *et al*. gave contradictory statements to their utility in prognosis, wherein TT was not associated with disease specific survival (DSS) or progression free survival (PFS) whereas, increasing DOI was positively associated with decreased DSS and negatively correlated to decreased PFS.[13]

Perivascular invasion (PVI) and perineural invasion (PNI) are correlated to tumor angiogenesis and neovascularization, initiating locoregional or distant metastasis. This corresponds to the microenvironment by-products acting both on host and tumor tissues, as evident through overexpressed vascular endothelial growth factor.[14] The prognostic value of PNI depends on number of foci, size, and location of nerve involved.[15] A study has shown a direct relationship of PNI with different grading and stages of OSCC.[16]

Deeper connective tissue structures, muscle bundles, and adipocyte intrusion correlate to advancing stage cancer and likelihood of occult LN metastasis, thus undetectable clinically. Sialadenotropism was exhibited by salivary glands as neoplastic cell-mediated metaplastic and dysplastic changes. In such a scenario, their inadequate excision ensues recurrences.[17] A study suggested that dysplasia or oral cancer extension from the overlying surface epithelium along the salivary glands and ducts is an uncommon finding. Salivary gland changes must

be included in the histopathological interpretations, as their detection decreases the overall morbidity.[18]

Case 1 depicted the involvement of nerves and vessels, whereas muscle bundles were completely obscured in all the three cases.

In addition, tumor cells attacked extracapsular space (ECS) of LN. Though ECS is a rare histopathological phenomenon, yet it embarks its prognostic significance in the patient survival. Cervical LN metastasis is the most significant, consistent, and independent prognostic factor, severing the survival rate by 50%. Although it passively identifies the tumor–host interaction, no confirmed prognostic literature evidence is present.[19] As per the literature, the number of positive lymph node systems has been regarded superior to the 8th American Joint Committee on Cancer neck lymph node classification. It provided a reliable method to instruct adjuvant treatment and a better tool for doctor-to-patient communication.[20] Cases 1 and 2 both showed lymph node involvement with ECS presented by Case 1.

Hanahan and Weinberg[21] mentioned tumor inflammatory microenvironment as the seventh hallmark of cancer contributing toward survival and proliferation of neoplastic cells, angiogenesis, metastasis, altered immunity, and decreased chemotherapeutic response, inducing genetic aberrancy in malignant cells. OSCC is characterized by abundance of varying immune cells. Increased tumor-infiltrating lymphocytes (TILs) corroborate better prognosis and are entailed as an independent marker of recurrence.[22] Tumor-associated tissue eosinophilia (TATE) correlates with tumor differentiation and nodal metastasis.[23] A study verified indirect link between TATE count and grade of invasion, emphasizing its defensive role in neoplastic cytotoxicity and progression.[12] Here, the cases reported the presence of lymphocytes, eosinophils, and plasma cells. A study found increased eosinophils in carcinoma and suggested that eosinophilic infiltration in dysplastic lesions should be looked into for invasiveness.[24] TILs in oral cancer have an impact on tumor biology and behavior, therapeutic response, and patient survival.[25]

TIF embarks a higher degree of cell dissociation, lower differentiation, and distinctive molecular profile than superficial areas, making it the most prognostic area of the tumor. The genomic shift at the TIF predicts the tumor biology with possible local recurrence and metastasis.[26] Tumor markers predict the recurrences and are found in higher quantities in cancerous tissue.[27] Proliferative markers aid in determining the cell proliferation velocity in tumors.[28] An increased proliferative activity correlates to deteriorated state and prognosis, equivalent to the present results, depicted through overexpressed p53, proliferating cell nuclear antigen, glucose transporter 1, and epidermal growth factor receptor.

Table 2: Well-differentiated squamous cell carcinomas diagnosed by various investigators with their prognostic implications

Reference	Diagnosis	Prognostic implication
Horie N *et al*. (2017)[29]	WDSCC mandibular alveolus (Stage II)	Showed secondary primary gingival carcinoma (Stage I) after 18 months, attributed to both blood and tissue eosinophilia
Akbulut *et al*.[30]	3 cases WDSCC mandible (Stage III) WDSCC mandible (Stage II) WDSCC palate (Stage III)	No recurrences shown by Case 1 after chemotherapy, Case 2 after radiotherapy, and Case 3 postradio-, chemotherapy
Sheikh and D'souza[31]	WDSCC gingival extraction socket (Stage II)	Recurrence after 2 months at base of tongue. Gingival carcinomas are considered under poor prognosis with worsening after LN metastasis
Bijai *et al*. (2014)[32]	WDSCC palate	No recurrence
Kayal *et al*.[33]	WDSCC tongue (Stage III)	Poor prognosis; death after 5 months postsurgery and radiotherapy
Pramanick and Ghose (2017)[34]	WDSCC mandible	No recurrence following surgery. PNI absent. Poor prognosis established in children, due to delayed presentation, or poor tumor behavior
Riju *et al*. (2017)[35]	WDSCC mandibular alveolobuccal complex and retrocommissural buccal mucosa	Multiple synchronous SCCs are aggressive with poor prognosis
Sirisha[36]	WDSCC lateral border of tongue	No recurrence since follow up
Tantray and Chauhan[37]	WDSCC buccal mucosa and vestibule	Poor prognosis
Abhyankar *et al*.[38]	WDSCC lateral border of tongue	PVI and PNI absent
Suga *et al*.[39]	3 cases WDSCC tongue and buccal mucosa WDSCC tongue with sublingual involvement WDSCC tongue	Case 2 presented with metastasis to LN neck and thoracic spine following chemo- and radiotherapy. Case 3 patient died
Present study	3 cases Posterior mandible, buccal mucosa and retromolar region WDSCC lateral border of tongue	All the 3 cases presented with all the poor prognostic features No recurrences at 1-month follow-up

WDSCC: Well-differentiated squamous cell carcinoma, LN: Lymph node, PNI: Perineural invasion, PVI: Perivascular invasion

Although the present cases were diagnosed as WDSCC, they all exhibited the poor prognostic parameters. Therefore, the patients were considered having poor phenotype with poor survival. Such cases demonstrate recurrent lesional episodes with anticancer therapy resistance. Various WDSCC case reports are summarized in Table 2 with their concluding results. This restricted case series of WDSCC highlights various parameters that can be evaluated histopathologically in order to attain the survival status of the patients. This shows that even with the diagnosis of WDSCC, the patient may have worse prognosis.

Limitations

The follow-up of the patients could not be done for more than 1 month. Furthermore, viral infectivity (human papillomavirus), which is regarded as an etiological agent in OSCC, was not detected, which might have added as an additional prognostic factor.

Conclusion

Understanding the exact tumor biology is important. A clarified molecular mechanism behind OSCC is crucial for early detection, treatment, and prognosis.

The present research and available data recommend STNMP, DOI, and others to be the dependable core prognosticators of OSCC. Despite therapeutic advances, OSCC maintains a challenging image in the field of malignancies; hence, implementing such histopathological prognosticators in diagnosis is a requisite for a conclusive future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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