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Verrucous carcinoma of the oral cavity: A clinical and pathological study of 101 cases

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Summary This paper studies the clinical and pathological predictors of local recurrence and disease-free survival (DFS) in patients with oral verrucous carcinoma (OVC) treated surgically, through a retrospective chart review. Three hundred and two patients with OVC were identified from January 1990 to December 2000, of which, 101 surgically treated patients who fulfilled our inclusion criteria were analyzed. A univariate analysis (UVA) of important prognostic factors, patterns of recurrence, and DFS is reported. Seventy-nine patients were male (M:F ratio, 3.6:1) and the mean age at presentation was 53.9 years (range, 23–90 years). The median follow up was 4.61 years (range, 0.51–14.3 years). The incidence of tobacco chewing, smoking, and alcohol intake was 77%, 42%, and 10%, respectively. Thirty-four patients (33.7%) had either leukoplakia or submucous fibrosis (SMF) on oral cavity examination. Early-stage tumors accounted for 39.7%; while 60.4% were late-stage tumors. On UVA, tumor location, presence of a premalignant lesion, smoking, and positive margins were statistically significant. Sixty-eight percent (19/28) recurred locally. The salvage rate for recurrent tumors was 66.7% (16/28) with a median post-recurrence survival of 16 months (range, 10–83 months). The five year DFS with surgical therapy was 77.6%. OVC has an excellent prognosis with surgical treatment. The significance of positive margins emphasizes the need for adequate surgical resection. Additionally, the presence of either leukoplakia or SMF and tumor location in the upper alveolar-palatal complex is associated with worse outcomes. Neck dissection, if considered, may be limited to a supra-omohyoid neck dissection (SOHND).

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Introduction

OVC is a rare variant of oral SCC. In 1948, Lauren V. Ackermann first described this neoplasm of the oral mucous membrane, which is now also know as ''Verrucous carcinoma of Ackermann'' or ''Ackermann's tumor''.[1] The oral cavity is the most common site of occurrence. In addition, it is known to occur in the larynx, pyriform sinus, esophagus, nasal cavity and paranasal sinuses, external auditory meatus, lacrimal duct, skin, scrotum, penis, vulva, vagina, uterine cervix, perineum, and the leg.[2,3] This tumor is predominantly seen in males over the sixth decade. In terms of tumor biology, OVC is distinct in its slow growth and ability to become locally aggressive if not treated appropriately. However, even with local tumors progression, it is intriguing that regional or distant metastasis is rare.[4] OVC has unique histopathological features. An accurate pathological diagnosis is challenging and is facilitated by an adequate tumor sample for study and more importantly, a close collaboration between the clinician and the pathologist.[4,5]

The etiopathogenesis of OVC is unclear, however, studies have shown strong associations with tobacco use, including inhaled as well as smokeless tobacco, alcohol, and opportunist viral activity associated with human papilloma virus (HPV).[4,6–8] More recently, studies have further confirmed the association between HPV and OVC by detecting HPV–DNA types 6, 11, 16 , and 18 by polymerase chain reaction (PCR), restriction fragment analysis, and DNA slot–blot hybridization.[9–11] Surgical excision with adequate margins of resection seems to be the clear preference for treatment. Recurrences are frequent and require additional treatments.[2,6] To date, the literature focusing on the clinicopathological features of OVC is not robust. Our aim was to study the clinical and pathological predictors of local recurrence and DFS in large cohort of patients with OVC treated surgically at one institution.

Materials and methods

A retrospective chart review was conducted at the a tertiary cancer institute for patients presenting with OVC over a 11 year period, i.e., January 1, 1990–December 31, 2000. Prior to embarking on this study; an approval from the hospital was obtained as per protocol. Three hundred and two consecutive cases diagnosed with OVC on histopathological examination were identified. The histological criteria employed for diagnosis of OVC required to tumor to have a well differentiated squamous proliferation exhibiting both exophytic and endophytic components and orderly maturation. The exophytic components were composed of papillae covered by orthokeratin and/or para keratin. The endophytic components were made up of typically broad, blunt rete pegs with pushing margins. The advancing edge of the tumors were well differentiated with minimal cytologic atypia. Subepithelial tissue contained lymphoplasmacytic inflammatory infiltrate.[1,5,12,13] Patients treated primarily with surgery, with no prior history of head and neck cancer treatment were included in the analysis. Patients with recurrent tumors and distant metastasis were excluded. In addition, patients with hybrid tumors (tumors containing components of both verrucous and squamous carcinoma) and verrucous hyperplasia were also excluded from the analysis. The final analysis was conducted on 101 patients with pathologically proven OVC who fulfilled our inclusion criteria. Statistical analysis was performed using the SPSS software version for 11.5 for Windows. Survival curves were plotted by the Kaplan–Meier method and compared by the log-rank test.

Results

There were 79 males and 22 females (ratio M:F, 3.6:1), with a mean age of 53.9 years (age range, 23–90 years). The median follow up for the entire surgical cohort was 4.61 years (range, 0.51–14.3 years). The incidence of tobacco chewing, smoking, and alcohol intake was 76.2% (77/101), 41.6% (42/101), and 9.9% (10/101), respectively. Due to the retrospective nature of this study, a history of the quantity, frequency, and duration of tobacco chewing, smoking, and alcohol usage could not be obtained in sufficient detail to merit further analysis. Among these patients 58% had t one of the three risk factors, while 32% had multiple risk factors. Thirty-four patients (33.7%) had either leukoplakia (18/34; 53%), SMF (12/34; 35.2%), or both lesions (4/34; 11.8%) on oral cavity examination. At presentation, the epicenter of the disease was most frequently the buccal mucosa, seen in 62 patients (61.4%), followed by the lower alveolus in 12 patients (11.9%) (Table 1). The most common morphological presentation was a 'proliferative' lesion followed by a 'verrucous' or 'wart-like' growth (Table 2). The *T* and *N* distribution for the entire study cohort is summarized in Table 3. The patients were staged according to the AJCC staging system.[14] Early-stage tumors accounted for 39.7% [stage I, 5% (5/101) and stage II, 34.7% (35/101)], while late-stage tumors accounted for 60.4% of all tumors [stage III, 32.7% (33/101) and stage IV 27.7% (28/101)]. All patients were treated with curative intent; 82% had surgery alone and 18% received surgery and postoperative radiotherapy.

Seventy patients (69.3%) were clinically N0 at presentation. Neck dissections were performed in 52 patients. Among the patients who had neck dissection, 48% (25/52) had palpable nodes at presentation. In addition, among patients with N0 necks who had neck dissection (27/52; 52%); all patients had tumor size equal to or greater than T2 at presentation. Radical neck dissections, modified radical neck dissections, and supra-omohyoid neck dissections

Table 1 Distribution of primary tumors by epicenter at presentation

Epicenter	Frequency (*N* = 101) (%)
Buccal mucosa	62 (61.4)
Lower alveolus	12 (11.9)
Lower GBS	10 (9.9)
Upper alveolus	06 (5.9)
Anterior oral tongue	05 (5.0)
Lip	04 (4.0)
RMT	01 (1.0)
Palate	01 (1.0)

Table 2 Morphological presentation of OVC

Morphology of tumor	Frequency (%)
Proliferative	35 (34.7)
Verrucous	34 (33.7)
Ulceroproliferative	18 (17.8)
Ulcerative	10 (9.9)
Submucous/infiltrative	02 (2.0)
Not recorded	02 (2.0)

Table 3 *T* and *N* distribution for the study cohort

	N0	N1	N2a	N2b	
T1	5	1	0	0	6
T2	35	6	0	1	42
T3	19	7	0	0	26
T4a	11	12	1	3	27
	70	26	1	4	101

Table 4 UVA: prognostic factors for OVC

Age (⩽40 years vs. >40 years)	0.9979 NS
Tobacco chewing	0.6771 NS
Smoking	**0.0431***
Alcohol consumption	0.1154 NS
SMF	0.1671 NS
Leukoplakia	0.5241 NS
SMF or Leukoplakia or Both	**0.0252***
Primary site	**0.0000***
Morphological type of lesion (clinical)	0.3568 NS
Clinical T size	0.5432 NS
Clinical lymphadenopathy	0.6845 NS
Clinical Stage	0.6600 NS
Neck dissection	0.1658 NS
Pathological T size	0.6303 NS
Pathological bone invasion	0.3546 NS
Positive cut margins	**0.0497***

(SOHND) were performed in 19.8% (20/52), 4% (4/52), and 27.7% (28/52), respectively. None of our patients had metastatic lymphadenopathy. The incidence of pathological bone involvement was 5.9% (6 patients). Out of the 16 patients with clinical impression of bone involvement, only six (37.5%) with clinical had pathological evidence of bony invasion. Two patients had muscle invasion, while skin involvement and soft tissue infiltration was found in five and three patients, respectively. None of the patients had evidence of PNI or lymphovascular invasion.

On UVA, smoking was found to impact the DFS. Tobacco chewing, alcohol consumption as well as the presence of multiple habits were not found to be statistically significant. Primary site of cancer was not statistically significant when the epicenter of tumor presentation were considered independently. However, when tumors were distributed into well established groups such as the gingivobuccal complex (GBC), oral anterior tongue, and upper alveolar-palatal complex; the primary site was found to be statistically significant for DFS. The rate of recurrence among patients with tumors of GBC, oral anterior tongue, and upper alveolar-palatal complex tumors was 26% (23/88), 57% (4/7), and 40% (2/5), respectively. The presence of premalignant lesions and positive margins were also found to be of statistical significance (Table 4). The overall rate of recurrence was 28%. The majority of patients failed locally, 19 (68%), i.e. [pure local failures were 16 (57%) and loco-regional failures were 3 (11%). The incidence of second primary cancer for this patient cohort was found 6.9% (7/101), (Table 5). The salvage rate after recurrence for our cohort of patients was 66.7% (16/28). The median post-recurrence survival was 16 months (range, 10—83 months). The 5-year DFS for the entire cohort was 77.6%.

Table 5 Patterns of recurrence

Site of recurrence	Frequency (% of recurrent tumors)
Local	16 (55.2)
Regional	02 (6.9)
Locoregional	03 (10.3)
Second primary tumors	07 (24.1)
Distant metastasis	01 (3.4)

Discussion

There are very few studies, especially from developing countries such as India, which have evaluated the clinical and pathological prognostic factors relevant to local recurrence and DFS for OVC. OVC traditionally occurs more commonly in older males, above the sixth decade.[4] We observed similar demographics wherein the male patients were more preponderant and the mean age at presentation was between the fifth and sixth decade. Although there is a striking male preponderance to OVC, there are studies where equal sex distribution[15] and female predominance has been demonstrated.[6,16] Tobacco chewing is a significant etiologic factor for the development of OVC.[2] Lesions often develop at the site where the tobacco was placed habitually.[13] In Ackerman's study, 11 out of 18 patients (61%) with buccal cancers were tobacco chewers. Majority of our patients (76.2%) chewed tobacco and had buccal cancer. Interestingly, tobacco chewing was not statistically significant for DFS in our analysis. We hypothesize that the true effects of tobacco chewing were confounded by smokers, since 62.3% (48/77) of tobacco chewers had a history of smoking as well. This hypothesis is further validated by the fact that the UVA demonstrated smoking to be of statistical significance ($p = 0.0431$) impacting DFS. The strong association of OVC with smoking, alcohol, and HPV infections is well known.[4,6—8]. Jacobson and Shear surveyed 198 cases of OVC and described 15 personally-observed cases, where incidence of smoking was found to be 77% (7 out of 9 patients).[7] However, their study was purely observational and could not offer any evidence to emphasize the relevance of smoking as an etiological factor for OVC. Although, alcohol has been described as a predisposing factor in oral cancer; previous studies as well as our analysis could not validate its association to OVC.[6]

Oral SCC and OVC are known to be associated with poor dental hygiene, ill-fitting dentures, low socioeconomic status, tobacco chewing, snuff and alcohol use, and smoking.[4,7,12] These are the same factors that predispose individuals to the development of premalignant lesions such as, leukoplakia, submucous fibrosis (SMF), and erythroplakia.[17] In the present study, 33.7% (34/101) patients had either leukoplakia, SMF or both lesions on oral cavity examination. Extensive leukoplakia and premalignant changes have been noted in other studies as well. Rajendran et al. recorded leukoplakia in association with OVC in 48% of their patients.[5,13] The clinical association with leukoplakia and OVC is significant since untreated longstanding leukoplakia could progress to a verrucous cancer in time.[16] The synchronous presentation of either a leukoplakia or SMF in association with an OVC was found to statistically impact DFS and local recurrence in our series ($p = 0.0252$).

As previously mentioned, the epicenter of OVC was most commonly the buccal mucosa (61.4%), followed by the lower alveolus (11.9%). These findings are in lieu with current literature, which suggest that verrucous carcinoma has a predilection for the oral cavity; in particular the buccal mucosa and the lower alveolus.[5,7,16,18] In addition, tumor location was statistically significant with worst outcomes for tumors involving the upper alveolus and palate. Although, this is consistent with our clinical experience, the statistical limitation to this observation is that upper alveolar-palatal tumors comprised of 6.9% of the study cohort.

OVC has a characteristic gross appearance. These lesions are almost always large, exophytic, soft, fungating, slow growing neoplasms with a pebbly mamillated surface (Fig. 1).[1,5] Though this is the most commonly presentation of OVC; we did observe other types of morphological presentations as well. Although the gross appearance was not statistically significant factor in the UVA; it must be borne in mind that OVC may not always appear as the typical warty exophytic lesion described in the literature.

Majority of the tumors presented with advanced stage (60.4%, stage III—IV). Clinical stage was not found to be an important prognostic factor on UVA. In general, OVC are locally aggressive, but have a low propensity for regional as well as distant metastasis.[4] Thirty-one patients in our study group presented with clinically palpable neck nodes. Among OVC, most enlarged lymph nodes at presentation are often reactive to a secondary infection or inflammation rather than true metastasis.[6,7] This is supported by the fact that none of our patients undergoing neck dissections had pathologically positive nodes. It must be noted that although it is a rare occurrence, metastasis from OVC has been reported. Ackerman reported one patient with a histological positive lymph node metastasis.[1] Similarly, Duckworth encountered a single node metastasis in one of his three patients.[19]

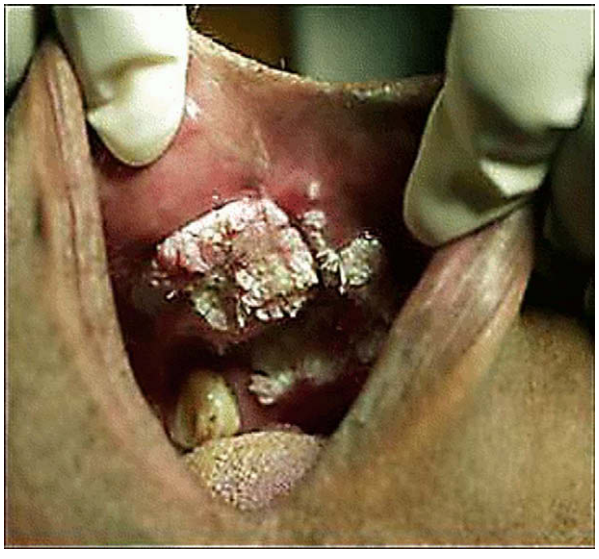

Figure 1 OVC presenting in the left buccal mucosa.

The need for neck dissection is an important consideration in planning therapy for OVC. The aggressive clinical presentation of the tumor often sways clinical judgment in favor of performing lymph node dissection, especially in the presence of clinical lymphadenopathy. This sentiment is reinforced by the fact that OVC is an extremely challenging pathological diagnosis and often even an adequate biopsy may miss areas of squamous differentiation. However, data from the present study as well as other studies, suggest that lymph node dissection in OVC should be confined to immediately adjacent lymph node groups only and in cases, where any possibility of increased morbidity or mortality may arise from inclusion of neck dissection with surgical excision, it could be omitted entirely. It is reasonable to consider a selective neck treatment such as a SOHND in situations where there is uncertainty regarding the pathological diagnosis in the face of clinically suspicious lymphadenopathy. Alternatively, a staged neck procedure is also a reasonable option if final tumor histology mandates it.

OVC tends to destroy bony structures such as the mandible, on a broad front, eroding with a sharp margin rather infiltrating the marrow spaces.[13] The incidence of pathological bone involvement in our study was 5.9% and was not statistically significant in our study. Rajendran et al., in their study of 426 cases of OVC, found the incidence of bone invasion to be 1.2%.[5] Oliveira et al. did not find bone invasion in their series.[4] Given the low incidence of pathological bone involvement; more conservative surgical options such as marginal mandibular resection may be considered while planning surgical therapy in these patients.

In our study, positive surgical margins was found to be statistically significant ($p = 0.0497$). Local recurrences can be attributed to inadequate surgical resection, which may be influenced by several factors. In extensive tumors with inflammatory changes, the margins may be difficult to define and frozen sections at surgery could be false negative.[6] It has also been proposed that the slow growth of OVC and lower invasive potential could induce inadequate surgical resections, compromising surgical margins.[7,19] However, it is noteworthy that local recurrences are observed despite clear surgical margins confirmed by histopathology.[4] Slaughter et al. emphasized the fact that in situ carcinoma involves the mucosa over wide surface area than in depth. The presence of carcinoma in situ microscopically in clinically negative resections can explain the phenomenon of recurrence of invasive cancer in apparently normal epithelium or previous excision sites.[20] Ackerman's reasoning mirrored this concept of ''field cancerization'' proposed by Slaughter; which could explain the high local recurrence

rates, second primary tumors and the occurrence of OVC at multiple sites.[4,21,22]

In the present study, the overall recurrence rate (28%) is comparable to the range reported in the literature, 6.12—40%.[7,20] The incidence of second primary cancer (6.9%) observed was lower than figures reported in other studies (10%).[4,13] In spite of a high incidence of local recurrence, OVC is often amenable to re-resections. This is exemplified by our high salvage rate for recurrent tumors (66.7%) and an excellent post-recurrence survival (range, 10—83 months). The five years disease-free survival with surgical therapy was found to be 77.6% which correlates well with control rates reported in the literature.[7]

Conclusions

OVC have an excellent prognosis with surgical management. The significance of positive margins emphasizes the need for surgical resection with adequate margins. The high incidence of local recurrences and propensity to developing second primary cancers makes it incumbent upon us to follow these patients closely. OVC are most commonly seen within the GBC, however OVC involving the hard palate and upper alveolus to be more aggressive. If the pathological diagnosis is uncertain, it is reasonable to consider neck treatment if the presence of clinical lymphadenopathy. Upfront neck dissection, if considered, may be limited to SOHND. The presence of leukoplakia or SMF in addition to OVC could indicate a predisposition for multi-centricity, ''field cancerization'', and higher local recurrence making a stronger argument for prolonged close follow up in these patients.

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None declared.

Conflict of Interest Statement

None declared.

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