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Original Research Article

Surgical Outcomes of Indolent Oral Verrucous Carcinoma Patients and Their Long Term Follow Up

Vijaya Lakshmi V V[1], Paramesh Shivanna[2], Rakesh S Ramesh[3]

[1]Assistant Professor, Department of Surgical Oncology, St Johns Medical College Hospital, Bengaluru, Karnataka, India

[2]Assistant Professor, Department of Surgical Oncology, ESIC Medical College and PGIMSR and Model Hospital, Rajajinagar, Bengaluru, Karnataka, India

[3]Professor, Department of Surgical Oncology, St Johns Medical College Hospital, Bengaluru, Karnataka, India

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Corresponding author: Vijayalakshmi V V
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Abstract

Background and Objectives: Oral verrucous carcinomas are uncommon tumours and they have favourable outcomes. They have a long latency period. This study was conducted to evaluate the surgical outcomes of oral verrucous carcinoma patients in a tertiary cancer hospital in South India.

Methods: This retrospective study was conducted in biopsy proven oral verrucous carcinoma patients who underwent treatment at the surgical oncology department of a tertiary care center in south India, from January 2014 to December 2020. The patients were followed up until December 2023.

Results: 133 patients underwent surgery for oral carcinoma during the study period. Of these, 8 patients had oral verrucous cancer. The mean age of presentation was 55.3 years. Buccal mucosa was the most common subsite affected, seen in 6 patients. Three patients had pT1, four patients had pT2, and one patient had pT3. Reexcision was done in two patients. None of our patients had recurrence in the follow up period.

Conclusion: Verrucous carcinoma is characterised by inherently favourable prognosis. It displays local aggressive behavior and uncommon regional or distant metastasis. Surgical excision with adequate margin is the most effective and standard treatment. There should be special emphasis on close follow up in view of high recurrence.

Keywords: Oral Verrucous Carcinoma, Surgical Management, Recurrence, Neck Dissection, Follow Up.

Introduction

Squamous Cell Carcinoma (SCC) is the commonest malignancy affecting head and neck region. According to Globocon 2020 the worldwide incidence of new cases is 377713. India contributes to one-third of them with 135929, and has a 5year prevalence of 300413 per 100000 population [1,2]. Verrucous carcinoma is a well demarcated slow growing clinicopathologic variant of SCC. Surgical management is the main modality of management. Robust guidelines on its management are lacking owing to its rarity. We present our case series of oral verrucous carcinoma and literature review.

Materials and Methods

This is a descriptive and retrospective study of eight consecutive patients diagnosed to have oral verrucous carcinoma (OVC) in the resected tumor, in our institution during the 6 year period from January 2014 to December 2020. An institutional review board approval was taken to conduct this study.

The patients were staged according to american joint committee on cancer guidelines for oral carcinoma (eigth edition) based on clinical and radiologic findings. Patient demographics, clinicopathological features, treatment details and outcomes were analyzed. To follow up patients,telephonic interview and electronic medical records were used. The patients were followed up until December 2023.

Statistical analysis was done using SPSS software for windows version 16.0 Chicago, SPSS Inc. Patient characteristics were compared using *t* tests for continuous variables and a $\chi 2$ test for categorical variables.

Results

Eight of the 133 oral cavity carcinoma patients operated between 2014 and 2020 were oral

verrucous carcinoma patients (5.7%). The mean age of presentation was 55.3 years (range 40 to 80 years). Four patients were male and the other four were female. Seven of the eight patients had tobacco exposure. Buccal mucosa was the most common subsite affected, seen in 6 patients. Lesion size ranged from 3 to 7 cm. Two patients had clinical T4 disease at presentation. Patient demographics are described in Table No.1.

Table 1: Patient characteristics

Patient	Age	Gender	Subsite	Premalignant lesion	Preoperative biopsy	Number of biopsies
1	80	F	buccal mucosa lower alveolus	--	Atypical squamous proliferation	2
2	53	M	Buccal mucosa Hard palate	Submucous fibrosis	Atypical squamous proliferation	1
3	46	M	RMT	Leukoplakia	Dysplasia	5
4	40	F	Both side Lip commissure	Leukoplakia	Pseudoepitheliomatous hyperplasia	3
5	57	F	Buccal mucosa	Leukoplakia	Atypical squamous proliferation	2
6	70	M	Buccal mucosa	--	Squamous papilloma	2
7	46	M	Right lip commissure with buccal mucosa	submucous fibrosis	hyperplastic epithelial lesion with lichenoid inflammatory infiltrate	2
8	50	F	Right buccal mucosa		pseudoepitheliomatous hyperplasia	1

Three patients had clinically enlarged lymph nodes at presentation.

All the patients were treated with curative intent in view of clinical suspicion. All the patients underwent wide local excision. Separate margins were taken in all the patients. Extensive surgery including bone resection was done in 2 patients, one patient had hemimandibulectomy and infrastructural maxillectomy and the second patient had marginal mandibulectomy. All the patients had R0 resection. Reconstruction was done using radial artery forearm free flap, regional pectoralis major myocutaneous flap, local flap and split thickness skin graft. Neck was surgically addressed in the three patients, who had clinically enlarged lymph nodes. Two patients had modified radical neck dissection and one patient had supraomohyoid neck dissection.

In the final histopathology report, all the patients had pure verrucous carcinoma. Three patients had pT1, four patients had pT2, and one patient had pT3. None of the patients had lymphovascular invasion, perineural invasion, pathological bone invasion and hybrid verrucous carcinoma. No patient developed distant metastasis. One patient received adjuvant radiation in view of clinical T4 stage following multidisciplinary tumour board consensus.

Treatment and pathology details are described in table no.2 and table no.3

Table 2: Treatment

Patient	Surgery	Bone resection	pTumour size	Reconstruction	Adjuvant treatment
1	WLE	Marginal mandibulectomy	pT3	Radial artery forearm free flap	--
2	WLE	Hemimandibulectomy Infrastructural maxillectomy	pT2	Pectoralis major myocutaneous flap	Adjuvant RT clinical T4
3	WLE	-	pT1	SSG	--
4	WLE	-	pT1	SSG	--
5	WLE	-	pT2	SSG	--
6	WLE	-	pT1	SSG	--
7	WLE		pT2	local flap (modified gilles fan flap)	--
8	WLE	-	pT2		--

WLE – wide local excision SSG- Split thickness Skin Graft

Table 3: Neck node management

Patient	Clinical N	Neck dissection	Pathological N
1		MRND	Not involved
2		MRND	Not involved
3		Not addressed	Not involved
4		Not addressed	Not involved
5		SOHND	Not involved
6		Not addressed	Not involved
7		Not addressed	Not involved
8		Not addressed	Not involved

MRND – Modified Radical Neck Dissection SOHND – Supraomohyoid neck dissection

Reexcision was done in two patients, in one patient after 4 years and in the other patient after 16 months of primary surgery, but the final histopathology was reported as hyperplasia in both the patients. None of our patients had recurrence in the follow up until the study period.

Discussion

Oral VC is a rare variant of oral squamous cell carcinoma, with inherently good prognosis. According to Globocon 2020 its worldwide incidence is 377713. India contributes to one-third of them with 135929, and has a 5year prevalence of 300413 per 100000 population [1,2]. OVC contributed to 5.7 % of head and neck malignancy in our study. It is a carcinoma of old age, with male preponderance, described by various names in the literature, as, Buschke-Lowenstein tumor, florid oral papillomatosis, epithelioma cuniculatum, and carcinoma cuniculatum. [6]

Tobacco smoking, betel nut chewing, snuff usage, alcohol consumption are well established risk factors of oral verrucous carcionoma. Other suggested risk factors are undesirable prosthesis, edentulous, earlier injuries and scars, poor oral hygiene and chronic inflammation. Role of human papilloma virus (HPV) infection in OVC development is controversial and needs further research .[15,17,18] .[21] . Long standing oral verrucous leukoplakia is the most common premalignant lesion turning into OVC. The time taken for malignant transformation of leukoplakia could be as long as 10 years. (19) Oral submucous fibrosis, oral lichen planus, and odontogenic keratocyst are the other premalignant lesions associated with OVC [5,9,10] Premalignant lesions were seen in 4 of our patients. Three patients had leukoplakia and 1 had submucous fibrosis. One patient had leukoplakia for 3 years before seeking treatment.

The characteristic pathological features as first described by Ackermann are “downgrowth of fingers of hyperplastic epithelium gradually pushing rather than infiltrating their way into deeper tissues. The verrucous carcinoma induces or produces its own basement membrane around the tongues of the true invasion and, thereby, masking invasion”. Hence, OVC is misdiagnosed, in upto half (51%) of the incisional biopsies as noted by Gokavarapu etal [11] In 20 % OVC, foci of SCC is present, known as hybrid verrucous carcinoma. It behaves like oral SCC, depending on the percentage of SCC component [12] [24]. To diagnose hybrid verrucous carcinoma, an adequate broad and deep biopsy sample extending to the underlying bone for examination of the periosteum and the mucosa connective tissue interface is required. [21] Gokavarapu et al reported that in an incisional biopsy, it is difficult to identify the presence of SCC in OVC, despite advances in molecular, genetic, flow cytometry and immunohistochemical analysis. [11]. Repeat biopsy was performed in 22 patients in vidyasagar et al study, which delayed the initiation of definitive treatment from 3 months to 2 years. [10] Multiple biopsies were taken in 4 of our study patients. None of our patients had OVC at biopsy. An accurate diagnosis is possible only after definitive surgery

Verrucous carcinoma is seen most commonly in buccal mucosa, lower gingiva, retromolar area followed by larnyx. The most common site of verrucous carcinoma in our series was buccal mucosa. They are known to occur elsewhere in the body as well. [21] According to clinical manifestations and prognosis, verrucous carcinoma is divided into three types- exophytic type, cystoid type, and infiltrative type. The exophytic type with cauliflower like warty lesion, has slow growth . The other two types exhibit rapid growth and have bean dreg like appearance with white dry keratosis. Cystoid and infiltrative types have poorer prognosis compared to the exophytic type.The 3 clinical classes have different ultrastructural basis. [26]

Its clinical appearance is typical and unmistakable, with large warty tumour that invades contiguous structures. Multiple subsites involvement , advanced stage at presentation is often reported in literature. Vidyasagar et al observed that about threefourth of their patients had T3 or T4 disease at presentation and Walvekar et al study recorded 60.4% OVC patients in stage 3 and 4. (9)(10)(16)More than one subsite involvement was present in 3 of our cases. Duration of symptoms ranged from 45 days to 36 months in the present

case series. Long symptom duration was reported by vidyasagar etal, ranging from 2 months to 8 years [10] The common clinical differential diagnosis of verrucous carcinoma are SCC, viral verruca, amelanotic melanoma, histoplasmosis, secondary syphilis,white spongy nevus. [27]

Verrucous carcinoma is staged and treated as oral squamous cell carcinoma. Treatment options for OVC include surgery, radiation therapy(RT), chemotherapy, cryotherapy, laser therapy, photodynamic therapy, treatment with recombinant alpha interferon. The most common and curative treatment modality is surgical resection [21,30]. The goal of surgery is to attain resection margin of atleast 1 cm. A retrospective study on 101 patients of verrucous carcinoma by Walvaker et al has found excellent prognosis with surgical resection with adequate margins [9] . A large population study of National Cancer Database with records of 2350 VC suggest that patients undergoing surgery alone had excellent survival . [30] OVC can extensively infiltrate and destroy the adjacent structures including cartilage and bone. Pathological bone invasion was not seen in any of our patients despite clinical bone involvement. Rajendran et al study had reported bone invasion in 1.2% of their 426 OVC cases and Walveker etal noted it in 5.9% of their 101 cases. [5,9] Considering the low incidence of bone invasion, it may suffice to do a marginal mandibulectomy rather than a more extensive and morbid bone resection.

Regional lymph nodes enlarge in the inflammatory phase of OVC, but their pathological involvement is uncommon .Clinical regional lymph node enlargement was seen in 31 of the 101 patients of Walvaker etal study, but , none had pathological nodal involvement [9] . In our series, 3 patients had enlarged neck nodes and underwent neck dissection. However, none of the patients had pathological node involvement . Ackerman has reported that one patient out of 31 had histologically positive lymph node. [4] This risk of occult metastasis is seen when invasive component is missed in the biopsy. Sentinel lymph node biopsy in OVC would be a good research area to consider, to limit unnecessary morbidity due to the neck surgery. At present, there is no literature available addressing this aspect. When the neck nodes are clinically enlarged, it is reasonable to perform neck dissection when the pathological diagnosis is uncertain. [9]

Radiation therapy can be used to treat OVC as a definitive treatment and as an adjunct to surgery. Definitive RT was given when OVC was considered incurable, surgical procedure was morbid and when extensive comorbidities preclude surgery. In early studies, recurrence with aggressive anaplastic transformation has been noted with definitive RT in upto 30% of patients on an average of 6 months following irradiation with external supravoltage therapy. [19,31,13]. One explanation for this transformation is the origin of a highly aggressive new neoplasm due to disregulation of the cell lines of a slow-growing tumor resulting from radiation injury and another explanation is the hidden undifferentiated areas that proliferate later [16,33] . Recent studies dismiss RT induced anaplastic transformation as a valid concern. [10,32] Adjuvant RT after surgery has been used in retromolar area where surgical margin was a concern. [33,30] Radiation therapy is considered to be less effective in OVC compared to conventional OSCC. [41] One patient in our series received adjuvant radiation in view of close margin, and he did not develop any recurrence in 4 years follow up.

Due to its well differentiated appearance and slow growth, OVC was not expected to benefit from chemotherapy. Nevertheless, there are some case reports of chemotherapy to treat OVC from Japan [34]. [35] oral verrucous carcinoma has been treated with intraarterial methotrexate in 15 patients not suited for surgery and have recorded 100% local control at a median followup time of 43 months. [36] Chemotherapy may be an acceptable alternative in selected patients.

None of our study patients had true recurrence and distant metastasis. OVC is known for its stubborn recurrence after treatment, ranging from 30 to 50%. [16,19] The overall recurrence after surgical treatment in the 101 retrospective case study by Walvaker et al was 28% ,while it was 31% after radiation theray in vidyasagar et al study [9, 10] The higher recurrence rate of verrucous carcinoma could be due to the field cancerisation like effect of the affected area. [37] Presence of premalignant lesions in association with verrucous carcinoma and positive cut margin could contribute to the high recurrence as observed by Walveker etal. Despite the high recurrence rates, they are amenable to salvage surgeries in 66.7% of patients [9] If left untreated, it has the potential to turn into invasive oral squamous cell carcinoma [5] Distant metastasis are considered rare in verrucous carcinoma, and if it occurs, it could be due to missed occult foci of squamous cell carcinoma [38,39].The overall survival of verrucous carcinoma is over 80% and it is known to have inherently good prognosis. [7,9,30,40] Hence it is extremely essential to closely follow up these patients.

Conclusion

Verrucous carcinoma is characterised by inherently favourable prognosis . It displays local aggressive behavior and uncommon regional or distant metastasis. Surgical excision with adequate margin

is the most effective and standard treatment. When pathological diagnosis is uncertain, it is reasonable to treat based on clinical judgement/suspicion. There should be special emphasis on close follow up in view of high recurrence

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