RESEARCH PAPER

Clinical Spectrum, Treatment and Relapse Patterns in 353 Patients with Squamous Cell Carcinoma of the Alveobuccal Complex Treated with a Curative Intent: A Retrospective Study

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Abstract

Aims and Objectives Oral cancer is one of the most common cancers in Indian subcontinent with alveobuccal complex as most common cancer sub site. Cancers of Alveobuccal complex provides maximum challenge and management guidelines are not clear. The aim of the present study is to provide comprehensive demographic, clinical and treatment outcome data of alveobuccal squamous cell carcinoma (SCC) patients treated at a tertiary care cancer center in North India.

Materials and Methods An analysis of prospectively maintained database in department of surgical oncology at Dr BRA-IRCH, AIIMS, Delhi, India was performed. All alveobuccal cancer patients who had undergone surgery from 1995 to 2010 were included for analysis.

Results A total of 353 patients were included for analysis. Mean age was 49.75 years (SD ± 12.04) with male and female ratio of 4:1. Composite resection without mandible

was done in 25 % patients and 75 % underwent mandibular resection. Neck dissection was performed in 347 patients. Nodal deposits were identified in 124 (35.73 %) neck dissection specimens. Margin negative resection was performed in 89.5 % cases. After a median follow up of 30 months, 87 (24.64 %) patients developed disease relapse and 25 (7.08 %) patients developed second primaries. Overall 5-year disease free survival (DFS) was 57.65 % and 5 year overall survival (OS) was 59.86 %. **Conclusion** Among Indian oral cancer patients alveobuccal complex is most common sub site. Majority presents in locally advanced stage and reasonably good outcomes can be achieved with quality control surgery and judicious use of radiotherapy.

Keywords Oral cancer · Alveobuccal complex · Mandibulectomy · Survival

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Introduction

Oral cancer is a heterogeneous group of cancers including various sub sites of oral cavity. According to GLOBOCAN 2012 data, oral cavity cancer (including lip) is one of the three most common cancers in India with an overall annual incidence of 7.6 % [1]. Oral cancer is the most common cancer among Indian male patients with annual incidence of 11.3 % in comparison to USA where annual incidence is 2.1 %. Oral cancer is the fifth common cause of cancer related death in India [1]. Unlike in western countries where tongue is the most common site of oral cavity malignancies, alveobuccal region is the most common location in Indian population due to widespread use of smokeless tobacco in the form of chewing tobacco, nut and lime [2–4].

The term “Alveobuccal complex” is frequently used in the literature, although it is not defined and described as a separate area in the 7th edition of American Joint committee on Cancer staging. The cancers arising in alveobuccal sulcus are given a separate disease code-C06.1, in the International Statistical Classification of Diseases and Related Health Problems (tenth revision)—World Health Organization version [5]. For broader classification and international comparison, this site is included in the region “Buccal mucosa”. Buccal cancer is often considered together with other sub sites of oral cavity in the clinical studies, resulting in difficulty in interpretation. Buccal squamous cell carcinoma presumed to be more aggressive compared to other oral cavity cancers. Growths over the buccal mucosa can grow aggressively within a short span of time, as there are no anatomical structures, which can hinder the growth. Buccinator muscle and buccal pad of fat can easily be infiltrated by the tumors and present in the cheek skin [6]. Contrary to that, few recent studies have shown comparable survival of buccal cancer patients to other oral cavity sub sites [7].

Management guidelines for the management of alveobuccal cancers are not clear. The aim of the present study is to provide comprehensive demographic, clinical and treatment outcome data of patients diagnosed with alveobuccal squamous cell carcinoma presenting to a tertiary cancer center in India. This data can be used to formulate future guidelines as applicable and acceptable to our population.

Materials and Methods

Patient Selection

An analysis of the prospectively maintained computerized database in department of surgical oncology at DR BRAIRCH, AIIMS, New Delhi, India was performed. Patients who had undergone surgical treatment during June 1995–December 2010 with the diagnosis of carcinoma buccal mucosa and alveobuccal sulcus were identified. Based on the morphological features with respect to extent of spread and imaging findings, primary surgical notes were considered as final in the classification of sub-site. All patients who have pathologically proven squamous cell carcinoma and age above 12 years were included. Those patients who had undergone primary surgery in a different centre or did not have complete clinical information were excluded from the present study.

Management Protocol

All the patients were initially evaluated in a multi-disciplinary head and neck cancer clinic. Detailed history

including clinical presentation, history of risk factors, comorbidity, and family history was recorded for all patients. A detailed clinical examination was done to know the anatomical extent of index lesion, presence of other lesions, and status of neck nodes. Punch biopsy was undertaken in all patients for histopathological confirmation of diagnosis. Clinical findings were supplemented with appropriate radiological imaging whenever required for anatomical disease extent assessment. All the patients were re-staged as per the AJCC staging system based on tumor, node and metastatic extent of lesions during the study.

Surgical Protocol

The surgical protocol for head and neck cancer surgery at the institute was developed by first two authors (NKS and SVSD). All patients underwent wide excision or composite resection with three dimensional margins (1 cm) all around with or without skin or mandible resection whenever required. After tumor resection taking separate mucosal, soft tissue, skin and whenever required bone margins were the standardized protocols in all oral cancer surgeries. All the surgeries were either directly performed or performed under direct supervision of first two authors (NKS and SVSD) and same principles were followed in all surgeries. Apart from surgery pathological orientation of specimen and margins was also standardized for proper histological assessment. Selective neck dissection (Neck lymph nodes level 1–3) was performed for clinically node negative patients and comprehensive neck dissection was performed in node positive patients. For reconstruction, standard reconstructive ladder approach was followed including primary closure, skin grafts, local and regional flaps and micro-vascular free flap reconstruction.

Adjuvant Therapy Protocol

Radiotherapy was started within 4–6 weeks of surgery. Radiation dosages ranged from 60 to 64 Gray in 30–32 fractions (5 days a week) over 5–6 weeks by parallel-opposed field. Post-operative radiotherapy was planned for AJCC T3-T4 lesions, high risk factors (Positive/close margins, presence of lymphovascular and perineural invasion, positive neck node. Concurrent chemo-radiotherapy was added in case of positive margins or extra-capsular spread.

After completing the planned treatment patients were followed up every 3 months once in the initial 2 years and every 6 months once in the next 3 years. After 5 years patients were followed every year. Tumor characteristics, clinical findings, demographics, management protocols, treatment outcomes, follow-up details and recurrence patterns were collected and analyzed.

Statistical Analysis

All the statistical analyses were done using STATA 11.2 version. Chi² test was used to know the significant difference between categorical variables. Survival analysis was done using Kaplan–Meier method. Log-rank test was used to know the significant difference in survival among different variables. Cox proportional hazards model was used for the analysis of various prognostic indicators. In multivariate analysis, TNM stage grouping was removed from the model because of the co-linearity between T and N stage with the overall TNM staging.

Results

Overall in 15 years period between 1995 and 2010, 740 patients of oral cavity squamous cell carcinoma were operated in the department. A total of 353 (47.7 %) patients were diagnosed with carcinoma alveobuccal complex and they qualified for the final analysis of the present study. Two hundred and three patients (57.51 %) had carcinoma buccal mucosa and the remaining patients (41.64 %) had alveobuccal sulcus cancer.

Clinical Presentation

Mean age of patients was 49.75 years (SD $\pm$ 12.04); it ranged from 15 to 80 years. Men predominated over women with male to female ratio of 4:1. Tobacco chewing was the major risk factor (77.34 %). Majority (97 %) of the patients presented with ulcer in the oral cavity and 176 (49.45 %) patients also complained of pain and only 23 (6.5 %) complained about any neck swellings. Mean duration of these symptoms before presentation was 6 months and trismus, either because of the disease process or because of sub mucosal fibrosis was seen in 43.71 % of patients. Grossly 186 patients (56.37 %) had Ulceroproliferative tumors, 138 (39.09 %) patients presented with Ulceroinfiltrative lesions and 16 (4.53 %) were recorded to have verrucous lesions. Cheek skin involvement was noted in 139 (39.38 %) patients in whom 25 (7.08 %) had oro-cutaneous fistula at presentation. Clinically palpable lymphadenopathy was seen in 276 (78.2 %) patients. As far as the clinical stage was concerned, 17 (4.8 %) patients were staged as stage I disease, 22 (6.23 %) as stage II, 56 (15.86 %) as stage III and 258 (73.08 %) as stage IV disease.

Surgical Management Pattern

The approaches for the primary resection included trans-oral in 17 (4.82 %) patients and lip split cheek flap approach in 336 (95.18 %) patients. Lip split was done

through the angle in 250 (74.40 %) cases and through midline in 86 (25.60 %) patients. Composite resection without the removal of mandible was done in 88 (24.93 %) patients and the rest (75.07 %) underwent mandibular resection. Maxillary alveolectomy was done in 28 (7.93 %) patients. Mandibular resection included marginal mandibulectomy in 8 % of patients, Segmental in 11 %, Hemimandibulectomy in 74 % and extended Hemi-mandibulectomy in 7 % of the patients. Majority of the patients (279, 79 %) underwent modified radical neck dissection (MND). Radical neck dissection was required in 33 (9.35 %) and 35 (10 %) underwent selective (Level 1–3) neck dissection. PMMC flap was used for reconstruction in majority (64 %) and folded or Bi-paddle PMMC was used for external skin defect in 80 (22 %) patients. Reconstruction of soft tissue also included radial forearm free flaps in 3 patients. Mandibular reconstruction plate (MRP) was used in 36 (10.2 %) patients. There was no perioperative mortality and details of postoperative complications are depicted in Table 1.

Histopathological Evaluation

Histopathological evaluation revealed squamous cell carcinoma in 346 patients, which included 12 verrucous carcinomas. Well differentiated tumors diagnosed in 274 (79.19 %) patients, moderately differentiated in 69 (19.94 %) patients and only 3 patients had poorly differentiated tumor. No tumor could be identified in seven patients because of the previous excision biopsy (5 patients) or preoperative therapy (2 patients). Mean tumor size as per histopathological evaluation was 3.9 cm. Pathological skin and bone invasion was identified in 123 (34.84 %) and 101 (33.22 %) patients respectively. Negative resection margin was achieved in 316 (89.52 %) with a margin positive rate of 10.48 %. Close resection margins of <0.5 cm was reported in 28 (7.95 %) patients. Mean total lymph nodal yield was 16, ranging from 2 to 58 nodes. Nodal deposits in the tumor were identified in 124 (35.73 %) neck dissection specimens. None of the patients

Table 1 Postoperative complications

Complication	Frequency
Surgical site infection	30
Donor side morbidity	2
Flap necrosis	11
Secondary hemorrhage	6
Parotid fistula	3
Partial flap necrosis	29
Neck skin necrosis	5

Table 2 Correlation between clinical and pathological nodal status

	pN0 (%)	pN+	pN1 (%)	pN2 (%)	Total
cN0	55 (77.5)	16 (22.5)	12 (16.9)	4 (5.6)	71 (100)
cN1	98 (67.1)	48 (32.25)	28 (19.18)	20 (13.7)	146 (100)
cN2	70 (54.68)	58 (45.31)	14 (10.93)	44 (34.37)	128 (100)
cN3	0	2 (100)	0	2 (100)	2 (100)
Total	229 (65)	124 (35)	54 (15)	70 (20)	347 (100)

Fig. 1 Kaplan–Meier survival estimate for disease free survival

with contralateral neck dissection had microscopic lymph nodal metastasis (Table 2).

Adjuvant Therapy

A Total of 222 patients (62.88 %) received post-operative radiotherapy. The planned treatment could not be given in 38 patients (10.75 %) either because the patient defaulted (76 %) or delayed because of the postoperative complications and logistic issues and hence not given (24 %). Systemic therapy in the form of either methotrexate or 5-fluorouracil and cisplatin based chemotherapy was given to 9.35 % patients.

Recurrence Patterns: Local, Regional and Systemic Relapse

Overall 87 (24.64 %) patients developed disease relapse and 25 (7.08 %) patients developed second primaries. Sites of recurrence included 49 (13.9 %) patients with only local site, 16 (4.5 %) only regional, 12 (3.4 %) patients with simultaneous loco-regional recurrence and 10 (2.83 %) patients developed systemic relapses with 2 of them having loco-regional disease as well. Among the patients who had loco-regional recurrences, 20 patients underwent curative surgical resection followed by adjuvant therapy. Among these 20 patients, 12 patients developed second recurrence,

Fig. 2 Kaplan–Meier survival estimate for overall survival

which could not be salvaged and received either palliative radiotherapy and/or chemotherapy or advised best supportive care.

Outcomes: Disease Free and Overall Survival

At a median follow up of 30 months, 256 (72.52 %) were alive and disease free, 20 (5.67 %) patients were alive with disease and 77 (21.81 %) patients were died of disease. Overall 5-year disease free survival (DFS) was 57.65 % and 5 year overall survival (OS) was 59.86 % (Figs. 1, 2).

Prognostic Factors

On univariate analysis margin status, nodal stage, skin invasion, size and final stage were significant for disease free survival. On multivariate analysis, tumor margins, nodal stage and post-operative radiotherapy compliance turned out to be predictors of disease relapse.

On univariate analysis margin status, bone invasion, nodal stage, skin invasion, final stage and postoperative radiotherapy compliance were significant for overall survival (Tables 3, 4). On multivariate analysis, tumor margins, tumor stage (T) nodal stage (N) and adjuvant radiotherapy compliance turned out be markers for overall survival (Tables 5, 6).

Table 3 Univariate analysis for disease free survival

Variable	Univariate hazards ratio (confidence interval)	<i>P</i> value
Positive tumor margins		0.001
Negative	1	
Positive	2.43 (1.43–4.14)	
Skin involved		0.001
No	1	
Yes	2.05 (1.34–3.14)	
T stage		
T1	1	
T2	1.35 (0.52–3.5)	0.53
T3	2.17 (0.78–6)	0.13
T4	3.48 (1.59–7.61)	0.002
N stage		
N0	1	
N1	1.78 (1.04–3.03)	0.03
N2	2.21 (1.30–3.75)	0.003
TNM stage		
Stage 1	1	
Stage 2	0.75 (0.2–2.8)	0.67
Stage 3	1.81 (0.64–5.13)	0.27
Stage 4	3.5 (1.41–8.7)	0.007
Post operative RT		
Planned but not received	1	
PORT completed	0.28 (0.15–0.50)	<0.001

Margin of Resection

Margin positive resection was a marker of poor prognosis for disease free and overall survival in both univariate and multivariate models. Among the patients with margin negative resection, 5-year disease free survival was 61 % and for the group with margin positive resection, it was 30 %. The difference in survival was statistically significant ($P = 0.003$). Hazard ratio for margin positive resection in comparison with margin negative resection was 2.43 (1.43–4.14, $P = 0.001$).

Nodal and Tumor Stage Grouping (AJCC)

On univariate analysis, nodal metastasis categorized as N0, N1 and N2 showed a significant difference in both disease free or overall survival. The hazard ratios (HR) of disease relapse for N1 and N2 were 1.78 (1.04–3.03, $P = 0.03$) and 2.21 (1.3–3.75, 0.003) respectively in comparison to the tumors with N0 disease (Tables 3, 4). On multivariate analysis, Nodal stage was an independent prognostic factor of disease relapse and overall survival (Tables 5, 6). T4a disease was marker of poor prognosis both for disease relapse and mortality in univariate analysis. Tumor stage as such was an independent prognostic marker of overall survival (higher the tumor stage lesser the survival).

Discussion

Oral cancer is one of the most common cancers in Indian subcontinent. Disparity exists in spectrum of oral cavity cancer and in India and due to peculiar habits of tobacco use alveobuccal complex is most common sub site [2–4]. To the best of our knowledge, this study is one of the largest retrospective analysis of the patients diagnosed as carcinoma alveobuccal region and curatively treated in India. All the data was recorded prospectively and uniform institutional management guidelines were followed. Various retrospective studies report single institutional or multi-institutional experience with carcinoma buccal mucosa from different parts of the world. Many of these studies include all the oral cavity sub-sites in a single prognostic model [8] or include the patients who did not receive any curative treatment [9] for prognostic analysis. The present study is from a group of patients who attended our tertiary cancer center situated in North India and completed treatment at a single institution.

In the present study 265 (75 %) patients required mandibular resection for clearing the primary. Compared to other contemporary studies [10], the mandibular resection rate is higher in our study. There is obvious discrepancy between number of mandibular resections (75 %) and final number of cases with pathological bone invasion (33 %).

Table 4 Univariate analysis for overall survival

Variable	Univariate hazards ratio (confidence interval)	<i>P</i> value
Tumor margins		
Negative	1	
Positive	2.41 (1.37–4.22)	0.002
Bone involved	1	0.03
No	1.68 (1.05–2.69)	
Yes		
Skin involved	1	<0.001
No	2.23 (1.44–3.44)	
Yes		
T stage	1	0.47
T1	1.46 (0.52–4.11)	0.36
T2	1.74 (0.53–5.7)	0.001
T3	4.42 (1.91–10.24)	
T4		
N stage		
N0	1	
N1	1.87 (1.09–3.24)	0.024
N2	2.14 (1.21–3.8)	0.009
TNM stage		
Stage 1	1	
Stage 2	1.05 (0.26–4.2)	0.95
Stage 3	1.88 (0.58–6.12)	0.27
Stage 4	4.67 (1.7–12.86)	0.003
Post operative RT	1	<0.001

Table 5 Multivariate analysis for disease free survival

Variable	Hazard ratio	Confidence interval	<i>P</i> value
Post operative RT compliance (protective role of RT)	0.29	0.18–0.48	<0.001
Tumor margins	2.13	1.25–3.63	0.005
Nodal (N) stage	1.39	1.07–1.79	0.012

Table 6 Multivariate analysis for overall survival

Variable	Hazards ratio	Confidence interval	<i>P</i> value
Post operative RT compliance (protective role of RT)	0.46	0.26–0.8	0.006
Tumor margins	2.28	1.29–4.01	0.004
Nodal (N) stage	1.45	1.1–1.9	0.008
Tumor (T) stage	1.42	1.11–1.83	0.005

Conventional mandibulectomy indications are not applicable to alveobuccal region because of proximity of cancer to the mandible and significant Para-mandibular soft tissue component. Hence a large number of patients have mandibulectomy even in absence of clinical involvement.

Microscopic margin negative resection is the ultimate goal of all the radical surgeries for oral cancers. In the present series we could achieve margin negative resection in up to 90 % of the patients. Reported margin positivity rates varied from 5 to 57 % in literature [10–14]. A low

margin negative rate was possible because of quality controlled surgery with a consistent aim to achieve three dimensional resection free margins and adopting defect oriented margin assessment methods.

As far as reconstruction of complex alveolo-buccal defects is concerned the priority is restoring soft tissue bulk and a significant proportion of patients with skin loss also need skin cover. Pectoralis major myocutaneous (PMMC) flap as a single or bi-paddle variant provides a simple, quick and reliable option in high volume resource

constrained centers [15] and recently free flaps are being used with increasing frequency.

Buccal carcinoma presumed to have less nodal metastasis compared to other sub sites of oral cavity. Clinical nodal involvement in present series was 78 % however pathological nodal positivity was 35 %. Reported Clinical and pathological nodal involvement varies from 24 to 38 % in other contemporary series in the literature [11, 16–19]. Deo et al. [20] from the same centre reported overtreatment of neck in oral cancer with clinical neck node enlargement in 76 % but only 38 % pathological nodal positivity. However recent randomized controlled trial from Tata memorial center has proven the benefit of elective neck dissection in oral cancer patients [21]. Table 2 shows the correlation between clinical and pathological node positivity in the present series. Higher frequency of clinical nodal involvement in our patients may be because of skin invasion and fungating, which results in infection and reactionary nodal enlargement.

Loco regional relapse are the most common failures in buccal cancer with rates of 25–55 % in most of the series [11, 14, 16, 17, 22]. Diaz et al. [16] reported overall recurrence of 45 % with local recurrence of 32 %. Jan et al. [11] reported 55 % loco regional recurrence rate in a series of 415 buccal cancer patients. Overall loco regional recurrences were observed in 62 (18 %) patients in whom 49 (14 %) had pure local recurrences in present series. These results highlight the importance of good quality control surgery and adjuvant PORT.

Overall 5-year disease free survival (DFS) of 57.65 % and 5 year overall survival (OS) of 59.86 % were slightly inferior to most of the contemporary series. Reported 5 year survival varies from 63 to 80 % in literature [10, 11, 14, 16]. Overall 73 % cases were of stage IV in present series which might be an explanation for poor survival figures. Reported 5 year survival for stage IV were 50 % by Diaz et al. [16] and 53 % by Jan et al. [11].

Similar to our study the various prognostic factors reported in the literature include Tumor size, Nodal positivity and extra-nodal extension, T stage, perineural extension, tumor thickness, Skin and bone invasion, Margin of resection [11–13, 18, 23].

Conclusion

Alveobuccal cancer is the most common sub site of oral cancers constituting around 50 % of all oral cavity cancers in India. Majority of the patients presents with loco-regionally advanced stage due to the lack of awareness and lack of access to comprehensive cancer facilities. A significant number of patients require mandibulectomy, neck dissection and flap reconstruction in-view of loco-

regionally advanced disease at presentation. However our experience has shown that good outcomes can be achieved with quality controlled radical surgery along with adjuvant radio or chemoradiotherapy.

Compliance with Ethical Standards

Conflict of interest Nootan kumar Shukla, S V Suryanarayana Deo, Ashish Jakhetiya, Manjunath NML, Vishnubhatla Sreenivas, Sanjay Thulkar, Suman Bhasker and Atul Sharma declare that they have no conflict of interest.

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