



Clinicopathologic Determinants of Outcome in Pathologic T4a (pT4a) Squamous Cell Carcinoma of the Gingivobuccal Subsite of the Oral Cavity

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Abstract

Carcinoma of the gingivobuccal complex is one of the most common cancers in India and patients usually present in an advanced stage. There is limited data in literature regarding the factors predicting outcome in pathological T4a patients. In this study, we aimed to study the clinic-pathological factors which may influence treatment outcomes in pT4a patients. This is a retrospective study of 121 patients who underwent surgery for oral squamous cell carcinoma between August 2011 and December 2016, staged pT4a. Overall survival (OS) and disease-free survival (DFS) were analyzed for variables including age, depth of invasion, margin status, differentiation, nodal status, extranodal spread, lymphovascular and perineural spread, and adjuvant treatment. The study cohort comprised 93 males with mean age 60.28 years (S.D. 11.25). Median DFS was 21 months (range 9 to 2374 days) whereas median OS was 24.5 months (range 9 to 2374 days). On univariate analysis, lymphovascular invasion, perineural invasion, cervical nodal metastasis, and extranodal extension had a statistically significant effect on both DFS and OS. On multivariate analysis, age ($p = 0.014$) and adjuvant radiotherapy ($p = 0.010$) were the statistically significant factors affecting OS. None of the factors affected DFS on multivariate analysis. Patients staged pT4a with cervical nodal metastasis, extranodal extension, lymphovascular invasion, and perineural invasion have reduced OS and DFS. On multivariate analysis, lower age at presentation and adjuvant radiation improved patient outcome.

Keywords Squamous cell carcinoma · Gingivobuccal subsite · Oral cavity · pT4a tumours

Introduction

Oral cancer is one of the commonest cancers seen in the Indian Subcontinent, of which the gingivobuccal (GB) complex (buccal mucosa, upper and lower alveolus, retromolar trigone) is closely linked to the habit of chewing betel quid containing tobacco [1]. In contrast to western populations, most Indian patients present in advanced stages [1]. Surgery with adequate three-dimensional margins with neck dissection and adjuvant

radiation or chemoradiation forms the mainstay of treatment in these patients.

There has been an expanded interest in describing survival outcomes in patients involving various oral cavity sub-sites. These efforts are primarily guided by attempts to provide evidence-based data on optimal management of primary sub-sites and the neck. pT4a disease of the oral cavity represents a heterogeneous group, comprising patients with involvement of intrinsic muscles of the tongue, involvement of bone or skin as per the American Joint Committee on Cancer (AJCC) edition 7 [2]. In Southeast Asia, GB complex carcinoma are thought to have different etiological and clinic-pathological characteristics when compared to oral tongue squamous cell cancer, raising the argument that these cancers should have a different staging system compared to other oral cavity cancers [1, 3]. Close proximity of gingiva-buccal (GB) complex tumors to alveolar bones makes them susceptible for early invasion in GB complex tumors as compared to tongue tumors [1].

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GB complex carcinoma poses unique challenges to surgeons due to early mandibular invasion and regional metastases [4]. Literature reporting outcomes of pathologically staged T4 (pT4a) lesions is sparse.

In this study, we aimed towards identifying factors that would prognosticate the outcome of patients with pT4a GB complex squamous cell carcinoma, in terms of disease-free survival (DFS) and overall survival (OS). We also compared the outcomes of these patients with respect to involvement of skin or bone, by virtue of which these tumors are staged as pT4a.

Materials and Methods

This is a retrospective study comprising patients who underwent surgery for oral squamous cell carcinoma from August 2011 to December 2016. All patients were included in this study who underwent tumor resection as their primary method of treatment for their GB complex tumor and the final histopathology was reported as pT4a. Patients were excluded from this study if their primary lesion did not originate from the GB complex, or they had history of prior treatment. Patients also were excluded if adequate follow-up data could not be obtained or accurately verified.

OS and DFS were the two outcome variables analyzed. Other study variables included adjuvant treatment with radiation or chemotherapy (any dosage or type of radiotherapy (RT) or chemoradiation (CTRT) used after primary resection recorded as yes or no), pN stage, tumor margin (involved (< 1 mm), close (1–4.9 mm), or free (5 mm or more)), tumor cell differentiation (as documented on the pathology report), and presence of lymphovascular invasion, perineural invasion, skin involvement, and cervical nodal metastasis. The TNM classification of malignant tumors, as defined by the AJCC (Edition 7), was used for staging each patient and pathologic pTNM stage was determined from the pathology reports [2].

Data were abstracted from the patients' medical records. Data analysis was done using SPSS 17 (SPSS, Inc., Chicago, IL). Kaplan-Meier survival curves were used to estimate OS and DFS by subgroups based on baseline prognostic factors. Log-rank tests were used for comparing survival curves in prognostic subgroups. A multivariate Cox proportional hazard model was used to test the hypothesis of increased hazard or risk of death. The level of statistical significance for all tests was < 0.05.

Observation and Results

In 696 patients who underwent surgery for oral squamous cell carcinoma from August 2011 through December 2016, 121 patients had pathological T4a disease of the GB complex.

The patient population comprised 93 males, with mean age of 60.28 years (S.D. 11.25). Mean depth of invasion was 1.91 cm with a standard deviation of 1.25. Amongst these, 121 patients, margins were free in 86 patients (71%). Twenty-four (20%) and 11 (9%) patients had close and involved margins respectively. Twenty-eight patients had extranodal extension amongst 55 who had cervical nodal metastasis (Table 1). Seven patients had tumor reported as well differentiated, while 99 patients had moderately differentiated tumors. Twenty-nine patients received adjuvant CTRT, whereas 76 patients received adjuvant RT. Eleven patients refused adjuvant treatment. The decision for the adjuvant treatment was taken after a multidisciplinary discussion. Weekly cisplatin 40 mg/m² was used as the chemotherapeutic agent in concomitant chemoradiation (CTRT) protocols, while RT was delivered in conventional dose of 2Gy/fraction, 5 days per week to a cumulative dose of 60–64 Gy.

Median DFS was 21 months (range 9 to 2374 days) whereas median OS was 24.5 months (range 9 to 2374 days) (Fig. 1). There were 25 instances of recurrence and 39 deaths in this cohort of patients. On univariate analysis using Kaplan-Meier survival analysis, lymphovascular invasion (LVI), perineural invasion (PNI), cervical nodal metastasis, and ENE had a statistically significant effect on both DFS and OS (Table 1).

In 25 patients who had recurrence, 12 patients had a local recurrence alone, while isolated nodal recurrence and distant metastasis was seen in 3 and 2 patients respectively. Five patients had a locoregional recurrence while one patient had locoregional failure along with distant metastasis. One and two patients had distant metastasis when they were diagnosed with local and nodal recurrence respectively. Other sub-sites in oral cavity were most commonly involved in local failure (70%), viz. buccal mucosa including upper and lower GB sulcus (10 patients), infratemporal fossa (6 patients), lower alveolus (2 patients), upper alveolus (one patient), and upper alveolus (one patient).

On multivariate Cox Regression analysis, age ($p = 0.014$) and adjuvant radiotherapy ($p = 0.010$) were statistically significant factors affecting OS. None of the factors affected the DFS on multivariate analysis (Table 2).

On analyzing the pathological features in patients who had skin involvement against those who had only bone involvement, there was no statistically significant difference except for tumor differentiation which was associated with bone invasion (Table 3). The DFS ($p < 0.001$) and the OS ($p < 0.001$) in patients with skin involvement was better than patients with bone involvement and both bone and skin involvement on Kaplan-Meier analysis (Fig. 2).

Amongst 55 patients who had positive nodes, level Ib was involved in 40 patients (33.05%) and was the only level involved in 23 patients. Isolated level II metastasis was seen in 8 (6.61%) patients. Levels IV and V were involved in only one case (0.82%) and two cases (1.65%), respectively. However,

Table 1 Factors affecting DFS and OS (univariate analysis, $N = 121$)

Factor	Number of patients (%)	Number of recurrences (%)	Number of deaths (%)	P value	
				DFS	OS
Differentiation					
Well	7 (5.78)	0	1 (14.28)	0.430	0.240
Moderate	99 (81.81)	22 (22.22)	31 (31.31)		
Poor	15 (12.39)	3 (20)	7 (46.67)		
Margin					
Free	86 (71.07)	22 (25.58)	26 (30.23)	0.103	0.509
Close	24 (19.83)	1 (4.16)	9 (37.5)		
Involved	11 (9.09)	2 (18.19)	4 (36.37)		
Lymphovascular invasion (LVI)					
Negative	81 (66.94)	13 (16.04)	21 (25.92)	0.061	0.037
Positive	40 (33.05)	12 (30)	18 (45)		
Perineural invasion (PNI)					
Negative	76 (62.80)	10 (13.15)	14 (18.42)	0.004	< 0.001
Positive	45 (37.19)	15 (33.33)	25 (55.56)		
Cervical nodal metastasis					
Absent	66 (54.54)	10 (15.15)	10 (15.15)	0.013	< 0.001
Present	55 (45.45)	15 (27.27)	29 (52.72)		
Extranodal extension (ENE)					
Absent	93 (76.85)	17 (18.27)	21 (22.58)	0.023	< 0.001
Present	28 (23.14)	8 (28.57)	18 (64.28)		
Adjuvant treatment					
None	11 (9.09)	4 (36.36)	4 (36.36)	0.182	0.805
RT	76 (62.80)	15 (19.73)	24 (31.57)		
CTRT	29 (23.96)	6 (20.68)	10 (34.48)		
Skin involvement					
Absent	97 (80.16)	21 (21.64)	32 (32.98)	0.808	0.989
Present	24 (19.83)	4 (16.67)	7 (29.16)		

levels IV and V were never involved in isolation without involvement of levels I, II, or III. Four cases had contralateral

level Ib metastasis and one patient had contralateral level IIa metastasis.

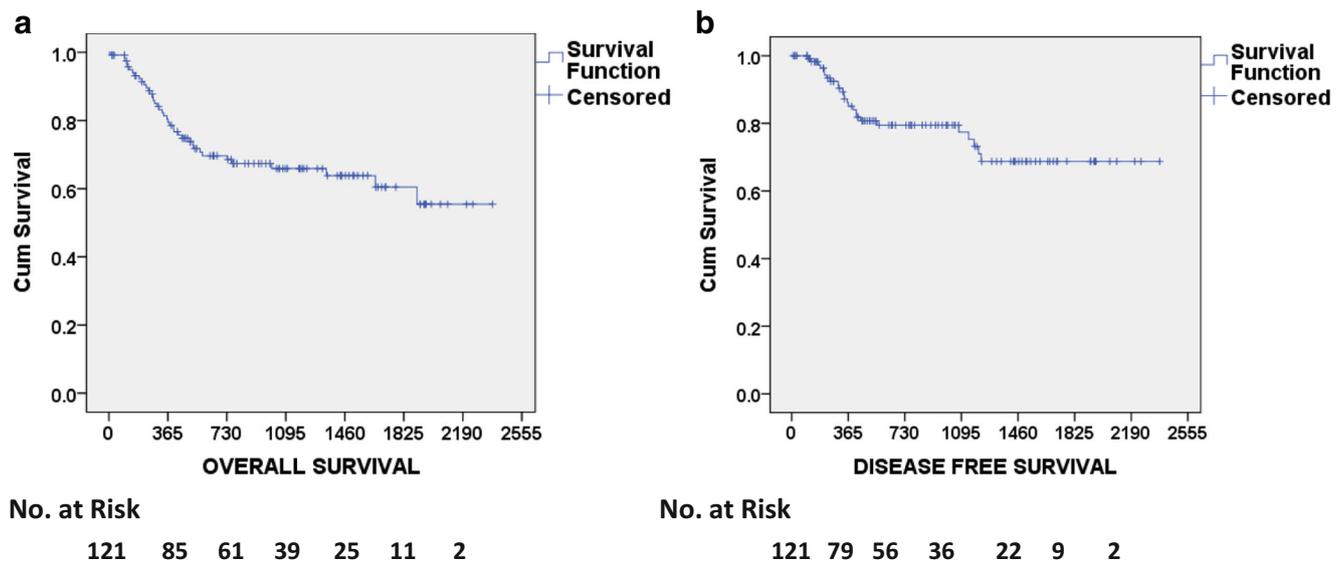


Fig. 1 Kaplan-Meier analysis. **a** Disease-free survival. **b** Overall survival

Table 2 Factors affecting DFS and OS (multivariate analysis)

Factor	P value	
	DFS	OS
Age	0.801	0.014
Gender	0.890	0.190
Maximum size	0.699	0.118
Depth	0.871	0.070
Well differentiated	0.908	0.257
Moderately differentiated	0.798	0.413
Poorly differentiated	0.502	0.352
Margin-free	0.900	0.171
Margin-close	0.778	0.504
Margin-involved	0.647	0.347
Lymphovascular invasion (LVI)	0.781	0.333
Perineural invasion (PNI)	0.652	0.074
Cervical node involvement	0.830	0.084
Extranodal extension (ENE)	0.826	0.239
Adjuvant treatment—none	0.716	0.028
Adjuvant treatment—RT	0.446	0.010
Adjuvant treatment—CTRT	0.807	0.366
Skin involvement	0.893	0.605

Discussion

Squamous cell carcinoma of the buccal mucosa is the most common form of oral cancer in Southeast Asian countries [5]. Cancer in this subsite is related to the habit of chewing dried and cured tobacco leaf, betel nut, and slaked lime [6]. This mixture is highly irritating to the oral mucosa and results in a variety of lesions, ranging from premalignant lesions to overt

malignancies. In sharp contrast to patients in the Western world where early presentation is more common, most patients in India present late, requiring mandibular resection for adequate clearance [1].

In this study, 75% of the patients were males. This high proportion of males in patients of GB complex carcinoma can be explained by the more common use of smokeless tobacco by Indian males [7]. The mean age at presentation is 60.28 years, which correlates with Chhetri et al., who reported the mean age of presentation in the fifth and early sixth decades in Asian populations [8].

According to AJCC classification 7th edition, GB complex tumors involving skin and/or bone on pathological examination are staged as pT4a. In our cohort of 121 patients, 97 patients had bone involvement, 13 patients had skin involvement alone, whereas 11 patients had both skin and bone involvement. Despite advanced pT stage, only 45.45% (55 out of 121) patients had nodal involvement.

The tumors staged as pT4a by virtue of bone involvement alone showed similar histopathological characteristics compared to those who had skin involvement, except for differentiation. We believe that the small number of well differentiated tumors (7, 5.78%) preclude any meaningful conclusion from the clinically significant difference in the tumor differentiation amongst these two groups.

In our study, 2-year OS and DFS in our patients was 80% and 69% respectively (Figs. 1 and 2). On univariate analysis, cervical nodal metastasis, LVI, PNI, and ENE were the factors that showed statistically significant impact on both OS and DFS. But on multivariate analysis, none of these factors were found statistically significant to predict DFS and OS. Age and adjuvant radiation significantly affected OS.

Table 3 Pathological features skin involvement vs bone involvement alone (univariate analysis)

Factor	Bone involvement only (%)	Skin involvement present (%)	P value
Differentiation			
Well	3 (3.09)	4 (16.67)	0.037
Moderate	82 (84.53)	17 (70.83)	
Poor	12 (12.37)	3 (12.50)	
Margin			0.094
Free	66 (68.04)	20 (83.33)	
Close	23 (23.71)	1 (4.16)	
Involved	8 (8.24)	3 (12.50)	
Lymphovascular invasion (LVI)			0.423
Negative	64 (65.97)	17 (70.83)	
Positive	33 (34.02)	7 (29.17)	
Perineural invasion (PNI)			0.323
Negative	64 (65.97)	12 (50)	
Positive	33 (34.02)	12 (50)	
Cervical node metastasis			0.572
Absent	53 (54.67)	13 (54.16)	
Present	44 (45.36)	11 (45.83)	
Extranodal extension (ENE)			0.411
Absent	76 (78.35)	20 (83.33)	
Present	21 (21.64)	4 (16.67)	

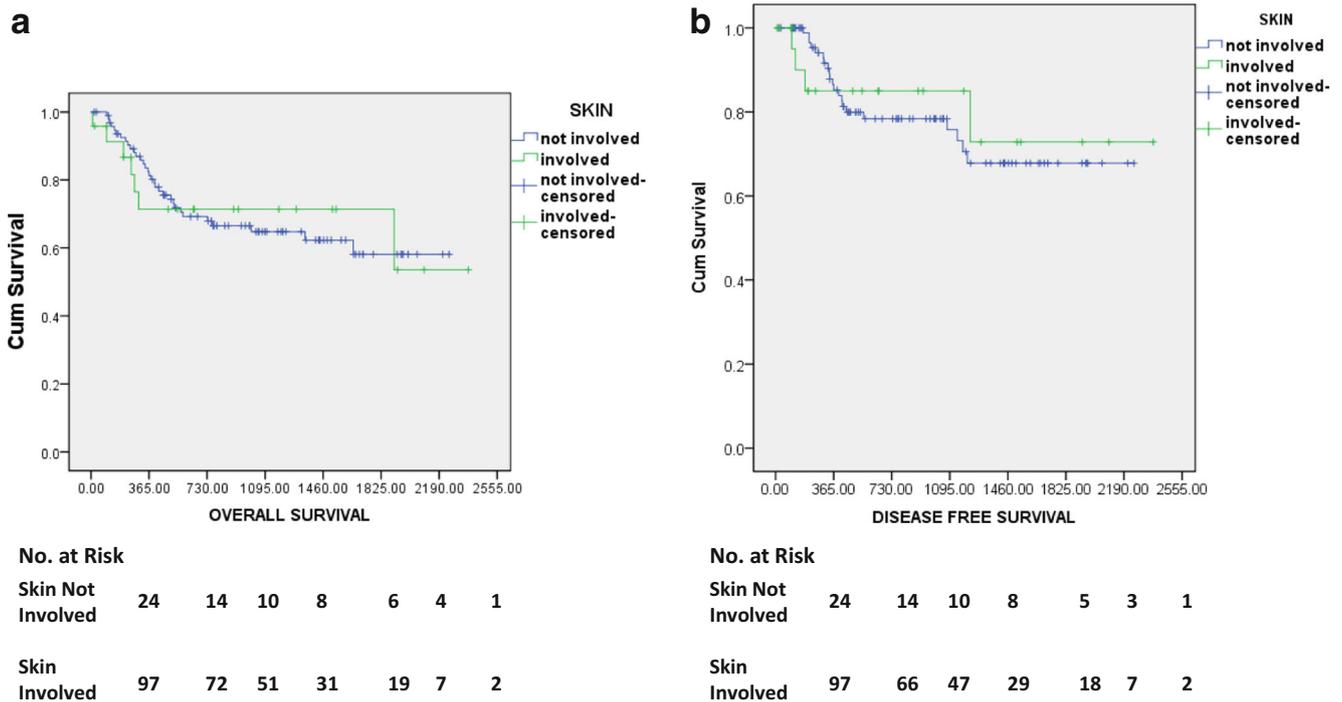


Fig. 2 Kaplan-Meier analysis for patients with and without skin involvement. **a** Overall survival. **b** Disease-free survival

Recurrence and survival of patients with GB complex cancers depend on various factors such as tumor size, nodal involvement, bone involvement, grade of tumor, and positive surgical margins [9–11]. Pathak et al. reported that skin infiltration, extracapsular extension of nodal disease, and adjuvant radiotherapy to be the only significant factors influencing disease-free survival [1]. Liao et al., when comparing the T4a and T4b lesions, found that lymph node (pN2) rather than tumor status was the sole significant adverse factor in T4a and T4b patients for 5-year local control, disease-free survival and overall survival [12].

In our study, surgical margins failed to show statistically significant impact on OS and DFS. There is increasing evidence on redefining the adequacy of surgical margins in oral cavity carcinoma from the arbitrary cutoff of 5 mm. Zanoni et al. showed that in patients with squamous cell carcinoma of oral tongue, margin of 2.2 mm stratified the risk for local recurrence better than the arbitrary 5.0-mm cutoff that has been traditionally used [13]. This study emphasizes the need to investigate more into the issue of what constitutes an adequate surgical margin.

Ipsilateral level Ib was the most common site for nodal metastasis, followed by ipsilateral level IIa. The first echelon nodes for squamous cell carcinoma of the GB complex are at level I or II [14]. Level IV and V nodal metastases were seen only in 3 cases, albeit these levels were never involved in isolation. D’Cruz et al. have recommended selective neck dissection clearing level I–III as a staging procedure to evaluate for occult metastatic

disease in clinically early, node negative oral cavity squamous cell carcinoma [15, 16].

In 25 patients who had recurrence, other sub-sites in oral cavity were most commonly involved in local failure (70%) probably reflecting field cancerization as a consequence of irritant substance abuse. Infratemporal fossa clearance was done in 42 patients in this cohort which could have contributed to a low recurrence rate in the infratemporal fossa. Similar observations have been noted in earlier studies on buccal cancers [1, 17]. This emphasizes the need for aggressive locoregional management for OSCC.

In 2005, Pathak et al. noted that T4 gingivobuccal cancers represent a diverse group, with tumors that are T4 by virtue of skin (soft tissue) infiltration faring much worse than those because of mandible (bone) invasion and it was important to distinguish between the two because of their different biologic behavior [1]. In our study, the histopathological features in patients having skin involvement were similar to those who did not have skin involvement. But the patients with skin involvement showed better OS and DFS as compared to the patients with bone involvement or involvement of both bone and skin. However, the number of patients in the groups were limited; drawing a definite conclusion from this outcome would be fallacious.

This study is limited by its retrospective design which makes it difficult to study the effect of different types of substance use and patient comorbidities on the incidence and outcome of the disease.

Conclusion

Overall survival and disease-free survival are reduced in pathological T4a patients with cervical nodal metastasis, extranodal extension, lymphovascular invasion, and perineural invasion. On multivariate analysis, lower age at presentation and adjuvant radiation improved patient outcome.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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