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# Prognostic determinants of locally advanced buccal mucosa cancer: Do we need to relook the current staging criteria?

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ABSTRACT

*Objectives:* Current guidelines advocate non-surgical treatment for T4b buccal mucosa carcinoma with surgery preferred in other stages. We investigated oncologic outcomes of this cohort in comparison with T4a cohort, treated by similar multi-modality approach of primary surgery followed by adjuvant treatment and identified prognostic determinants of survival.

*Materials and methods:* Oncologic outcome of prospectively accrued 282 patients with cT4a and cT4b buccal mucosa squamous cell carcinoma were evaluated for overall survival (OS) and disease free survival (DFS) at 2 years of the whole cohort and for the subgroups of T4a and T4b patients. Multivariate Cox proportional hazards regression analysis was performed to identify prognostic determinants.

*Results:* Of 277 eligible patients treated and followed for a median period of 21 months, the OS was comparable between T4a and T4b as 64% vs 58%, ($p = 0.354$). The DFS between the two subgroups was 64% vs 61%, ($p = 0.316$). Although there was 47% pathologic down staging from the clinical stage, there was no significant difference in oncologic outcome between pT4a and pT4b (OS, 57% vs 58% for T4a and T4b, $p = 0.687$; DFS, 58% vs 60% for T4a and T4b, $p = 0.776$). On multivariate analysis, extra capsular spread ($p = 0.042$), lateral pterygoid muscle involvement ($p = 0.035$) and defaulting adjuvant treatment ($p < 0.001$) were independent predictors of outcome for the T4b cohort when other factors were controlled.

*Conclusions:* Primary surgery followed by adjuvant chemo-radiotherapy offers comparable results in selected T4b gingiva and buccal mucosal cancer, suggesting the need to relook the staging criteria for oral cavity cancer.

## Introduction

Oral squamous cell carcinoma (OSCC), the sixth most common cancer globally, has significant heterogeneity in its risk factors, sub-site susceptibility and geographic predilection [1–3]. Tongue and floor of mouth (CO2.0, CO4.0) [4] are the common subsites of oral cancer in low-prevalent European and North American populations [1]. However, in high-prevalent South-East Asian populations, where chewing ofarecanut and tobacco products is the primary risk-factor, buccal mucosa (CO6.0, CO6.2) [4] is the predominant subsite [1–3].

*Abbreviations:* OS, overall survival; DFS, disease free survival; OSCC, oral squamous cell carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; 3DCRT, three dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; BSA, body surface area; PNI, perineural invasion; LVI, lymphovascular invasion; ECS, extra capsular spread

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**Table 1**
Demographic, tumor and treatment data of cT4a and cT4b buccal mucosa cancer patients.

| Demographic parameter | | cT4a n-96 (34.7%) | cT4b n-181 (65.3%) | p |
|---|---|---|---|---|
| Age | | 53.54 (SD:12.55) | 52.02 (SD:12.84) | 0.343 |
| Gender | Male | 55 (57.3%) | 110 (60.7%) | 0.448 |
| | Female | 41 (42.7%) | 71 (39.2%) | |
| Radiologic parameters | Class I | NA | 130 (71.8%) | |
| | Class II | NA | 43 (23.8%) | |
| | Class III | NA | 8 (4.4%) | |
| | Bone involvement | 82 (85.4%) | 143 (79.0%) | |
| | Skin involvement | 44 (45.8%) | 35 (19.3%) | |
| | Nodal involvement | 55 (57.3%) | 144 (79.6%) | |
| Risk habits | Tobacco chewing | 80 (83.3%) | 90 (49.7%) | |
| | Tobacco smoking | 40 (41.7%) | 60 (33.1%) | |
| | Alcohol | 70 (72.9%) | 125 (69.1%) | |
| Karnofsky Performance status | 90–80 | 96 | 181 | |
| N-stage | N0 | 41 (42.7%) | 37 (20.4%) | |
| | N+ | 55 (57.3%) | 144 (79.5%) | |
| | ycT4a/T4b | 16 (16.7%) | 15 (8.3%) | |
| | ycN0 | 8 (8.3%) | 3 (1.6%) | |
| | ycN+ | 8 (8.3%) | 12 (6.6%) | |
| Adjuvant treatment | RT * (116, 41.8%) | 50 | 66 | |
| | CTRT (122,44.0%) | 31 | 91 | |
| Defaulted treatment | RT | 5 | 3 | |
| | CTRT | 10 | 8 | |

cT4a, clinical T4a; cT4b, clinical T4b; SD-standard deviation; NA-not applicable; N-stage-nodal stage, N0-node negative; N+ node positive; y-post induction chemotherapy; RT-radiotherapy; CTRT-chemoradiation.

* Intensity modulated radiotherapy (IMRT): n = 190(80%), Three dimensional conformal radiotherapy (3DCRT) : n = 48(20%).

The extent of tumor invasion is the primary criteria that determines the T- classification of OSCC, with involvement of skin and bone stratifying the patients as T4a, whereas masticator space, pterygoid plates, skull base and internal carotid artery involvement is classified as T4b [5,6]. While involvement of skin, bone and masticator space is a late event for oral tongue as it requires traversing many anatomic spaces, the proximity of buccal mucosa to bone, skin and muscles of mastication, leads to early involvement of these structures in buccal mucosa cancers. This leads to a large proportion of the buccal tumors being classified as either T4a or T4b [7,8].

According to the current management guidelines, all oral cavity tumors irrespective of subsites, classified as T4b are considered very advanced disease with recommendation for non-surgical treatment whereas, surgery is the primary curative-intent treatment modality for all other T-classes of oral cancer [6,9].

This treatment recommendation for T4b buccal mucosa squamous cell carcinoma was recently questioned by few authors who have observed favorable outcomes when treated with surgery [10–13].

Herein we report oncologic outcome of multi-disciplinary treatment of moderately advanced (T4a) and selected very advanced (T4b) buccal mucosa cancers. We have further evaluated the T4b cohort based on prognostic determinants to improve precision in staging.

## Materials and methods

### *Patients*

This was a prospective study of 282 consecutive patients with locally advanced (cT4a, cT4b) biopsy proven squamous cell carcinoma of gingiva and buccal mucosa (CO6.0, CO6.2) [4] treated at a tertiary cancer center from July 2009 to December 2016. Prior approval from the institutional review board was obtained. The primary imaging modality used was contrast enhanced computed tomography (CT) scan of the head, neck and chest. Magnetic resonance imaging (MRI) was carried out in eight patients with a concern of skull base or perineural invasion. The inclusion criteria for the study were (a) biopsy proven OSCC, (b) patients who have received prior non-surgical treatment (induction chemotherapy/chemoradiation) with persistent biopsy proven disease and clinically staged as either yT4a or yT4b. Surgical treatment was considered only if R0 resection was feasible.

The exclusion criteria for the study were (a) intracranial extension of the tumor, (b) involvement of the internal carotid artery, (c) patients with poor performance status.

Five patients with the aforementioned criteria were excluded from the study. The cohort of 31 patients treated by primary non-surgical modality were those who underwent treatment elsewhere and referred for possible salvage surgery. All these patients presented with residual local disease staged as either yT4a or yT4b. There were 16 patients staged as yT4a and 15 patients as yT4b. Twenty patients had persistent nodal disease. Induction chemotherapy was used as the primary modality in 30 patients and radiotherapy in one patient.

The demographic data is presented in Table 1 and Supplementary Table 6. The study cohort is depicted in the CONSORT Diagram, Fig. 1.

### *Treatment protocol*

The treatment decision was made in a multidisciplinary tumor board. The patients underwent curative-intent surgery followed by adjuvant treatment based on the final histopathology [6]. The surgery entailed compartmental composite resection including the contents of infratemporal fossa [13–15] and neck dissection. The defect was reconstructed using either a free soft tissue flap or regional flap. Positive resection margins with or without presence of extracapsular nodal extension of tumor received chemoradiation whereas presence of multiple nodes, pT3 or pT4, presence of PNI, LVI received adjuvant radiotherapy [16].

### *Protocol for adjuvant treatment*

Adjuvant radiotherapy was given within six weeks of surgery using either 3-dimensional conformal radiotherapy (3DCRT) or Intensity Modulated Radiotherapy (IMRT) technique to the primary surgical field and bilateral neck region with inclusion of the infratemporal fossa (Table1). Concurrent chemotherapy used Cisplatin 100 mg/m$^2$ body surface area (BSA) on days 1, 22, 43 or 30–40 mg/m$^2$ BSA in weekly regimen [17].

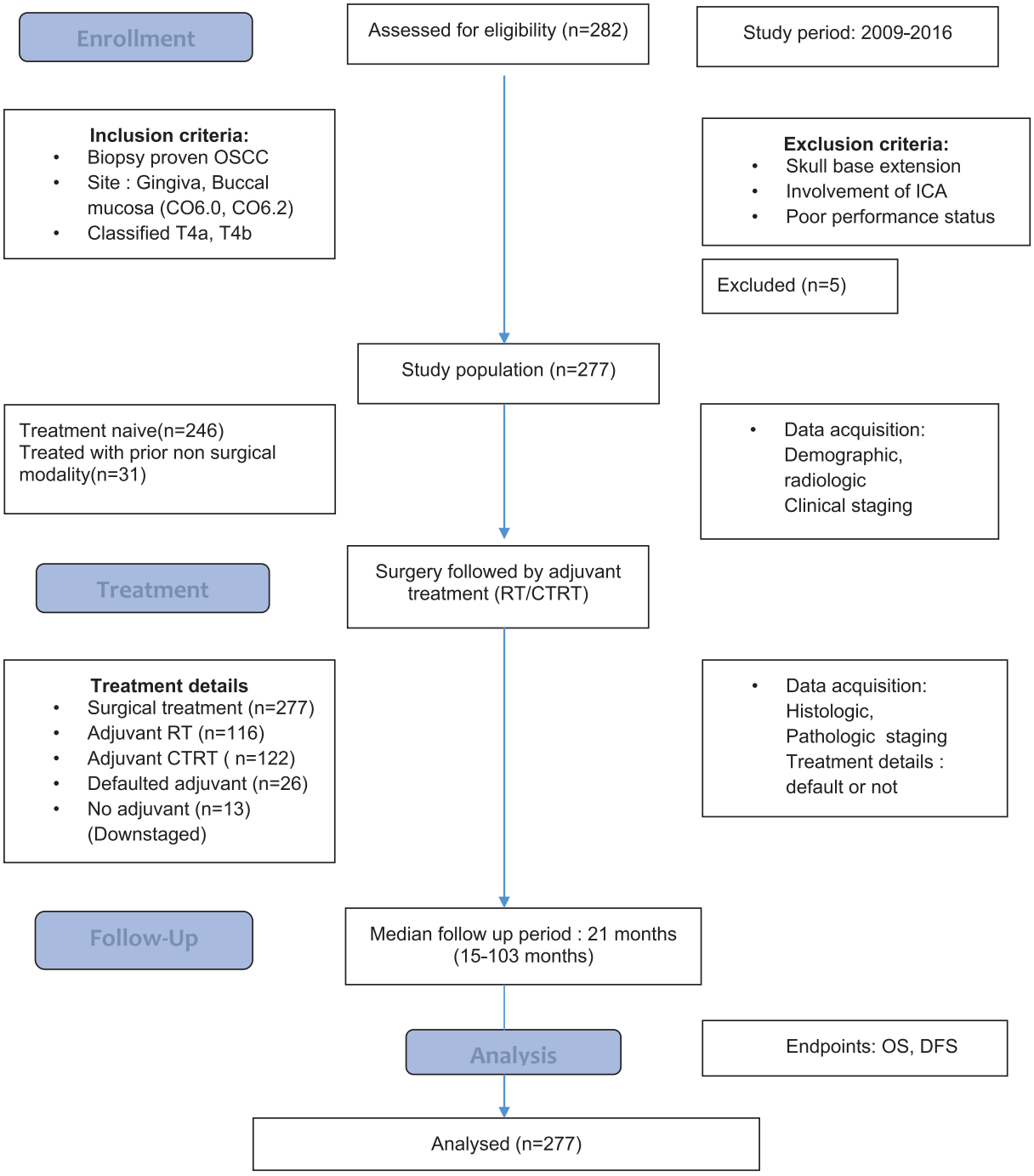


**Fig. 1.** CONSORT Diagram depicting the study design. Abbreviations: OSCC, oral squamous cell carcinoma; ICA, internal carotid artery; RT, radiotherapy; CTRT, chemoradiation; OS, overall survival; DFS, disease free survival.

*Surveillance protocol*

The patients were reviewed every month during the first 6 months and subsequently every 2–3 months for the next 6 months. During the second year, the follow up was every 3–4 months and every 4–6 months in the third year. The patients underwent a baseline post treatment CT scan at 3–4 months after completion of treatment [6]. Additional scans were obtained depending on the clinical indications. Patients were evaluated for any evidence of loco-regional or distant disease relapse. Patients who were lost to follow up were censored after the last follow up.

*Data acquisition and analysis*

The patient information was retrieved from a prospectively designed clinical data base. The data obtained included demographic details, risk-habits, Karnofsky performance score, clinical staging as per AJCC 7th edition criteria [5], detailed imaging interpretation of the of the primary and nodal disease, date of treatment initiation and completion, details of surgery and adjuvant treatment and synoptic surgical pathology report [18].

A single radiologist evaluated all the imaging studies and enlisted the structures that were involved by the tumor. This included the involvement of specific muscles of mastication (masseter, medial pterygoid, lateral pterygoid, temporalis), pterygoid plates, foramen ovale,

**Table 2**
Pathologic stage migration.

| Stage migration | n | Percentage | Pathologic stage | | n | Percentage |
|---|---|---|---|---|---|---|
| cT4b to pT4a | 64 | 35.4% | pT4a | | 117 | 42.2% |
| cT4a to pT4b | 22 | 22.9% | pT4b | | 118 | 42.6% |
| | | | | Class I | 79 | 66.9% |
| | | | | Class II | 28 | 23.7% |
| | | | | Class III | 11 | 9.3% |
| cT4b to less than T4 | 21 | 11.6% | < T4 | | 42 | 15.2% |
| cT4a to less than T4 | 21 | 21.9% | | | | |

n, number; cT4a, clinical T4a; pT4a, pathologic T4a; pT4b, pathologic T4b; cT4b, clinical T4b.

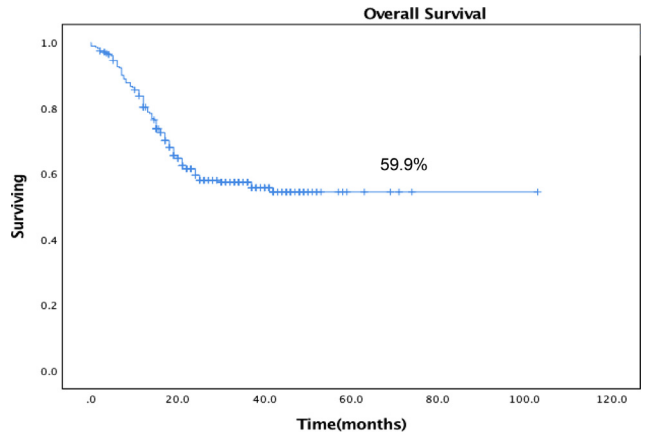


**Fig. 2a.** Kaplan Meier analysis. Depicting overall survival at 2 years for the T4 cohort of buccal mucosa cancer patients.

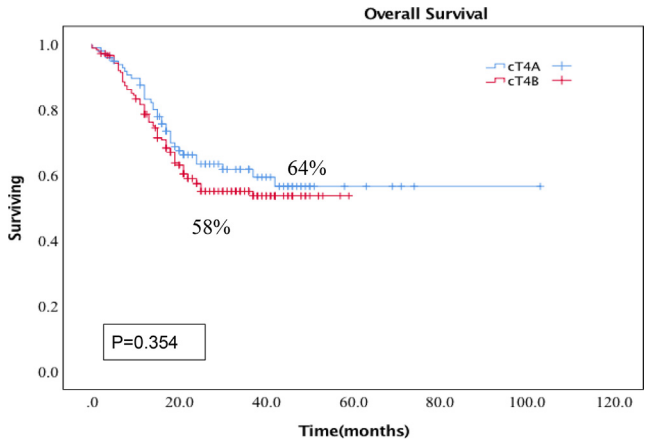


**Fig. 2b.** Kaplan Meier analysis. Comparing overall survival at 2 years for cT4a and cT4b cohort of buccal mucosa cancer patients.

foramen rotundum, inferior orbital fissure, pterygomaxillary fissure, maxillary and mandibular bone and skin. The status of perineural spread, nodal metastasis and lungs were also noted.

Based on this information the patient cohort was subdivided as cT4a, cT4b. The T4b category was further sub-classified into Class I, II, III based on the classification system proposed by Trivedi et al. [8]. Class-I: involvement of any of the following structures below the sigmoid notch-masseter and medial pterygoid (lower masticatory space, infra-notch), Class-II: involvement of lateral pterygoid, temporalis above the sigmoid notch (intermediate masticatory space, low supra-notch), and Class III: involvement of pterygomaxillary fissure, inferior orbital fissure and intracranial space (high-masticatory space, high supra-notch).

Following surgery, the histopathologic parameters were analyzed that included differentiation, tumor thickness, presence or absence of perineural invasion (PNI), lympho-vascular invasion (LVI), involvement of skin, bone (mandible, maxilla). The margin status has been recorded as per the AJCC staging criteria (as R0, R1, R2) [5] and as free (> 1.0 mm), close or involved (< 1.0 mm), and gross tumor at the surgical margins (cut-through margins) [19,20]. The location of the close margin was recorded for the skin, mucosa, bone and deep soft tissue.

In addition, the muscles involved, and the invasion of the pterygoid plates were recorded. The lymph nodes were assessed for metastasis and extra-capsular spread (ECS). Based on this information patients were pathologically restaged. The pT4b category was further subdivided into Class I, II, III as per the criteria described before [8]. According to the pathological staging the adjuvant treatment was recommended. The patients were followed up till March 2018 as per the protocol described before. All patients were followed for at least 15 months (median 21 months) after the completion of the treatment or until death.

### *Statistical analysis*

Statistical analysis was carried out using SPSS 25.0 (IBM) software. The OS was defined as the time from diagnosis to death from any cause or time of last contact. DFS was defined as the period from the date of completion of treatment till the date of first recurrence, either local, regional or distant. The OS and DFS were calculated for the whole cohort and separately for the cT4a and cT4b, and pT4a and pT4b cohorts. OS and DFS were estimated by the Kaplan Meier method. Univariate analysis by log rank test was carried out to examine the significance of the clinical and pathological prognostic variables on survival at two years. Prognostic variables identified in this analysis were considered in univariable Cox proportional hazards regression and those with $p < 0.05$ were subsequently considered in a multivariate Cox proportional hazard model to simultaneously examine the effect of these variables.

## Results

The study population consisted of 165 (59.6%) males and 112 (40.4%) females. The age of the patients ranged between 25 and 86 years with a median of 52 years. According to the TNM staging, 96 (34.7%) patients were classified as cT4a and 181 (65.3%) as cT4b.

Radiologic evaluation revealed 130 (71.8%) as class I, 43 (23.8%) as class II and 8 (4.4%) as class III. The demographic features and treatment were comparable between the T4a and T4b groups as shown in Table 1.

The histopathologic characteristics of the T4a and T4b groups were comparable (Supplementary Tables 1 and 2). The number of close or positive surgical margins (R1) were 1 (0.9%) in T4a cohort and 8 (6.8%) in T4b cohort. The distribution of site of close/involved margins is as follows- skin margins 1 and 3 patients and deep soft tissue margin from the infratemporal fossa in 0 and 5 patients in T4a and T4b cohort respectively. None of the bone margins were close or positive (Supplementary Table 2).

Pathologic examination of the surgical specimen revealed significant stage migration, predominantly to a lower pathologic stage. Overall stage migration was observed in 44.7% of T4a and 46.9% of T4b patients as shown in Table 2 and Supplementary Fig. 1. The histopathologic sub-classification of the pT4b group showed 66.9% Class I, 23.7% Class II and 9.3% Class III. The most commonly involved muscles that stratified the tumor as pT4b were the medial pterygoid (n = 81, 68.6%) followed by the masseter (n = 66, 55.9%), lateral pterygoid (n = 30, 25.4%) and the temporalis (n = 13, 11.0%). The pterygoid

**Table 3**
Factors affecting overall survival (Univariate and Multivariate Analysis).

| Parameter | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | p | HR | 95% CI | p |
| pT4a | WDSCC | 1.437 | 0.770–2.682 | 0.254 | | | |
| | MDSCC | 1.894 | 0.772–4.647 | 0.163 | | | |
| pT4b | WDSCC | 1.385 | 0.684–2.803 | 0.366 | | | |
| | MDSCC | 2.222 | 0.845–5.848 | 0.106 | | | |
| PNI + | pT4a | 1.152 | 0.665–1.998 | 0.614 | | | |
| | pT4b | 2.360 | 1.345–4.140 | 0.003 | 1.620 | 0.826–3.176 | 0.161 |
| LVI + | pT4a | 1.830 | 1.028–3.256 | 0.040 | 1.095 | 0.569–2.109 | 0.785 |
| | pT4b | 3.080 | 1.768–5.366 | < 0.001 | 2.087 | 1.018–4.279 | 0.044 |
| ECS + | pT4a | 2.039 | 1.175–3.537 | 0.011 | 1.591 | 0.844–2.998 | 0.151 |
| | pT4b | 2.368 | 1.360–4.123 | 0.002 | 1.728 | 0.920–3.244 | 0.002 |
| Skin involvement | pT4a | 2.011 | 1.160–3.488 | 0.013 | 2.476 | 1.382–4.435 | 0.002 |
| | pT4b | 1.207 | 0.643–2.267 | 0.558 | | | |
| Mandibular bone + | pT4a | 0.858 | 0.489–1.506 | 0.594 | | | |
| | pT4b | 0.809 | 0.455–1.437 | 0.469 | | | |
| Maxillary bone + | pT4a | 1.589 | 0.869–2.904 | 0.133 | | | |
| | pT4b | 1.078 | 0.617–1.884 | 0.792 | | | |
| Soft tissue (ITF) margin | pT4a | 1.131 | 0.352–3.636 | 0.836 | | | |
| | pT4b | 1.372 | 0.883–2.132 | 0.160 | | | |
| Muscle involvement (all pT4b) | Masseter | 0.847 | 0.488–1.472 | 0.556 | | | |
| | Medial pterygoid | 0.894 | 0.503–1.588 | 0.702 | | | |
| | Lateral pterygoid | 1.798 | 1.011–3.196 | 0.046 | 1.616 | 0.877–2.978 | 0.123 |
| | Temporalis | 1.077 | 0.428–2.711 | 0.875 | | | |
| Defaulting adjuvant treatment | pT4a | 7.208 | 3.570–14.553 | < 0.001 | 8.210 | 3.864–17.447 | < 0.001 |
| | pT4b | 5.932 | 2.832–12.426 | < 0.001 | 7.117 | 3.252–15.574 | < 0.001 |
| Class II & III | pT4b | 1.332 | 0.754–2.351 | 0.323 | | | |

HR, hazard ratio; CI, confidence interval; pT4a, pathologic T4a; pT4b, pathologic T4b; WDSCC, well differentiated squamous cell carcinoma; MDSCC, moderately differentiated squamous cell carcinoma; PNI, perineural invasion; LVI, lymphovascular invasion; ECS, extra capsular spread; ITF, infratemporal fossa.

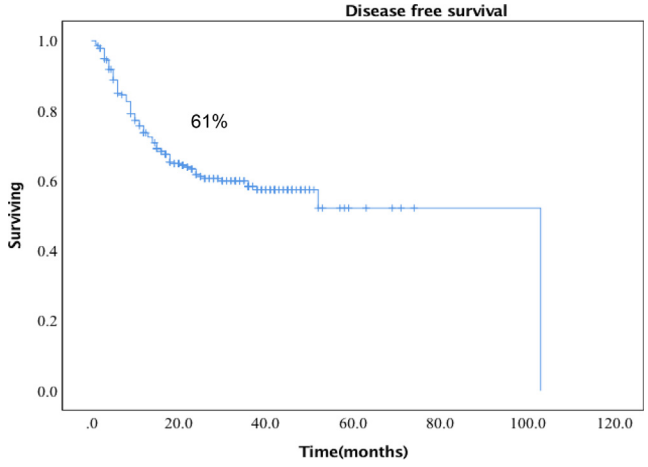


**Fig. 2c.** Kaplan Meier analysis. Depicting disease free survival at 2 years for the T4 cohort of buccal mucosa cancer patients.

plates were involved in 11 patients (9.3%).

All but 13 patients (4.7%) were recommended adjuvant treatment as they were pathologically down-staged to less than Stage III. One hundred and sixteen patients (41.8%) received adjuvant radiotherapy, 122 patients (44%) received adjuvant chemoradiation. Twenty-six patients (9.38%) defaulted adjuvant treatment (Table 1). The median follow-up period of the patient cohort was 21 months (15–103 months).

*Patterns of failure*

Distant metastasis was seen in 75 patients (27.1%), local recurrence in 49 patients (17.7%) and regional recurrence in 28 patients (10.1%). One-hundred-and-twenty-three patients were disease free at the last follow up. There was no significant difference in recurrence between T4a and T4b cohorts and the T4b sub-classes as shown in Supplementary Fig. 2(a), (b) and (c) and Supplementary Table 3.

*Overall survival estimates*

The overall survival at two years was 59.9% for the whole cohort (Fig. 2a), 64% and 58% for cT4a and cT4b respectively (Fig. 2b). For pT4a and pT4b it was 57% and 58% respectively, Supplementary Fig. 3(a). The mean overall survival for the T4a cohort was 64.8 months (95% CI, 55.06–74.54; p = 0.500) and for the T4b cohort 38.4 months (95% CI, 34.80–41.93; p = 0.500). In the T4b cohort the mean overall survival for Class I, II and III were 40.2 months (95% CI, 36.17–44.23; p = 0.027) and 29.7 months (95% CI, 23.23–36.23; p = 0.027) respectively. The clinico-pathological variables associated with the survival are summarized in Supplementary Table 4.

The parameters that were significant on univariate analysis in the T4a cohort, were LVI (p = 0.040), ECS (p = 0.011), skin involvement (p = 0.013) and defaulting adjuvant treatment (p < 0.001). Multivariable Cox regression analysis identified presence of skin involvement (p = 0.002) and defaulting adjuvant treatment (p < 0.001) to be significant determinants of overall survival such that the hazard ratio for defaulting adjuvant treatment was 8.2 (Table 3). For T4b cohort, the variables that were significant on univariate analysis were PNI (p = 0.003), LVI (p < 0.001), ECS (p = 0.002), lateral pterygoid involvement (p = 0.046) and defaulting adjuvant treatment (p < 0.001). On multivariable Cox regression analysis the presence of LVI (p = 0.044) and defaulting adjuvant treatment (p < 0.001) were significant determinants of overall survival for the T4b cohort as shown in Table 3.

*Disease free survival estimates*

The DFS at two years of the whole patient cohort was 61%, Fig. 2(c), 64% and 61% for cT4a and cT4b respectively, Fig. 2(d). For pT4a and pT4b groups it was 58% and 60% respectively, Supplementary Fig. 3(b). The variables that were associated with DFS are shown in Supplementary Table 5. The mean disease free survival time for the T4a cohort was 62.0 months (95% CI, 56.28–67.71; p = 0.325) and for the T4b cohort was 47.2 months (95% CI, 43.67–50.75; p = 0.325). The

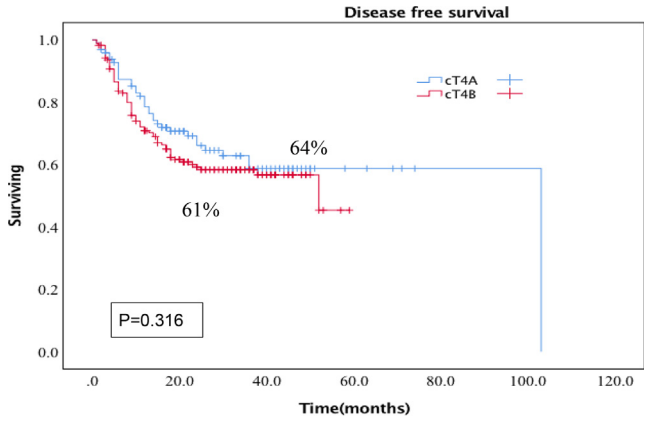


**Fig. 2d.** Kaplan Meier analysis. Comparing disease free survival at 2 years for cT4a and cT4b cohort of buccal mucosa cancer patients.

significant prognostic factors of DFS for the whole cohort were nodal status along with defaulting adjuvant treatment.

For the T4a cohort, the factors that were significantly associated with DFS on univariable analysis were ECS (p = 0.017), maxilla involvement (p = 0.036) and defaulting adjuvant treatment (p < 0.001). All these associations were significant in the multivariable Cox regression analysis of DFS (Table 4).

The factors that were significantly associated with DFS in T4b cohorts on univariable analysis were ECS (p = 0.005), LVI (p = 0.007), defaulting adjuvant treatment (p < 0.001) and lateral pterygoid involvement (p = 0.039). Multivariable Cox regression analysis also identified ECS (p = 0.042), LVI (p = 0.066), lateral pterygoid involvement (p = 0.035) (Fig. 3c) and defaulting adjuvant treatment (p < 0.001) (Fig. 3d) to be statistically significant (Table 4). In the T4b cohort the DFS for Class I, II and III were 64%, 51% respectively. (Supplementary Table 5) The survival was not significantly different between Class I and pT4a, p = 0.172 (Fig. 3a) and the various subdivisions of the T4b cohort, p = 0.151 (Fig. 3b).

*Survival estimates in the salvage cohort*

For the subgroup of 31 patients who had received primary non-surgical modality of treatment followed by surgical salvage, the overall and disease free survival was significantly lower in comparison to primary surgery followed by adjuvant treatment (2 year overall survival between salvage and primary surgery cohort, 36.7 vs 64.6, 95% CI 25.841–47.477, p = 0.026; disease free survival between primary surgery and salvage cohort, 62.1 vs 32.8, 95% CI 53.623–70.521, p = 0.023). At the last follow up only 12 patients (38.7%) were disease free in this cohort (Supplementary Tables 4, 5).

## Discussion

Over 70 to 90% of oral cancer patients present with loco-regionally advanced stage [2,3]. However, there is paucity of data in the literature to guide treatment of this cohort of patients [6]. Although induction chemotherapy followed by surgery and/or chemo-radiotherapy have been attempted, because of the lack of clinical impact, surgery followed by adjuvant radiation or chemo-radiation remains the standard of care as curative-intent treatment [6,21–26]. For T4b tumors surgery is technically challenging, leading to triaging many of these patients to non-surgical modalities.

The current NCCN guideline recommends non-surgical treatment for oral cavity cancers with masticatory space involvement [6], with reported overall survival of 6.68 months [12]. Attempts have been made to improve resectability in patients with technically unresectable buccal cancers with induction chemotherapy followed by surgery and concurrent chemo-radiotherapy. Adopting this approach, Patil et al in a series of 721 patients with technically unresectable buccal cancers reported response rate of 43% to induction chemotherapy and overall

**Table 4**
Factors affecting disease free survival (Univariate and Multivariate Analysis).

| Parameter | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95% CI | p | HR | 95% CI | p |
| pT4a | WDSCC | 1.745 | 0.887–3.433 | 0.107 | | | |
| | MDSCC | 2.421 | 0.951–6.164 | 0.063 | | | |
| pT4b | WDSCC | 1.209 | 0.590–2.474 | 0.817 | | | |
| | MDSCC | 2.358 | 0.895–6.215 | 0.083 | | | |
| PNI + | pT4a | 1.059 | 0.490–2.288 | 0.884 | | | |
| | pT4b | 1.670 | 0.674–4.142 | 0.268 | | | |
| LVI + | pT4a | 1.695 | 0.754–3.812 | 0.201 | | | |
| | pT4b | 3.488 | 1.414–8.605 | 0.007 | 1.900 | 0.958–3.768 | 0.066 |
| ECS+ | pT4a | 2.009 | 1.131–3.569 | 0.017 | 1.851 | 0.987–3.470 | 0.055 |
| | pT4b | 2.328 | 1.298–4.174 | 0.005 | 1.968 | 1.024–3.780 | 0.042 |
| Skin involvement | pT4a | 1.444 | 0.812–2.567 | 0.211 | | | |
| | pT4b | 1.221 | 0.639–2.335 | 0.545 | | | |
| Mandibular bone + | pT4a | 0.898 | 0.502–1.609 | 0.719 | | | |
| | pT4b | 1.121 | 0.629–1.998 | 0.699 | | | |
| Maxillary bone + | pT4a | 2.329 | 1.055–5.138 | 0.036 | 2.118 | 1.081–4.150 | 0.029 |
| | pT4b | 0.593 | 0.213–1.647 | 0.316 | | | |
| Soft tissue (ITF) margin | pT4a | 1.216 | 0.377–3.921 | 0.743 | | | |
| | pT4b | 1.261 | 0.777–2.045 | 0.348 | | | |
| Muscle involvement (all pT4b) | Masseter | 0.754 | 0.423–1.344 | 0.339 | | | |
| | Medial pterygoid | 0.980 | 0.529–1.817 | 0.949 | | | |
| | Lateral pterygoid | 1.875 | 1.032–3.404 | 0.039 | 1.854 | 0.992–3.467 | 0.035 |
| | Temporalis | 1.243 | 0.491–3.147 | 0.647 | | | |
| Defaulting adjuvant treatment | pT4a | 7.769 | 3.826–15.778 | < 0.001 | 6.536 | 3.094–13.807 | < 0.001 |
| | pT4b | 7.406 | 3.338–16.428 | < 0.001 | 8.549 | 3.704–19.728 | < 0.001 |
| Class II & III | pT4b | 1.539 | 0.859–2.758 | 0.147 | | | |
| Salvage surgery | pT4a | 2.912 | 1.436–5.906 | 0.003 | 3.436 | 1.644–7.179 | 0.001 |
| | pT4b | 0.755 | 0.234–2.439 | 0.639 | | | |

HR, hazard ratio; CI, confidence interval; pT4a, pathologic T4a; pT4b, pathologic T4b; WDSCC, well differentiated squamous cell carcinoma; MDSCC, moderately differentiated squamous cell carcinoma; PNI, perineural invasion; LVI, lymphovascular invasion; ECS, extra capsular spread; ITF, infratemporal fossa.

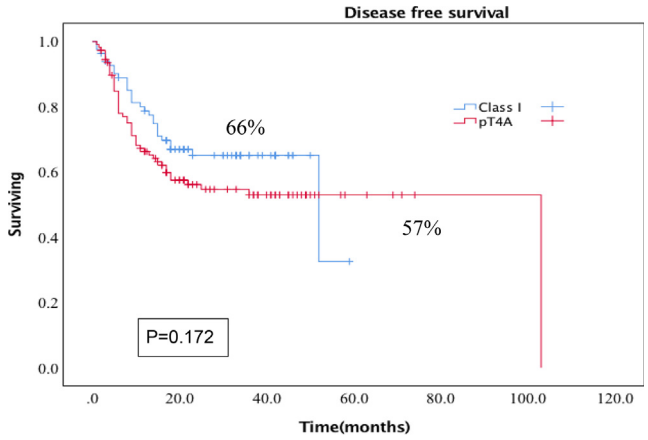


**Fig. 3a.** Kaplan Meier analysis. Comparing disease free survival at 2 years of T4a with Class I T4b cohort of buccal mucosa cancer patients.

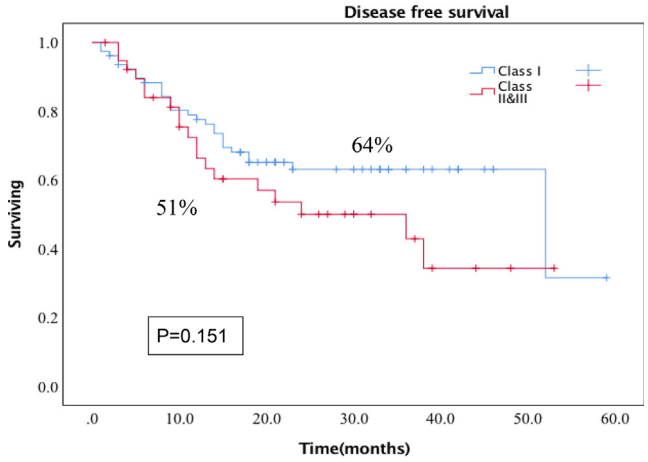


**Fig. 3b.** Kaplan Meier analysis. Comparing disease free survival at 2 years of Class I with Class II and III T4b buccal mucosa cancer patients.

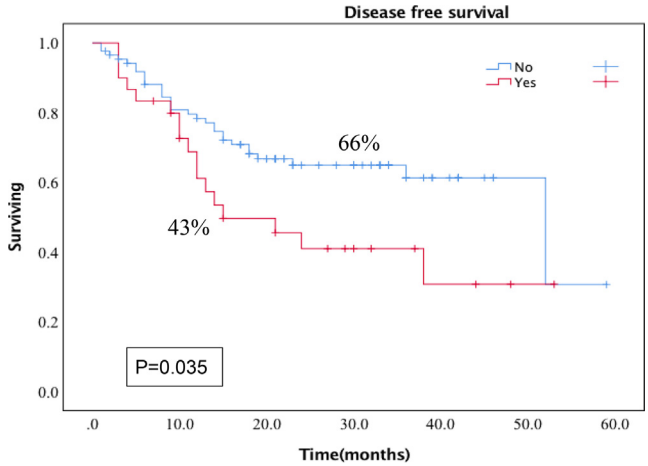


**Fig. 3c.** Kaplan Meier analysis. Depicting disease free survival at 2 years of T4b buccal mucosa cancer patients with and without lateral pterygoid involvement.

survival of 47% with surgery and 20% without surgical intervention [27]. This data emphasizes the need for surgery as part of the treatment for advanced buccal mucosal cancer involving masticatory space. It is unclear how many patients were unable to tolerate at least two cycles of induction chemotherapy or if disease progressed on chemotherapy and the oncologic benefit of chemotherapy in comparison to primary surgery.

Our group has previously described a standardized technique of compartment resection for excising tumors involving masticatory space, which was adopted in this study [13–15]. The present study observed an acceptable incidence of positive margins (3.2%) even when including tumors with supra-notch (Class II and III) involvement. The OS and DFS at 2 years in the T4 cohort in this study was 59.9% and 61.0% respectively. The difference in local disease control rate between T4a and T4b was not statistically significant. Liao et al reported a similar finding of comparable DFS of 66% in T4a and 57% in T4b ($p = 0.348$) buccal mucosal carcinomas [10]. Mair et al, recently reported favorable disease outcome in T4b buccal mucosa cancer patients treated by multimodality treatment of primary surgery and adjuvant radiotherapy or concurrent chemo-radiotherapy. The loco-regional control, disease-free survival and overall survival were 68.2%, 54.7% and 48.7% respectively. Their cohort excluded patients with supra-notch disease. The study observed significant difference in oncologic outcome with respect to adequacy of surgical margin related to local control (49.6% vs. 41.1%, $p = 0.025$) and disease-free survival (65.3% vs. 42%, $p = 0.035$); confirming the importance of achieving uninvolved surgical margins when undertaking primary surgery [12].

Clinical staging is the cornerstone for treatment selection. The current staging criteria for oral cancer uses anatomic extent of tumor invasion without distinguishing anatomic origin of the tumors. The same T-stage criteria is applicable for oral tongue and floor of mouth (CO2.0 CO 4.0) [4] and gingiva and buccal mucosa (CO6.0, CO6.2) [4] cancers. Invasion of muscles of mastication is one the key criteria that stratifies the disease as T4b. Due to the proximity of the buccal mucosa to the masticator space, tumors of this sub-site have high propensity to invade the muscles of mastication, categorizing many of these tumors as T4b. The present study reports forty-seven percent of the patients staged as T4b were pathologically down-staged to a lower T-stage. As many patients with buccal mucosal cancers in Indian subcontinent have associated submucous fibrosis, caused by chewing of tobacco products, there is stiffness of buccal mucosa and trismus. Combination of trismus and inability to apply the traditional “puffed-cheek” technique during image capture can potentially lead to the buccal mucosal tumor to abut the masseter and medial pterygoid muscles without necessarily invading the muscles. This could be the primary reason for radiologic over-diagnosis of the tumors. The loss of fat-planes between tumor and muscles used as radiologic criteria of early invasion of muscles of mastication may not be reliably applied in buccal cancers. The buccal pad of fat, which lies between the muscles of mastication, is often indistinct between buccal mucosa and the muscles. Trismus, the clinical sign of masticatory muscle involvement cannot also be applied as many patients suffer from trismus from preexisting oral sub mucous fibrosis. These limitations need to be kept in mind during the clinical and radiologic evaluation of gingival-buccal complex cancers.

Even with pathologic involvement of muscles of mastication, there was no difference in the OS for pT4a and pT4b ($p = 0.687$) and DFS of pT4a and pT4b ($p = 0.776$) cohorts. When patients were analyzed with adequate surgical margins (> 5 mm), the local recurrence rate was similar for T4a (26/135; 19.3%) and T4b (15/66; 22.7%), underscoring the importance of resection with adequate surgical margin rather than invasion of muscles of mastication. In this context it is important to recognize that all muscle involvement is not equal. pT4b patients with only medial pterygoid muscle involvement had outcomes comparable with patient with pT4a tumors (Fig. 3a), necessitating the need for a more precise staging system that can account for these anatomic determinants.

Selection of the patients for surgery with advanced buccal cancer is critical as 78% of the patients with inadequate surgical margins can lead to local recurrence [12]. In order to guide selection of patients likely to obtain uninvolved surgical margins, we have previously reported a classification system based on the extent of involvement of masticatory space [8]. The most commonly involved muscle in the

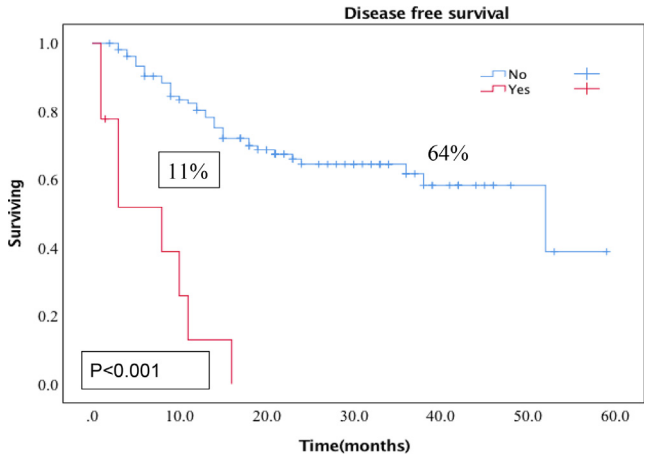


**Fig. 3d.** Kaplan Meier analysis. Depicting disease free survival at 2 years of T4b buccal mucosa cancer patients with defaulting adjuvant treatment.

present series was the medial pterygoid (68.6%) followed by the masseter (55.9%), lateral pterygoid (25.4%), temporalis (11%) and the pterygoid plates (9.3%). This stratified the patients as Class I in 71.8% (n = 130), Class II 23.8% (n = 43) and Class III 4.4% (n = 8). Incidence of close/positive margins in Class III and II was higher than that of Class I (11.5% vs 2.2%). However, the DFS between Class I and class II and III combined (64% vs 51%) was not statistically significant. The data from the present study, Liao et al [10] and Mair et al [12] suggest the notion of considering the entire masticatory component as one unit needs to be revisited. The oncological outcome of class I and Class II is similar to that of T4a disease. However, the Class III disease portends poor prognosis.

In this series of buccal cancers with advanced stage disease, we observed only 52.7% incidence of nodal metastasis. This may be the reason for better outcomes for advanced buccal mucosal cancer compared to those of tongue and floor of mouth and needs to be factored in when making treatment decisions [12].

One of the significant factors that determined disease outcome in multivariate analysis of both T4a and T4b cohorts was defaulting recommended adjuvant treatment. All but 9.38% patients were able to undergo the indicated post-operative adjuvant radiation or chemo-radiation. The poor oncologic outcome of patients who defaulted adjuvant treatment, (DFS 9.7% and OS 10.1% for T4b), underscores the importance of multi-disciplinary treatment to manage advanced oral cavity cancer.

To our knowledge, this is the largest reported series of advanced buccal mucosal cancer where oncologic outcome of T4b stage was compared with T4a cohort.

The result of this study has significant clinical implications as it suggests the need to relook the current staging criteria for advanced buccal carcinomas.

Our data demonstrates that the T4b category is a heterogenous cohort and cannot be generalized into a single group. The result also emphasized the need for multi-modality treatment comprising primary surgery followed by adjuvant treatment for advanced oral cavity cancer.

## Declaration of Competing Interest

All authors have no conflict of interest to disclose.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.05.021.

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