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Impact of radical treatments on survival in locally advanced T4a and T4b buccal mucosa cancers: Selected surgically treated T4b cancers have similar control rates as T4a

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ABSTRACT

Introduction: In the absence of any robust data supporting the TNM classification of T4 buccal mucosa cancers, we did this prospective study to compare the oncologic outcomes of T4a and T4b buccal mucosa cancer patients.
Patients and methods: This is a prospective study of 210 treatment naïve T4 buccal mucosa cancer patients. All patients underwent upfront radical surgery followed by adjuvant radiotherapy (RT)/chemoradiotherapy (CCRT). This is the largest prospective series in the literature on T4 buccal cancers.
Results: T4a disease was seen in 135(64.3%) patients and T4b in 75(35.7%) patients. On comparison between all T4a and T4b cases, a significant difference was observed with regard to 3-year local control (49.6% vs. 41.1%: p-0.025) and disease-free survival (DFS) (65.3% vs. 42%: p-0.035) with a slightly higher incidence of distant metastasis in T4b patients (17.3% vs. 9.6%). Inadequate cut margin (< 5 mm) was seen only in 7.4% patients with T4a disease and 12% patients with T4b disease. When patients with adequate cut margins were considered for analysis, local recurrence rate was similar for T4a (26/135; 19.3%) and T4b (15/66; 22.7%) disease suggesting the importance of radical surgery in infra-notch T4b buccal cancers. While the 3-year survival for T4a patients who received adjuvant RT alone was 72.2%, it was only 42.1% for similar T4b patients suggesting a need to intensify adjuvant treatment for these patients.
Conclusion: Surgery should be considered as the primary modality of treatment for T4b patients, where clear margins are achievable. The benefit of treatment intensification with adjuvant CCRT should be explored in T4b buccal cancers.

Introduction

The American Joint Committee on Cancer (AJCC) staging system classifies locally advanced squamous cell carcinoma of the buccal mucosa as T4a (moderately advanced local disease) when it invades the bone, skin or extrinsic muscles of the tongue and T4b (very advanced local disease) when it invades masticator space (MS), pterygoid plates (PP), skull base, and/or encases the internal carotid artery [1]. The purpose of this separation into T4a and T4b was to emphasize the high rate of unresectability, local recurrence [2,3] and poor prognosis in T4b tumors [4]. While this may be true for tongue cancers with masticator space involvement (T4b), a subset of similarly staged buccal mucosa tumors are resectable with good outcomes [2]. Therefore, putting all patients of oral cancer with masticator space and pterygoid plate involvement in one group (T4b) may not be appropriate [5]. However, in the absence of a large series evaluating the AJCC classification, we prospectively collected the data of T4 buccal mucosa cancer patients treated under a uniform protocol at our institute.

Materials and methods

This is a prospective study of 210 consecutive treatment naïve locally advanced buccal mucosa cancers treated at a tertiary cancer center between January 2010 and January 2014. All patients were evaluated before surgery with history, clinical examination, complete hemogram, blood biochemistry and head and neck magnetic resonance imaging (MRI) or computed tomography (CT) scan. Subsequently, they were grouped as T4a or T4b as per the AJCC classification (7th edition) [1]. However, patients with disease (T4b) extending above the mandibular notch, the involvement of skull base or carotid artery were excluded from the study. Surgery with neck dissection was the primary modality of treatment for all patients. Subsequently, all patients

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received adjuvant radiotherapy (RT) as per the institutional protocol and concurrent chemotherapy (CCRT) was added when there were involved margins or neck nodes showing extracapsular spread (ECS). One hundred and thirty patients (61.95%) received adjuvant RT and 80 (38.1%) received adjuvant CCRT. All patients were under regular clinical follow up at 3 monthly intervals and in case of a clinical suspicion of recurrence, confirmation was done with biopsy and or by imaging (CT/PET-CECT). Overall, 95 patients developed recurrences, PETCECT was done in 43 patients, while Contrast enhanced Computed tomography scan of head and neck along with thorax was done in 47 patients. Five patients on follow-up came to us with histologically proven distant metastasis and as they were not planned for any definitive treatment, imaging was not done for them.

Statistical analysis

Statistical analysis was done using the software SPSS 20.0 (IBM, Armonk, NY). Disease-free (DFS) and overall survival (OS) was calculated by Kaplan Meier method. DFS was defined as the period from the date of diagnosis till the date of the first recurrence; ether loco-regional or systemic. The OS is defined as the period from the date of diagnosis until death from any cause. We did a univariate survival analysis by log-rank test using the variables selected based on their clinical relevance or from those previously described in the literature. All significant ($P < 0.05$) variables were subsequently tested (multivariate) with Cox-regression analysis using forward stepwise selection.

Results

There were 173 males (82.38%) and 37 females (17.61%). The median age of the study patients was 49 years (range: 26–73 years). Among these 210 patients, 135(64.28%) were classified as T4a and 75(35.71%) as T4b based on clinico-radiological findings. Bone involvement was seen in 134 patients (63.8%), skin involvement in 64 patients (30.5%) and nodal metastasis in 111 patients (52. 85%). Among these 111 patients, 31 were N1, 79 were N2 and one had N3 nodal disease. Among the 75 T4b patients, 45 (60.5%) had involvement of masseter muscle, 17/75(22.66%) had involvement of medial pterygoid muscle, and 13 (17.33%) had involvement of both. The tumor and patient characteristics are given in Table 1. Most of the poor prognostic factors are distributed equally in both the groups.

Clinical course and survival analysis of T4a patients (n = 135)

The median and mean follow-up period for patients with T4a disease was 24 and 25 months respectively. At the time of analysis, 74 (54.8%) were alive and disease free, nine (6.7%) were alive with disease, 40 (29.6%) died due to cancer, 8 (5.9%) patients died due to other causes and follow-up details were not available for four patients. Overall 51 patients developed recurrences and salvage surgery was possible only in two patients. Local recurrences were seen in 27/51 (52.94%) patients, regional recurrences in 10/51 (19.60%), distant metastasis in 13/51 (25.49%) and second primary cancer in one patient (1.96%). Factors affecting disease-free survival and overall survival in T4a patients are given in Table 2 and we found perineural Invasion (PNI) and nodal metastasis as independent prognostic factors.

Clinical course and survival analysis of T4b patients (n = 75)

The median and mean follow-up period for patients with T4b disease was 20 months and 22 months respectively. At the time of analysis, 29 (38.7%) were alive and disease free, nine (12%) were alive with disease, 35 (46.7%) died due to cancer, one (1.3%) died due to other causes and follow details was not available for one patient. Local recurrences were seen in 22/44 (50%) patients, regional recurrences in 6/44 (13.63%) patients, distant metastasis in 13/44 (29.54%) patients, and second primary in 3/44 (6.81%) patients. Factors affecting DFS and OS in T4b patients are given in Table 3. We found nodal metastasis as the only independent prognostic factor for disease-free and overall survival. A trend towards poorer survival was also noticed in patients who had inadequate margins (p-value – 0.062).

Table 1
Distribution of patient and Tumor characteristics among T4a and T4b patients.

Factors	T4a (Percentage) n-135	T4b (Percentage) n-75	Total (Percentage) n-210	P-value (chi square test)
Age				
Mean	49	48		0.61
Median	50	48		
Gender				
Male	110(74.07)	63(84)	173(82.38)	0.71
Female	25‘(18.51)	12(16)	37(17.61)	
Grade				
WDSCC	13(9.62)	6(8)	19(9.04)	0.42
MDSCC	90(66.66)	45(60)	135(64.28)	
PDSCC	32(23.7)	24(32)	56(26.66)	
PNI				
Present	17(12.59)	16(21.33)	33(15.71)	0.10
Absent	118(87.4)	59(74.66)	177(84.28)	
LVE				
Present	3(2.22)	1(1.33)	4(1.90)	0.9
Absent	132(97.77)	74(98.66)	206(98.09)	
Nodal metastasis				
Present	68(50.37)	43(57.33)	111(52.85)	0.4
Absent	67(49.62)	32(42.66)	99(47.14)	
Extracapsular spread				
Present	48(35.55)	32(42.66)	80(38.09)	0.30
Absent	87(64.44)	43(57.33)	130(61.90)	
Margins				
Adequate (≥5 mm)	125(92.59)	66(88)	191(90.95)	0.3
Inadequate (< 5mm)	10(7.40)	9(12)	19(9.04)	
Total	135(100)	75	210	

Factors affecting disease-free survival and overall survival in all patients (n= 210)

Factors affecting disease-free survival and overall survival in all patients are given in Table 4. As expected, PNI and nodal metastasis were the two independent prognostic factors affecting DFS and OS. While T stage (T4a vs. T4b) had an impact on DFS (P 0.035), it did not have a significant impact on OS (p-0.518). Patients with nodal metastasis had poorer survival and T4b patients with these adverse factors had the worst prognosis (Fig. 1).

Comparison of T4a vs. T4b

The local control, loco-regional control, disease-free survival and overall survival for all patients at 3 years were 74%, 68.2%, 54.7% and 48.7% respectively. On comparison between all T4a and T4b cases, a significant difference was observed with regard to 3-year local control (49.6% vs. 41.1%: p-0.025) and DFS (65.3% vs. 42%: p-0.035). However, no significant difference was observed in 3-year loco-regional control (71.1% vs. 61.8%: p-0.107) and OS (49.6% vs. 41.1%: p-0.518) (Fig. 1). As per current practice, the patients with ECS or margin positivity received CCRT and others received only RT. The 3-year DFS for T4a and T4b patients who received chemo-radiation was 41.6% and 33.6% respectively while those who received only radiation alone was 72.2% and 42.1% respectively. The T4b patients treated surgically without any adverse features like ECS, nodal metastasis and cut margin positivity have similar outcome as those of T4a cases with these adverse factors. The incidence of distant metastasis was slightly higher in T4b

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