

Clinical Outcomes and Patterns of Failure of Post-Operative Buccal Mucosa Cancers Treated with Adjuvant Radiotherapy- A Retrospective Study in A Tertiary Care Hospital

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Abstract

Background: Buccal mucosa carcinoma is the most prevalent oral cavity malignancy in India, which is commonly related to the use of tobacco and alcohol. Standard practice is to use adjuvant radiotherapy to treat advanced-stage disease, which helps control the disease but is not a cure against recurrence. The objective of this study was to determine the demographics, clinical, pathologic, and treatment-related variables that impact the occurrence and disease-free survival (DFS) in patients who are operated on and receive adjuvant radiotherapy for buccal mucosa carcinoma. **Material and Methods:** A retrospective study of 149 surgically resected patients with carcinoma of the buccal mucosa who underwent adjuvant radiotherapy was conducted. Demographic data, clinical presentation data, tumor staging data, pathological data, recurrence patterns data, metastasis data, and DFS data were gathered and compared. The recurrence was evaluated using appropriate statistical tests to assess associations between patient/tumor characteristics and recurrence. **Results:** The average age was 57.38 years, with a male-dominated distribution (82.6% prevalence). The majority of the patients were tobacco users (91.9%) and alcohol abusers (54.4%). The most frequently reported presenting complaints were pain (45.6) and ulceration (38.9), with a median duration of 5 months. Those with advanced clinical (cT3–T4a, cN2–N3), pathological, high-grade, positive margins, perineural invasion, depth of invasion above 4 mm, and extracapsular extension were significantly associated with recurrence. The infield recurrence was seen in 36.9% and outfield in 12.1%, and the distant in 20.1%. The average DFS was 24.97 months, with a median of 18 months. **Conclusion:** The risk factors for the recurrence of buccal mucosa carcinoma include high-risk pathological features, advanced stage, and lifestyle factors. Early diagnosis and extensive surgery, plus close post-operative observation, are necessary to enhance DFS.

Keywords: Buccal mucosa carcinoma, adjuvant radiotherapy, recurrence, disease-free survival, oral cancer.

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INTRODUCTION

Head and neck cancers form a significant health burden in the whole world, and they are the sixth most common malignancy in the world.^[1] There is substantial geographic disparity, with around 57.5 percent of the entire head and neck cancer burden in the Asia region, with 57.5 percent being in India, which bears a near 30 percent cancer burden.^[2] Oral cavity cancer is one of the worst and deadliest health issues of the Indian subcontinent in head and neck cancers. Estimates on GLOBOCAN 2020 display that cancer of the oral cavity is the second most prevalent cancer in India, but the 11th in the world.^[3] Buccal mucosa squamous cell carcinoma is the oral cavity pathology with the highest incidence in India. It contributes to nearly a quarter of the total oral cancer burden in the nation.^[4] According to the National Cancer Registry Programme (Population-Based Cancer Registries) data, the highest age-adjusted incidence rate of mouth cancer is observed in males in Ahmedabad urban (18.11 per 100,000) and in Bhopal (14.2 per

100,000).^[5] The reports by the Hospital-Based Cancer Registry also prove that oral cavity cancer has the highest site among males in the city of Mumbai, and it is among the leading five cancer sites among males in most registries in India.^[6] Conversely, carcinoma of the buccal mucosa is relatively rare in developed nations, and different epidemiological patterns indicate its prevalence.^[7] The reason why buccal mucosa cancer is common in India is because these people extensively use smokeless tobacco products including gutkha and betel quid

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chewing which is either tobacco-free or mixed with tobacco.^[8] Such practices have been noted to be a major trigger towards oral submucous fibrosis, a known premalignant lesion, thus leading to an upsurge in oral cancer that occurs more frequently in young people.^[9] Despite improvements in surgical technique and adjuvant radiotherapy, loco-regional recurrence remains a significant factor in treatment failure, and it is important to study clinical outcomes and patterns of failure in post-operative buccal mucosa cancers under adjuvant radiotherapy.^[10]

It is a retrospective study that assessed clinical outcomes as well as failure rates among post-operative patients with buccal mucosa carcinoma cases who were placed under adjuvant radiotherapy in a tertiary care hospital. Early stage of the tumor, high grade of the tissue, negative tumor margins, presence of perineural invasion, and ability to lead a lifestyle greatly contributed to the recurrence and disease-free survival. The infield recurrence was greater than the outfield or distant recurrence, and the liver and lungs were the most common sites of metastasis. Early detection, extensive surgical intervention, and close follow-up are critical to improve outcomes and reduce recurrence.

MATERIALS AND METHODS

Type of study: Retrospective observation study in one institution.

Place of study: Department of Radiotherapy, R.G. Kar Medical College & Hospital, Kolkata.

Period of study: From 1st November 2014 to 31st October 2019.

Study Population: All histologically proven cases of buccal mucosa attending the Radiotherapy Department from November 2014 to October 2019, and who had completed treatment before 30.12.2019, were included in this study. These patients were followed through May 2022 to determine the locoregional response and the pattern of failure.

Sample size: 150.

Inclusion Criteria:

- Adult patients (18-70 years)
- Histopathologically proven buccal mucosa cancers.

- All non-metastatic buccal mucosa cancer patients treated with surgery /radiation/chemoradiation.
- ECOG Performance Status 0-2.
- No history of prior Radiotherapy/Chemotherapy for buccal mucosa cancers.
- Willing to sign informed consent.

Exclusion criteria:

- Patients receiving neoadjuvant chemotherapy or radiotherapy before the treatment of our study.
- Patients having a tumor in any site other than the buccal mucosa.
- ECOG Performance status >2.
- Patients not willing to participate in the study.

Study Variable:

- Infield recurrence (Yes / No)
- Outfield recurrence (Level V, VI, VII, No recurrence)
- Bone, Liver, Lung, No distant metastasis)
- Age
- Gender (Male / Female)
- Religion (Hindu / Muslim)
- Socioeconomic status, Family history of cancer
- Tobacco use
- Alcohol abuse
- Chief complaint
- Pathological T stage
- Pathological N stage

Statistical Analysis: Data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while data were entered into Excel and analyzed using SPSS and GraphPad Prism. Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests were used to compare independent groups, while paired t-tests accounted for correlations in paired data. Chi-square tests (including Fisher's exact test for small sample sizes) were used for categorical data comparisons. P-values ≤ 0.05 were considered statistically significant.

RESULTS

Table 1: Age Distribution of Patients

Age Group	Mean (years)	Median (years)	N	SD	Minimum	Maximum	Range
< 50 years	43.78	45	9	3.93	38	49	11
50-60 years	55.95	55	80	2.98	52	60	8
> 60 years	61.33	61	60	0.48	61	62	1
Total	57.38	59	149	4.94	38	62	24

Table 2: Distribution of Patients According to Demographic and Lifestyle Factors

Characteristic	Category	Count	Percentage (%)
Sex	Female	26	17.4
	Male	123	82.6
Religion	Hindu	71	47.7
	Muslim	78	52.3
Family History of Cancer	No	85	57
	Yes	64	43
Socioeconomic Status	Lower	55	36.9

	Lower Middle	46	30.9
	Upper Middle	48	32.2
History of Tobacco Use	No	12	8.1
	Yes	137	91.9
Alcohol Abuse	Yes	81	54.4
	No	68	45.6

Table 3: Correlation of Recurrence/Disease Progression with Baseline Clinical and Demographic Characteristics

Variable	Category	Recurrence / Progression - Yes	Recurrence / Progression - No	P value
Gender	Female	9 (8.7%)	17 (37.0%)	0.000
	Male	94 (91.3%)	29 (63.0%)	
Age Grouping	< 50 years	6 (5.8%)	3 (6.5%)	0.442
	50–60 years	52 (50.5%)	28 (60.9%)	
	> 60 years	45 (43.7%)	15 (32.6%)	
Chief Complaint	Bleeding	9 (8.7%)	5 (10.9%)	0.768
	Pain	45 (43.7%)	23 (50.0%)	
	Swelling	6 (5.8%)	3 (6.5%)	
	Ulcer	43 (41.7%)	15 (32.6%)	
Duration of Symptoms	1 month	2 (1.9%)	9 (19.6%)	0.004
	3 months	23 (22.3%)	7 (15.2%)	
	4 months	24 (23.3%)	7 (15.2%)	
	5 months	41 (39.8%)	16 (34.8%)	
	6 months	13 (12.6%)	7 (15.2%)	
Alcohol Abuse	Yes	66 (64.1%)	15 (32.6%)	0.001
	No	37 (35.9%)	31 (67.4%)	
History of Tobacco Use	Yes	100 (97.1%)	37 (80.4%)	0.001
	No	3 (2.9%)	9 (19.6%)	
Clinical T Stage (cT)	T1	6 (5.8%)	0 (0.0%)	0.001
	T2	19 (18.4%)	7 (15.2%)	
	T3	31 (30.1%)	29 (63.0%)	
	T4a	47 (45.6%)	10 (21.7%)	
Clinical N Stage (cN)	N0	13 (12.6%)	4 (8.7%)	0.109
	N1	17 (16.5%)	2 (4.3%)	
	N2	69 (67.0%)	36 (78.3%)	
	N3	4 (3.9%)	4 (8.7%)	
Pathological T Stage (pT)	T1	0 (0.0%)	2 (4.3%)	0.045
	T2	23 (22.3%)	14 (30.4%)	
	T3	62 (60.2%)	27 (58.7%)	
	T4	18 (17.5%)	3 (6.5%)	
Pathological N Stage (pN)	N0	0 (0.0%)	1 (2.2%)	0.009
	N1	6 (5.8%)	10 (21.7%)	
	N2	36 (35.0%)	16 (34.8%)	
	N3	61 (59.2%)	19 (41.3%)	
Degree of Differentiation	Grade 2	34 (33.0%)	23 (50.0%)	0.049
	Grade 3	69 (67.0%)	23 (50.0%)	
Margin Status	Negative	40 (38.8%)	26 (56.5%)	0.045
	Positive	63 (61.2%)	20 (43.5%)	
LVSI	Yes	95 (92.2%)	43 (93.5%)	0.788
	No	8 (7.8%)	3 (6.5%)	
PNI	Yes	91 (88.3%)	33 (71.7%)	0.012
	No	12 (11.7%)	13 (28.3%)	
Depth of Invasion (DOI)	< 4 mm	44 (42.7%)	30 (65.2%)	0.011
	> 4 mm	59 (57.3%)	16 (34.8%)	
ECE	Yes	61 (59.2%)	19 (41.3%)	0.043
	No	42 (40.8%)	27 (58.7%)	
Maxilla Involvement	Yes	26 (25.2%)	10 (21.7%)	0.644
	No	77 (74.8%)	36 (78.3%)	
Mandible Involvement	Yes	35 (34.0%)	8 (17.4%)	0.039
	No	68 (66.0%)	38 (82.6%)	

Table 4: Distribution of Chief Complaints, Symptom Duration, and Clinical Staging in Patients

Characteristic	Category	Count	Percentage (%)
Chief Complaint	Pain	68	45.6
	Swelling	9	6
	Bleeding	14	9.4
	Ulcer	58	38.9
Duration of Symptoms Before Treatment	1 month	11	7.4
	3 months	30	20.1

	4 months	31	20.8
	5 months	57	38.3
	6 months	20	13.4
Clinical T Stage (cT)	T1	6	4
	T2	26	17.4
	T3	60	40.3
	T4a	57	38.3
Clinical N Stage (cN)	N0	17	11.4
	N1	19	12.8
	N2	81	54.4
	N3	32	21.5
Overall Clinical Stage	Stage I	2	1.3
	Stage II	16	10.7
	Stage III	18	12.1
	Stage IV A	104	69.7
	Stage IV B	9	6

Table 5: Table: Patterns of Recurrence and Sites of Distant Metastasis

Parameter	Category	Count	Column N %
Infield Recurrence	Yes	55	36.90%
	No	94	63.10%
Outfield Recurrence	Level V	8	5.40%
	Level VI	6	4.00%
	Level VII	4	2.70%
	No recurrence	131	87.90%
Site of Distant Metastasis	Bone	5	3.40%
	Liver	13	8.70%
	Lung	12	8.10%
	No distant metastasis	119	79.90%

Table 6: Disease-Free Survival (DFS) Statistics

Parameter	Mean	Std. Error	95% Confidence Interval
Survival Analysis (DFS, in months)	24.974	1.523	21.988 – 27.959
	18	3.54	11.062 – 24.938

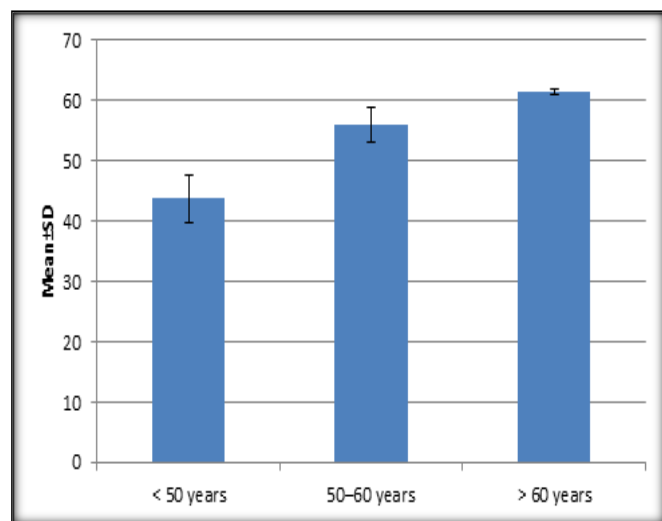


Figure 1: Mean Age Distribution of Patients

The age distribution of the study population is summarized as follows. The overall mean age was 57.38 years with a median of 59 years, ranging from 38 to 62 years. Among the age groups, participants younger than 50 years had a mean age of 43.78 years (median 45 years, SD 3.93, range 38–49, n = 9). Those aged 50–60 years had a mean of 55.95 years (median 55 years, SD 2.98, range 52–60, n = 80), while participants older than 60 years had a mean age of 61.33 years (median 61 years, SD 0.48, range 61–62, n = 60).

[Table 1]

The demographic profile of the study population is as follows. The majority of patients were male (82.6%), with 17.4% female. Regarding religion, 52.3% were Muslim, and 47.7% were Hindu. Family history of cancer was present in 43% of patients, while 57% had no such history. In terms of socioeconomic status, 36.9% belonged to the lower class, 30.9% to the lower-middle class, and 32.2% to the upper-middle class. A significant proportion of patients had a history of tobacco use (91.9%), and 54.4% reported alcohol abuse, whereas 45.6% did not. [Table 2]

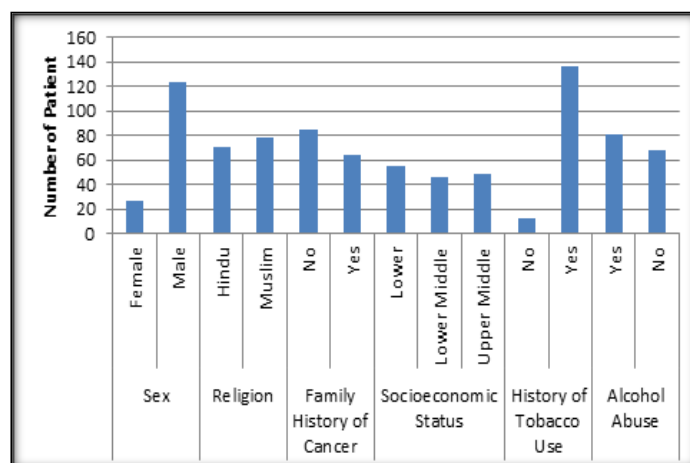


Figure 2: Distribution of Patients According to Demographic and Lifestyle Factors

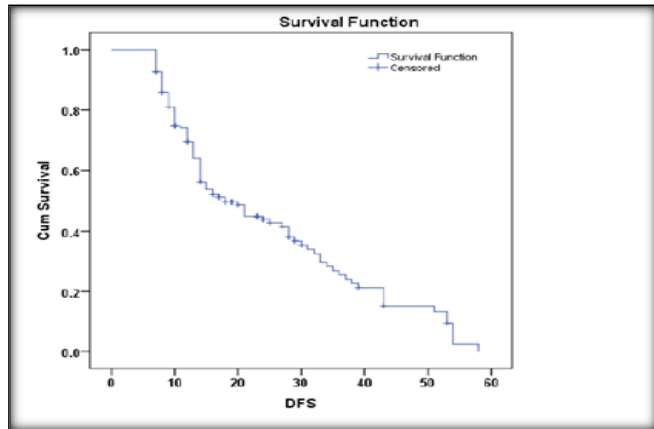


Figure 3: DFS KM survival analysis of entire study population

The inter-rater reliability analysis of recurrence/disease progression predictors in the study population brought several considerable results. Gender also strongly predicted recurrence, with males (91.3%) more likely to have a recurrence than females (8.7%) ($p = 0.000$). There was also a significant difference in the duration of symptoms before treatment ($p = 0.004$), with longer symptom duration associated with greater recurrence. Recurrence was strongly correlated with alcohol abuse and previous tobacco use ($p = 0.001$ in both cases), indicating that lifestyle factors are significant. Clinical staging was significant: clinical T stage (cT) ($p = 0.001$), pathological T stage (pT) ($p = 0.045$), and pathological N stage (pN) ($p = 0.009$). Recurrence was also dependent on tumor biology, with higher grade tumors (Grade 3) ($p = 0.049$), positive margins ($p = 0.045$), presence of perineural invasion (PNI) ($p = 0.012$), depth of invasion >4 mm ($p = 0.011$) and extracapsular extension (ECE) ($p = 0.043$) significantly associated with recurrence. There was significant mandibular involvement ($p = 0.039$), which increased the risk of recurrence. [Table 3]

The clinical profile of patients in the study showed that the most common chief complaint was pain (45.6%), followed by ulcer (38.9%), bleeding (9.4%), and swelling (6%). Regarding the duration of symptoms before treatment, the majority of patients presented after 5 months (38.3%), followed by 4 months (20.8%), 3 months (20.1%), 6 months (13.4%), and 1 month (7.4%). In terms of tumor staging, the most common clinical T stage (cT) was T3 (40.3%) and T4a (38.3%), with fewer patients in T2 (17.4%) and T1 (4%). For clinical N stage (cN), N2 (54.4%) was most frequent, followed by N3 (21.5%), N1 (12.8%), and N0 (11.4%). [Table 4]

The recurrence and metastasis profile of the patients showed that in-field recurrence occurred in 36.9% of cases, while 63.1% had no in-field recurrence. For outfield recurrence, the most commonly involved level was Level V (5.4%), followed by Level VI (4.0%) and Level VII (2.7%), with 87.9% of patients showing no outfield recurrence. In the case of distant metastasis, the most commonly used sites were the liver (8.7%), the lung (8.1%), and bone (3.4%), and 79.9% of the patients had no sign of distant metastasis. It means that most patients did not develop distant metastases, and in-field

recurrence was more frequent than out-of-field recurrence. [Table 5]

The disease-free survival (DFS) analysis indicated that the mean of DFS was 24.97 months (SD=1.52 SE) and the confidence range of DFS was 21.99-27.96 months. The median DFS was 18 months (3.54SE) and 11.06 to 24.94 months with the 95 percent CI, showing that half of the patients had not experienced disease progression within 18 months. [Table 6]

In our study, the mean disease-free survival (DFS) was 24.97 ± 1.52 months (95% CI: 21.99–27.96), while the median DFS was 18.00 ± 3.54 months (95% CI: 11.06–24.94). Censored data with the longest survival time were used to estimate DFS, indicating variability in patient outcomes over the follow-up period. [Figure 3]

DISCUSSION

The current study aimed to assess the role of demographic, clinical, pathological, and treatment-related variables in recurrence and disease-free survival (DFS) outcomes in patients with buccal mucosa carcinoma. The average age of our study population was 57.38 years, and the patients were largely in the middle-aged to elderly age group, in agreement with previous research, whereby tobacco and alcohol consumption are more prevalent among men.^[11,12] On lifestyle risk factors, it is also found that greater contributions were on the disease recurrence, where the majority of patients are between the ages of 50 and 60 years.^[13] The majority of the patients were light tobacco users (91.9%), and more than half of them were alcohol abusers (54.4%). Both of them were highly related to recurrence ($p = 0.001$), which echoed the previous research where tobacco and alcohol were identified as risk factors,^[14] that are independent of each other, with a median of 5 months before the treatment was administered, which demonstrates the importance of delays in seeking care. Increased recurrence with longer symptom duration ($p = 0.004$) has been reported in the literature, indicating that late diagnosis worsens the stage of presentation and improves survival outcomes.^[15] The tumor stage was a very important determinant of recurrence. In our group, more intense clinical T stages (cT3–T4a) and N stages (cN2–N3) were linked to increased recurrence as well as pathological variables such as increased tumor grade (Grade 3), positive margins, perineural invasion (PNI), depth of invasion >4 mm, and extracapsular extension (ECE) were linked to recurrence, in agreement with other studies underlying that such histopathological factors are indicators of lack of locoregional control.^[16] The recurrence and metastasis rates of LVSI and maxilla were not significantly associated, indicating that, in the field, recurrence was higher than the rest or distant metastases, and the liver and lungs were the most common metastatic sites in our study. These results are corroborated by previous studies that reported locoregional recurrence as the most prevalent manifestation of buccal mucosa carcinoma,^[17] with distant metastases being less common. In terms of disease-free survival, we found the mean of DFS was 24.97 months, and the median was 18 months. While lower than the 5-year DFS reported in large multicenter cohorts (60–75%),^[18] we find results similar to those of other tertiary-care retrospective studies with high-stage disease at presentation.^[19] Stage at diagnosis and the high prevalence of adverse

pathological features influence survival outcomes in our research, with a mean disease-free survival (DFS) of 24.97 +1.52 months (95% CI: 21.99-27.96) and a median DFS of 18.00 +3.54 months (95% CI: 11.06-24.94). Censored data on the greatest lifetime of the patient was a limitation to the estimation of DFS, which captured the variability of the outcomes of patients with buccal mucosa carcinoma with male gender, lifestyle, advanced stage, and high-risk pathological characteristics. These results support the notion that early diagnosis, extensive surgical resection, and postoperative follow-up should be pursued to enhance DFS and reduce recurrence, consistent with previously reported literature.^[20]

CONCLUSION

To sum up, in our population study, the male-dominated buccal mucosa carcinoma was primarily experienced by middle-aged to older individuals; tobacco and alcohol use were the prevalent risk factors. High-grade tumor, advanced clinical and pathological tumor stages, positive surgical margins, perineural invasion, depth of invasion more than 4 mm, and extracapsular extension were factors that were highly correlated with recurrence and less disease-free survival. Recurrence in the field was more prevalent than in the out-field, and the most common distant metastases were to the liver and lungs. Such results demonstrate the effect of timely presentation and the presence of high-risk tumor characteristics on the disease and the significance of early diagnosis, radical surgery, and close follow-up to increase disease control and survival in patients with buccal mucosa carcinoma.

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Conflicts of interest

There are no conflicts of interest.

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