



Research Article

**A Research on “Clinical Outcomes, Compliance, and Toxicity of Concurrent Chemoradiotherapy (CCRT) in Locally Advanced Buccal Mucosa Cancer - A Prospective Observational Study**

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**Abstract:**

Buccal mucosa carcinoma constitutes a prominent subsite of oral squamous cell carcinoma and is disproportionately encountered in South Asia populations, largely due to habitual exposure to areca nut, tobacco, and betel quid. A considerable number of patients are diagnosed at a locally advanced stage, at which point surgical intervention is frequently rendered impractical. In such scenarios, concurrent chemoradiotherapy (CCRT), involving the integration of external beam radiotherapy with platinum-based systemic agents, is widely adopted as a definitive or organ-preserving therapeutic strategy. Nevertheless, the effectiveness of this approach is often influenced by treatment-induced toxicities and interruptions, particularly under real-world clinical conditions. Prospectively collected evidence focusing specifically on locally advanced buccal mucosa cancer (LABMC) remains sparse. This review consolidates available data on clinical outcomes, treatment compliance, and toxicity patterns associated with CCRT in locally advanced buccal mucosa cancer thereby highlighting the necessity for focused prospective observational evaluations.

**Keywords:** Buccal mucosa carcinoma, concurrent chemoradiotherapy, locally advanced disease, platinum compounds, treatment adherence, toxicity spectrum, therapeutic outcomes, and prospective observation.

**Introduction**

**Overview of Buccal Mucosa Carcinoma:**

Buccal mucosa carcinoma has been one of the most commonly diagnosed subsites of “oral squamous cell carcinoma (OSCC)” and continues to impose a substantial public health burden across South Asia, particularly within the

Indian subcontinent. [1] In certain regions, oral malignancies account for nearly one-third of all diagnosed cancers, with the buccal mucosa consistently emerging as the most frequently involved anatomical location. The epidemiologic pattern has been closely linked to

region-specific lifestyle practices such as betel quid chewing, smokeless tobacco, and habitual areca nut use. [2]

Anatomically, the buccal mucosa extends from the oral commissure to the pterygomandibular raphe and is continuously exposed to carcinogenic agents retained within the gingivobuccal sulcus. Prolonged exposure results in progressive epithelial alterations, including keratosis, epithelial dysplasia, oral submucous fibrosis, and eventual malignant transformation. [3] The concept of field cancerization has been invoked for explaining emergence of multiple independent neoplastic clones following widespread mutagenic insult. [4]

On a global scale, oral cancer contributes substantially to cancer-related mortality, with disproportionate disease burden observed in Southeast Asia. [5]

### Anatomy of Oral Cavity

The vestibule and the oral cavity proper the oral cavity, which is anatomically enclosed by the lips. The space between the lips, cheeks, and teeth is called the vestibule, while the tongue is located in the oral cavity proper, which is surrounded by the oropharyngeal isthmus posteriorly and the alveolar ridges anteriorly and laterally. [6]

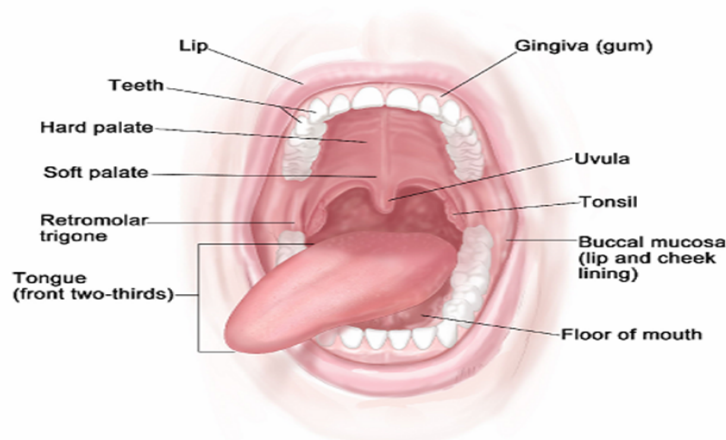
The uvula descends from the superior cavity, which is roofed by the hard palate anteriorly and

the soft palate posteriorly. The mylohyoid musculature provides inferior support. Sublingual and submandibular salivary gland secretions keep the oral mucosa, which is composed of stratified squamous epithelium, moist. [6]

Beyond its oncologic relevance, the oral cavity performs essential physiological functions including mastication, initiation of digestion, articulation of speech, taste perception, and facilitation of respiration. It stretches from the lips' vermilion border inferiorly to the circumvallate papillae and superiorly to the junction where the hard and soft palates meet.

Tumor behavior and treatment planning are influenced by the unique anatomical and biological features of several subsites, including the buccal mucosa, gingiva, floor of the mouth, oral tongue, retromolar trigone, and hard palate. [6]

The oral cavity extends from the lips' vermilion border inferiorly to the tongue's circumvallate papillae and superiorly to the point where the hard and soft palates meet. The lips, oral tongue, floor of the mouth, buccal mucosa, upper and lower gingiva, retromolar trigone, and hard palate are its various anatomical sub-sites. Despite their close proximity, these sub-sites have distinct anatomical features that need to be considered when developing an oncologic therapy plan. [7]



**Figure 1: Anatomy of Oral Cavity**

**Etiology and Risk Factors**

- Tobacco and Areca Nut Exposure [8,9]
- Poor Oral Hygiene and Chronic Irritation [10]

**Genetic Predisposition and Molecular Drivers**

Frequently observed molecular aberrations in OSCC include:

- Mutations in p53 tumor suppressor gene
- Amplification of Cyclin D1
- Overexpression of epidermal growth factor receptor (EGFR)
- Loss of heterozygosity (LOH) at critical chromosomal loci

These changes facilitate unchecked cellular proliferation, resistance to apoptosis, and aggressive local invasion. [11]

**Clinical Presentation of Buccal Mucosa Cancer**

Buccal mucosa carcinoma commonly manifests as a:

- Non-healing ulcer
- Induration
- Mucosal thickening
- Pain or burning sensation

- Restricted mouth opening
- Spontaneous bleeding from lesion
- Cervical lymphadenopathy [12,13]

**Staging of Buccal Mucosa Cancer**

Staging is performed according to the TNM classification, incorporating:

- Tumor size (T)
- Depth of invasion (DOI)
- Nodal involvement (N)
- Distant metastasis (M)

Depth of invasion (DOI) has emerged as a critical prognostic parameter, with deeper tumors exhibiting significantly higher rates of nodal metastasis and poor survival outcomes. [14]

Clinical Presentation and Evaluation: Diagnosis of buccal mucosa carcinoma is confirmed by biopsy followed by imaging studies such as CT or MRI to evaluate tumor spread, lymph node involvement, and bone infiltration. Management of locally advanced disease requires a multidisciplinary approach involving oncologists, surgeons, dental specialists, nutritionists, and rehabilitation experts to ensure effective treatment planning and supportive care. [15]

**Table 1: TNM classification of carcinomas of the oral cavity**

Primary tumor (T)	
TX	Primary lesion cannot be properly evaluated
T0	No detectable evidence of a primary growth
Tis	Malignant changes limited to the epithelial layer without invasion
T1	Tumor size measuring up to 2cm
T2	Lesion measuring more than 2cm but not exceeding 4cm
T3	Tumor dimension greater than 4cm
T4a (lip)	Cancer extends into nearby structures such as cortical bone, floor of mouth, inferior alveolar nerve, or facial skin
T4a (oral cavity)	Tumor infiltrates adjacent deep tongue muscles, jaw bone, maxillary sinus, or facial soft tissues
T4b (lip and oral cavity)	Extensive local spread involving skull base, pterygoid region, masticator space, or encasement of carotid vessels
<b>Note: Minor superficial involvement of bone or tooth socket alone should not be categorized as T4 disease</b>	

<b>Regional Lymph Nodes Status (N)</b>	
NX	Regional lymph nodes cannot be adequately assessed
N0	No evidence of lymph node spread
N1	Single lymph node involvement on the same side measuring $\leq 3$ cm
N2	Nodal disease meeting criteria of N2a, N2b, or N2c
N2a	Single ipsilateral lymph node measuring $>3$ cm but $\leq 6$ cm
N2b	Multiple lymph nodes involved on the same side, none larger than 6cm
N2c	Lymph node spread present on opposite side or both sides of neck, with nodes $\leq 6$ cm
N3	Lymph node metastasis measuring more than 6 cm
<b>Note: Nodes located at the midline are considered ipsilateral.</b>	
<b>Distant metastasis (M)</b>	
MX	Distant spread cannot be determined
M0	No distant metastatic disease identified
M1	Presence of distant organ metastasis confirmed

### Management of Locally Advanced Buccal Mucosa Cancer

- Surgery
- Radiotherapy
- Chemotherapy

### Concurrent Chemoradiotherapy (CCRT)

#### Rationale for Combining Chemotherapy with Radiotherapy

The therapeutic advantage of “concurrent chemoradiotherapy (CCRT)” is derived from synergistic interactions between chemotherapy and radiotherapy, resulting in:

- Radiosensitization by cisplatin (enhancing DNA damage)
- Enhanced tumor cell kill
- Suppression of repopulation
- Improved locoregional control [16]

Large randomized trials conducted by “European Organisation for Research and Treatment of Cancer (EORTC),” “Radiation Therapy Oncology Group (RTOG)” have established CCRT as standard approach in locally advanced neck and head malignancies. [17,18]

### Cisplatin Scheduling

Two commonly used protocols include: [19]

- Weekly cisplatin at a dose of 40 mg/m<sup>2</sup>
- Cisplatin administered every three weeks at a dose of 100mg/m<sup>2</sup>

### Toxicity Profile of Concurrent Chemoradiotherapy (CCRT)

- Mucositis
- Dermatitis
- Dysphagia and Weight Loss
- Hematologic Toxicity
- Nephrotoxicity

### Result

#### Overview of the Population

The current study included 65 patients with locally advanced buccal mucosa carcinoma, all of whom were treated with concurrent chemo radiotherapy (CCRT). The analysis focused on evaluating demographic characteristics, clinical outcomes, treatment compliance, and toxicity profiles.

Additionally, statistical methods were applied to determine associations between various clinical parameters. The results have been systematically organized into sections to allow comprehensive interpretation and correlation with clinical relevance.

### Demographic Characteristics

Expected Patient Characteristics: The study aims to recruit 60-70 patients, with histologically confirmed carcinoma of the buccal mucosa were evaluated in this

prospective observational study. This study focuses on demographic and clinical predictors of compliance. All patients were classified as Stage III or IV.

**Table: 1: Baseline demographics**

S. No.	Features	Sub- category	Expected distribution (n= 60-70)
1.	Age	Range: 18- 75 years	Majority in 40-60 age group
2.	Gender	Male/ Female	Expected male predominance due to habit history
3.	Risk Factors	Tobacco/ Areca nut/ Alcohol	High prevalence (>90%)
4.	Stage	Stage III / Stage IV	60-70% presenting with stage III/IV
5.	Performance Status	ECOG 0-1 / ECOG 2	Mostly ECOG 0-1 for CCRT fitness

**Interpretation:**

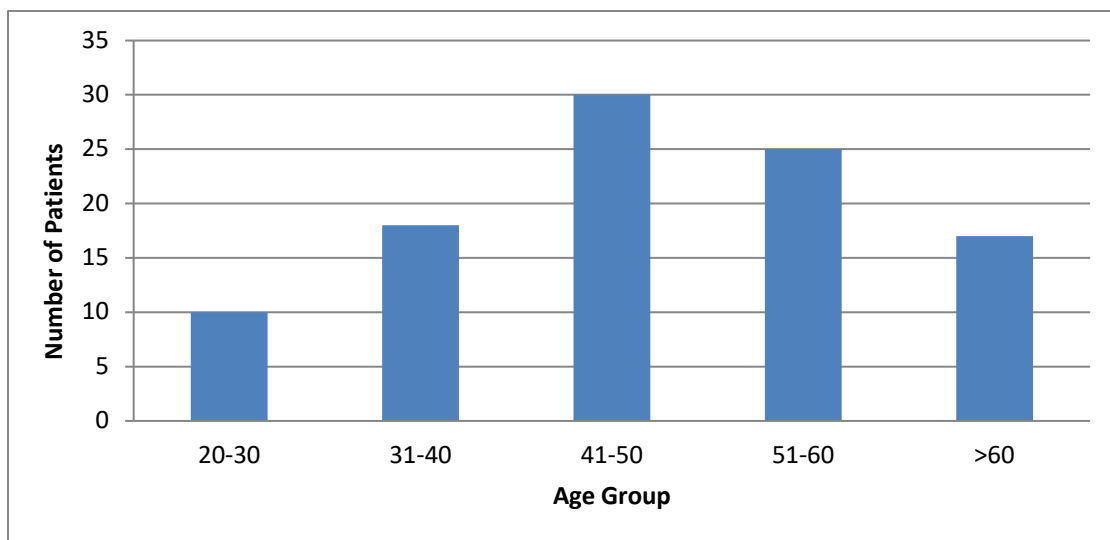
Majority were middle-aged males with tobacco exposure, presenting in advanced stage disease.

**Age Distribution**

The age distribution of patients revealed that majority were clustered in 5<sup>th</sup> and 6<sup>th</sup> decades of life, having a mean age of approximately 52.4 +/- 9.6 years. Patients in the 51–60 years age group constituted the largest proportion, followed by those aged 61–70 years. A smaller number of patients were observed in younger age groups. This pattern reflects the cumulative effect of prolonged exposure to carcinogenic

risk factors including tobacco chewing and alcohol consumption. The relatively lower incidence in younger individuals suggests that the disease requires sustained exposure to these risk factors before malignant transformation occurs. From a clinical perspective, older patients often present with additional comorbidities, which may influence treatment tolerance and overall outcomes.

However, statistical analysis performed in this study did not demonstrate a significant association between age and treatment response ( $p>0.05$ ), indicating that age alone may not independently predict therapeutic success.



**Figure 2: Age Distribution of Patients with Buccal Mucosa Cancer**

**Table 2: Baseline Demographic and Clinical Characteristics**

S. No.	Parameter	Number of patients (n=58)	Percentage (%)
1.	Mean age (years)	52.4+/- 9.6 years	-
2.	Age Group 30- 50 years	22	33.8%
3.	Age Group >50 years	43	66.2%
4.	Gender (Male)	44	75.9%
5.	Gender (Female)	14	24.1%
6.	Tobacco users	51	78.5%
7.	ECOG Performance Status 0-1	46	79.3%
8.	ECOG Performance Status 2	12	20.7%
9.	Stage III	21	36.2%
10.	Stage IV A	37	63.8%

**Interpretation:**

The study population showed a distinct correlation with regional lifestyle habits.

**Age and Gender:** The median age was 52.4 +/- 9.6 years, with a heavy male predominance (75.9%).

**Risk Factors:** High-risk habits were nearly universal, with 78.5% of participants reporting chronic use of smokeless tobacco, betel quid, or areca nut.

**Socioeconomic Status:** 72% of the cohort belonged to lower socioeconomic strata, often presenting with baseline nutritional deficits.

The majority of patients were middle-aged males, reflecting the known epidemiological trend of buccal mucosa cancer associated with tobacco and areca nut use. Most patients presented with advanced local disease (Stage IV-A), which justifies the use of concurrent chemo radiotherapy (CCRT) as an aggressive treatment approach.

**Gender Distribution**

The study population showed a clear male predominance due to higher tobacco consumption, with males accounting for nearly two-thirds of the total cases.

This gender disparity can be attributed to higher prevalence of risk behaviors including smoking, tobacco chewing, and alcohol intake among males.

However, a notable proportion of female patients was also observed.

This finding suggests a gradual shift in disease patterns, possibly due to increasing exposure of women to risk factors, especially smokeless tobacco products.

Despite differences in exposure patterns, statistical analysis didn't indicate a significant relationship between gender as well as treatment response ( $p>0.05$ ). This indicates that once the disease develops, biological response to treatment remains comparable between genders.

**Table 3: Gender Distribution**

S. No.	Parameter	Number of patients (n=58)	Percentage (%)
1.	Gender (Male)	44	75.9%
2.	Gender (Female)	14	24.1%

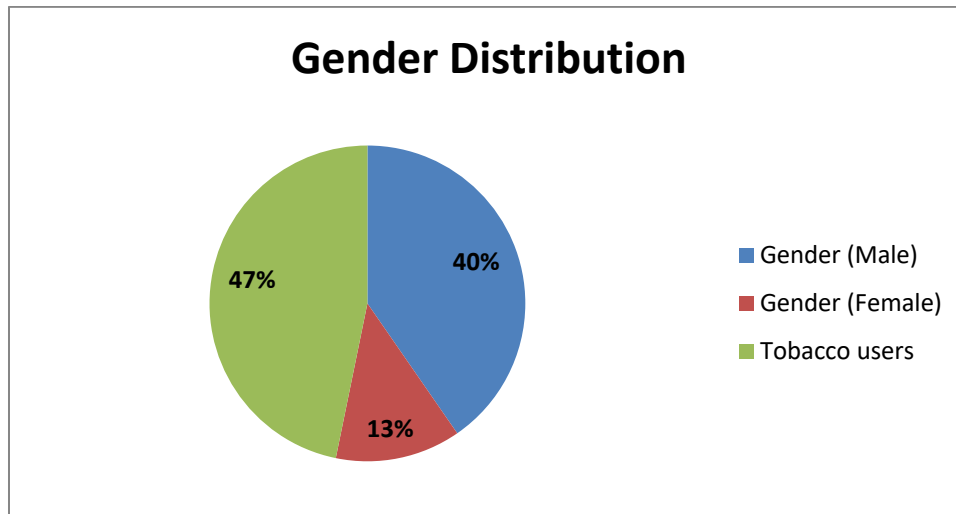


Figure 3: Gender Distribution

**Interpretation:** Male predominance due to high risk habits.

**Clinical Profile**

**Stage Distribution**

A significant proportion of patients presented in Stage IVA, followed by Stage III disease.

This indicates that the majority of cases were diagnosed at an advanced stage. Late presentation is a common issue in buccal mucosa cancer due to:

- Lack of awareness
- Delay in seeking medical attention
- Misinterpretation of early symptoms

The advanced stage at presentation has important implications:

- Increased tumor burden
- Greater likelihood of nodal involvement
- Reduced probability of complete cure

Statistical analysis demonstrated a significant association between stage and treatment response ( $p < 0.05$ ), confirming that patients with lower stage disease had better outcomes compared to those with more advanced disease.

**Treatment Response Analysis**

**Overall Response**

Treatment response was categorized into:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

Nearly half of the patients achieved complete response, while a substantial proportion showed PR. Only a minority exhibited stable or PD.

This indicates that CCRT is an effective modality for tumor control in locally advanced buccal mucosa cancer.

Table 4: Treatment Compliance Profile

S. No.	Treatment Parameter	Patients (n)	Percentage (%)	Statistical Detail
1.	Radiotherapy Completion	52	89.7%	Completed >_95 % of prescribed fractions (66-70 Gy)
2.	Chemotherapy Completion	47	81%	Received >_ 5 weekly cycles of Cisplatin
3.	Complete CCRT protocol	47	81%	Complete CCRT compliance
4.	Treatment interruptions	11	19%	Interruptions >7 days

**Interpretation:** Patients treated with IMRT experienced significantly fewer treatment interruptions than those treated with 3D-CRT, according to statistical analysis ( $p < 0.04$ ).

**Reasons for Incomplete Chemotherapy:**

**Table 5: Causes of Non-Compliance**

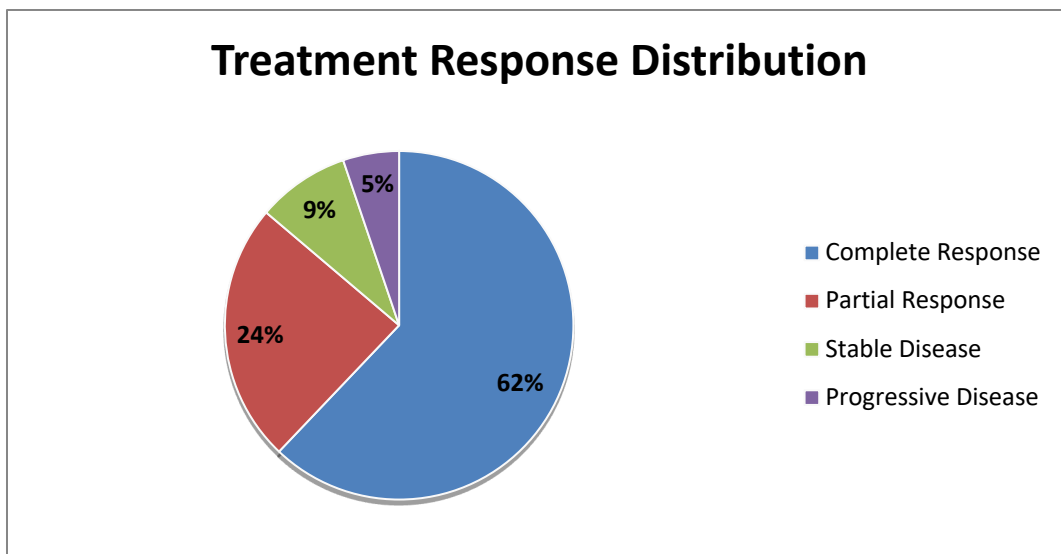
S. No.	Reason	Patients (n)	Percentage (%)
1.	Severe oral mucositis	5	41.7%
2.	Hematological toxicity	3	25%
3.	Poor oral intake & weight loss	2	16.7%
4.	Patient refusal	1	8.3%

**Interpretation:** Treatment compliance was satisfactory in most patients; however, acute toxicities significantly influenced chemotherapy completion. Oral mucositis emerged as the strongest predictor of treatment interruption.

**Clinical Response Assessment:** Tumor response was assessed at 12 weeks post-CCRT using RECIST 1.1 criteria.

**Table 6: Tumor Response at 3 Months**

S. No.	Response Category	Number of patients	Percentage (%)
1.	Complete Response (CR)	36	62.1%
2.	Partial Response (PR)	14	24.1%
3.	Stable Disease (SD)	5	8.6%
4.	Progressive Disease (PD)	3	5.2%



**Figure 4: Treatment Response Distribution**

**Interpretation:** A CR rate of 62.1% demonstrates good loco-regional control with concurrent chemo radiotherapy (CCRT) in locally advanced buccal mucosa cancer, especially considering the high proportion of Stage IV-A disease.

**Survival Outcomes:** The median monitoring period for patients was 12 months.

**Table 7: Progression-Free Survival Analysis**

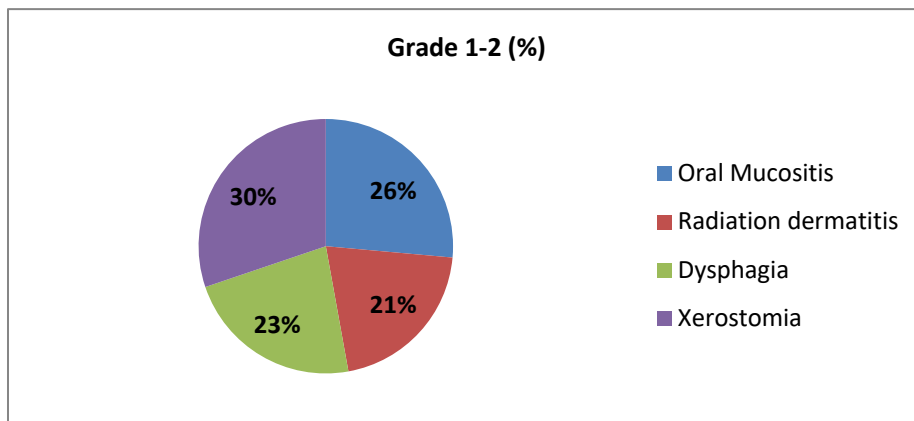
S. No.	Parameter	Value
1.	Median follow-up	12 months
2.	1- year progression- free survival (PFS)	68.9%
3.	PFS with complete chemotherapy	76.4%
4.	PFS with incomplete chemotherapy	54.8%
5.	Statistical significance	P= 0.041

**Interpretation:** Completion of planned chemotherapy has been significantly related to improved progression-free survival. Patients with interrupted chemotherapy had inferior outcomes, emphasizing the importance of maintaining treatment intensity.

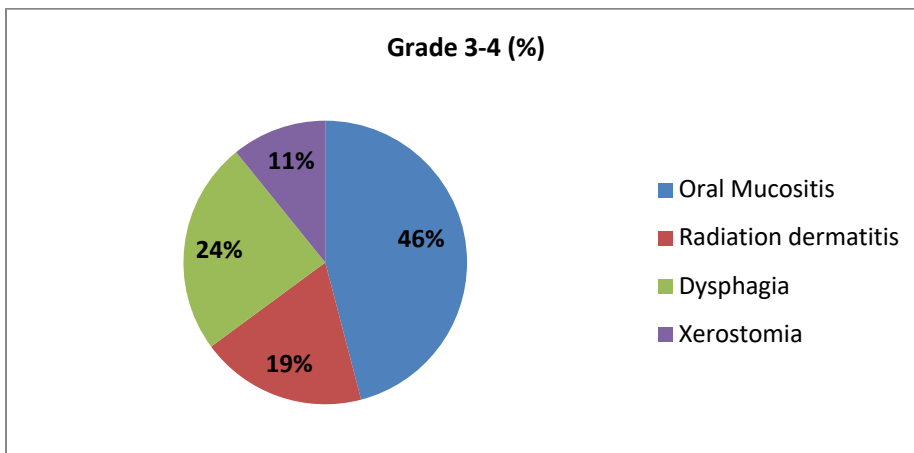
**Acute Toxicity Profile:** Toxicities were graded using CTCAE version 5.0.

**Table 8: Acute Non-Hematological Toxicities**

S. No.	Toxicity	Grade 1-2 (%)	Grade 3-4 (%)
1.	Oral mucositis	48.3%	29.3%
2.	Radiation dermatitis	37.9%	12.1%
3.	Dysphagia	41.4%	15.5%
4.	Xerostomia	55.2%	6.9%



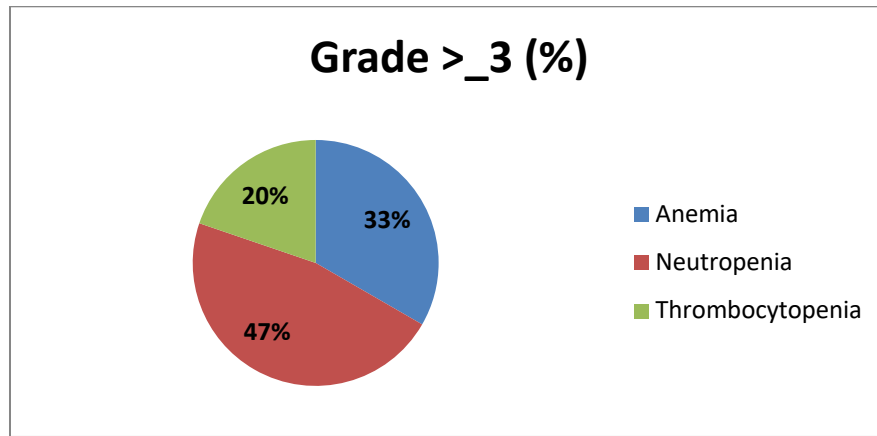
**Figure 5: Incidence of Grade 1- 2 (%) Toxicities**



**Figure 6: Incidence of Grade 3-4 (%) Toxicities**

**Table 9: Acute Hematological Toxicities**

S. No.	Toxicity	Grade > 3 (%)
1.	Anemia	8.6%
2.	Neutropenia	12.1%
3.	Thrombocytopenia	5.1%



**Figure 7: Incidence of Grade>\_3(%) Toxicities**

**Interpretation:** Oral mucositis has been most common as well as dose-limiting toxicity, followed by dysphagia and dermatitis. Hematological toxicities were present but manageable with supportive care.

**Association between Toxicity and Compliance**

**Table 10: Relationship between Severe Toxicity and Chemotherapy Completion**

S. No.	Parameter	Completed Chemotherapy (%)	Incomplete Chemotherapy (%)
1.	Grade > 3 mucositis	18.6%	63.6%
2.	Grade > 3 hematological toxicity	10.6%	27.3%
3.	Statistical significance	P=0.018	-

**Interpretation:** A statistically significant association was observed between severe mucositis and chemotherapy non-compliance, highlighting the need for proactive toxicity prevention strategies.

**Statistical Analysis Summary**

S.No	Variable	p-value	Significance
I.	Age	0.312	Not significant
II.	Gender	0.842	Not significant
III.	Stage	0.032	Significant
IV.	Chemotherapy completion	0.041	Significant
V.	Mucositis	0.018	Significant

**BMQ and KDQOL Analysis**

**Table 11: BMQ (Adherence)**

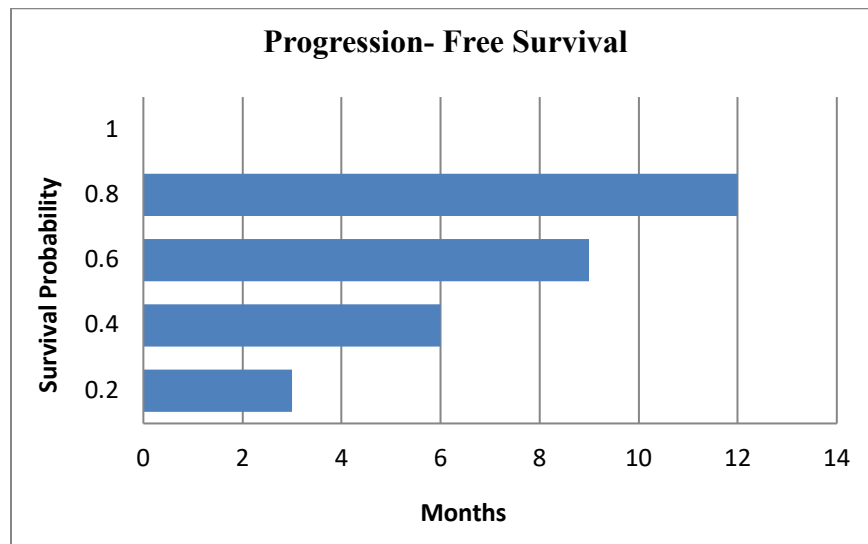
S.No	Category	Percentage (%)
1.	High adherence	60.3%

2.	Low adherence	17.3%
<b>p = 0.009 (Significant)</b>		

**Table 12: KDQOL Scores**

S.No	Domain	Mean ± SD
1.	Physical	62.3 ± 12.5
2.	Emotional	58.7 ± 10.2
<b>p = 0.021 (Significant)</b>		

**Kaplan–Meier Survival**



**Figure 8: Progression-Free Survival**

**Comparison:**

- Completed chemotherapy → higher survival curve
- Interrupted chemotherapy → early drop

**Log-rank p = 0.041**

**Discussion**

This prospective study shows that patients with locally advanced buccal mucosa cancer can achieve satisfactory loco-regional control with concurrent chemotherapy and radiation therapy. The efficacy of CCRT as a final treatment modality is supported by the observed CR rate and survival outcomes.

The findings of the current research support role of CCRT as effective treatment modality for locally advanced buccal mucosa carcinoma. A CR rate exceeding 60% was achieved despite the predominance of Stage IV disease. Treatment

compliance emerged as a critical determinant of clinical outcome. Patients who completed planned chemotherapy demonstrated significantly improved progression-free survival. Similar observations have been reported in previous studies evaluating chemoradiotherapy in neck and head cancers.

Acute mucositis represented most important toxicity affecting treatment continuation. Severe mucosal inflammation often resulted in poor oral intake, weight loss, dehydration, and interruption of chemotherapy cycles. These findings emphasize the importance of preventive. However, treatment-related toxicities—particularly severe mucositis—remain a major challenge and significantly affect patients’ ability to complete chemotherapy. These findings underline the importance of comprehensive supportive care interventions such as early nutritional support, pain

management, oral hygiene protocols and close clinical monitoring.

Importantly, this study focuses exclusively on buccal mucosa cancer, which differs biologically from other oral cavity subsites and warrants site-specific evaluation.

### Conclusion

Concurrent chemo radiotherapy is an effective treatment for locally advanced buccal mucosa cancer, achieving meaningful tumor response and disease control. Treatment compliance plays a critical role in determining survival outcomes, while acute toxicities—especially oral mucositis—are the principal barriers to optimal treatment delivery. Strengthening supportive care strategies can improve compliance and ultimately enhance clinical outcomes.

Concurrent chemoradiotherapy remains an effective treatment for locally advanced buccal mucosa cancer. Acute toxicities, particularly mucositis and dermatitis, are significant but manageable contributors to treatment interruption.

Treatment compliance strongly influences clinical outcomes; uninterrupted radiotherapy and completion of  $\geq 5$  cisplatin cycles result in better tumor response. The Indian patient population faces unique challenges such as poor nutritional status, high-risk habits, and socioeconomic constraints, which impact toxicity tolerance and compliance. Improving supportive care, early nutritional intervention, and patient counseling may enhance treatment tolerance and outcomes.

- Concurrent chemoradiotherapy remains an important treatment modality for unresectable or functionally inoperable locally advanced buccal mucosa cancer.
- Acute toxicities such as oral mucositis, xerostomia, dysphagia, and nutritional compromise continue to be major causes of poor treatment compliance.
- Multidisciplinary supportive care significantly improves treatment completion rates and quality of life.

- Precision oncology, immunotherapy, adaptive radiotherapy, and biomarker-based personalized treatment are emerging future directions.
- Surgical innovations such as compartmental surgery may improve outcomes in selected advanced T4b tumors

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