

# Comparative Study of Response between Concurrent Chemoradiation and Sequential Chemoradiation in the Treatment of Locally Advanced Base of Tongue Carcinoma in a Limited Resource Setting

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## Abstract:

**Introduction:** Base tongue carcinoma is commonly diagnosed an advanced stage in low-resource settings. Concurrent chemoradiotherapy (CCRT) and sequential chemoradiotherapy (SCRT) after induction chemotherapy are both used, but their comparative effectiveness remains unclear in such contexts.

**Aim of the study:** The study aimed to compare the treatment response and acute toxicities between concurrent chemoradiotherapy and sequential chemoradiotherapy in patients with locally advanced base of tongue carcinoma in a limited-resource setting.

**Methods:** The study was conducted using a purposive sampling technique at the National Institute of Cancer Research and Hospital (NICRH), Dhaka, over 12 months (June 2016–May 2017). A total of 60 patients with histopathologically confirmed squamous cell carcinoma of the base of tongue at stage III or IVA were enrolled and randomized into two equal groups. Arm A received concurrent chemoradiotherapy (CCRT) with external beam radiotherapy (66 Gy in 33 fractions over 6½ weeks) using the 3D Conformal Radiotherapy (3DCRT) technique, along with weekly cisplatin (40 mg/m<sup>2</sup>). Arm B received three cycles of induction chemotherapy (cisplatin 75 mg/m<sup>2</sup> on Day 1 and 5-FU 750 mg/m<sup>2</sup>/day for 3 days, every 3 weeks), followed by the same CCRT as Arm A. Data were analyzed using SPSS v22.0, employing descriptive statistics and Chi-square/Fisher's exact tests, with  $p<0.05$  considered statistically significant.

**Results:** In this study involving 60 patients with unresectable locally advanced esophageal cancer, baseline characteristics such as tumor location ( $p=0.564$ ), stage ( $p=0.558$ ), and histological grade ( $p=0.739$ ) were comparable between the concurrent and sequential CRT groups. The complete response rate was higher in the sequential CRT arm (56.7%) compared to the concurrent arm (46.7%), though this difference was not statistically significant ( $p=0.578$ ). There were no significant differences in hematologic toxicity (e.g., anemia:  $p=0.793$ ; leukopenia:  $p=0.630$ ; neutropenia:  $p=0.278$ ; thrombocytopenia:  $p=0.682$ ) or non-hematologic toxicity (e.g., nausea/vomiting:  $p=0.907$ ; mucositis:  $p=0.517$ ; dysphagia:  $p=0.794$ ; esophagitis:  $p=0.541$ ; fatigue:  $p=0.898$ ; anorexia:  $p=0.759$ ) between the two treatment groups across follow-ups. These findings suggest that both concurrent and sequential CRT offer similar efficacy and safety profiles in the management of locally advanced esophageal cancer.

**Conclusion:** Both concurrent and sequential chemoradiotherapy demonstrated comparable efficacy and tolerable toxicity profiles in treating locally advanced base of tongue carcinoma in a limited resource setting. Either approach can be considered a viable treatment option depending on patient factors and resource availability.

**Keywords:** Carcinoma, Chemoradiotherapy, Induction, Toxicity, Tongue.

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## Introduction

Head and neck cancers rank as the sixth most common malignancy globally, with tumors arising at the base of the tongue (BOT) constituting a significant proportion of cases<sup>1</sup>. The incidence of tongue cancer, particularly in South Asian countries such as India and Bangladesh, is notably high, though comprehensive epidemiological data remain limited in these regions. According to a hospital-based cancer registry report published by the National Institute of Cancer Research and Hospital (NICRH) in Bangladesh, from January 2008 to December 2010, a total of 27,281 patients attended NICRH, among whom 1,586 (5.81%) were diagnosed with oral cavity

cancers. Of these, 473 (1.73%) were cases of tongue cancer, placing carcinoma of the tongue consistently among the top ten malignancies during that period<sup>2</sup>. Similarly, data from India's National Cancer Registry Programme report an incidence rate of 6.5 per 100,000 population per year for tongue cancer<sup>3</sup>. The elevated incidence of base of tongue carcinoma in these populations has been linked to specific lifestyle and environmental factors. Chewing betel nut and betel leaf with lime, habits prevalent in South Asia, are strongly associated with increased risk. Additional risk factors include the use of unfiltered cigarettes, dark air-cured tobacco products, and alcohol consumption, which further exacerbate the likelihood of developing BOT carcinoma.<sup>4</sup> Human papillomavirus (HPV) infection has also emerged as a significant etiological factor, alongside nutritional deficiencies such as vitamin C deficiency and general malnutrition. Other contributory risks include ill-fitting dentures, poor oral hygiene, prolonged exposure to ultraviolet light, and occupational exposure to wood dust. Conversely, diets rich in antioxidants such as vitamin A, beta carotene, and alpha-tocopherol may provide a protective effect against carcinogenesis in the oral cavity<sup>4</sup>. Histologically, over 95% of base of tongue cancers are squamous cell carcinomas, which are classified based on differentiation as well, moderately, or poorly differentiated<sup>5</sup>. Clinically, BOT cancer often presents with symptoms such as persistent sore throat, referred otalgia, difficulties in speech and swallowing (dysphagia), and sometimes a foul odor<sup>6</sup>. Due to the anatomical complexity and late presentation, the majority of patients are diagnosed with locally advanced disease. Approximately 75% of these patients exhibit clinically positive cervical lymph nodes at diagnosis, with 30% presenting bilateral nodal involvement. Locally advanced disease (stage III and IVA, non-metastatic) often involves tumor extension into adjacent structures such as the floor of the mouth, tongue musculature, tonsillar pillars, hard palate, epiglottis, and medial pterygoid muscles<sup>5</sup>. Prognosis in advanced locoregional BOT cancer remains poor, with a high rate of local recurrence and distant metastasis. Approximately 50-60% of patients experience local recurrence within two years, and 20-30% develop metastatic disease despite treatment<sup>6</sup>. These challenges underscore the difficulty in managing this disease effectively, requiring complex treatment strategies.

Current treatment for locally advanced BOT carcinoma involves multimodality therapy, with two predominant approaches<sup>7</sup>. The first is definitive concurrent chemoradiotherapy (CCRT), which combines cisplatin-based chemotherapy with radiotherapy, improving organ preservation, locoregional control, and disease-free survival. Concurrent administration shortens the overall treatment duration but is associated with significant combined toxicities due to overlapping side effects<sup>7</sup>. The second approach involves induction chemotherapy followed by sequential chemoradiotherapy. This strategy aims to reduce distant metastasis risk and achieve tumor downstaging before local treatment, potentially enhancing locoregional control. However, this approach is limited by chemotherapy resistance, inability to overcome tumor hypoxia, increased treatment duration, and higher costs<sup>8</sup>. The study aimed to compare the treatment response and acute toxicities between concurrent chemoradiotherapy and sequential chemoradiotherapy after induction chemotherapy in patients with locally advanced base of tongue carcinoma in a limited-resource setting.

### Methods:

The study was conducted using a purposive sampling technique at the National Institute of Cancer Research and Hospital (NICRH), Dhaka, over 12 months (June 2016–May 2017), enrolling 60 patients who met the inclusion criteria. Patients were randomized into two equal groups: Arm A received concurrent chemoradiotherapy (CCRT) with external beam radiotherapy (66 Gy in 33 fractions over 6 ½ weeks) and weekly cisplatin (40 mg/m<sup>2</sup>); Arm B received three cycles of induction chemotherapy (cisplatin 75 mg/m<sup>2</sup> on Day 1 and 5-FU 750 mg/m<sup>2</sup>/day for 3 days, every 3 weeks), followed by the same CCRT as Arm A. RT planning was performed using the conformal radiation technique (3DCRT). GTV includes primary tumor and lymph nodes over 10mm in short axis dimension. CTV T includes whole base of tongue, tonsillar fossa, glossotonsillar sulcus, vallecula, pre-epiglottic space, tip of uvula; if epiglottic involvement occurs then entire supraglottic larynx included in CTV. CTV N includes bilateral levels II-IV & retropharyngeal lymph node; level IB included if primary tumor extends to oral cavity. PTV includes CTV +0.5 cm margin. Patients who completed 66 Gy were included in the study. Those who completed sequential chemotherapy followed by CCRT were also included. Baseline evaluation included history, physical examination, fiber-optic laryngoscopy, CECT of head and

neck, chest X-ray, and laboratory tests. Treatment response was assessed 6 weeks post-radiotherapy using RECIST v1.1 criteria. Follow-up was done at 3 and 6 months to evaluate disease control and late toxicities. Acute toxicities were graded using RTOG criteria and monitored throughout treatment and follow-up. Data were analyzed in SPSS v22.0 using descriptive statistics and Chi-square/Fisher's exact tests, with  $p < 0.05$  considered significant.

#### Inclusion Criteria:

- Histologically proven squamous cell carcinoma
- Disease stages III ( $T_3N_0M_0$  or  $T_{1-3}N_1M_0$ ) and Stage

IVA ( $T_{1-3}N_2M_0$  or  $T_4N_0-2M_0$ ), non-metastatic

- Karnofsky performance status  $> 70$
- Age less than 70 years

#### Exclusion Criteria:

- Histology other than squamous cell carcinoma
- Evidence of distant metastasis on clinical or radiographic examination
- Age above 70 years

#### Results

#### Discussion

**Table-I**

Baseline Characteristics of Study Participants by Treatment Arm (n = 60)				
Variable	Category	Arm A (n=30)	Arm B (n=30)	p-value
Age Group (years)	30–39	0 (0.0%)	0 (0.0%)	—
	40–49	9 (30.0%)	14 (46.7%)	
	50–59	15 (50.0%)	13 (43.3%)	
	60–69	6 (20.0%)	3 (10.0%)	
Mean Age $\pm$ SD	—	49.97 $\pm$ 9.53	48.83 $\pm$ 8.31	—
Sex	Male	22 (73.3%)	21 (70.0%)	—
	Female	8 (26.7%)	9 (30.0%)	—
Smoking Status	Smoker	21 (70.0%)	18 (60.0%)	0.417
	Non-smoker	9 (30.0%)	12 (40.0%)	
Tobacco Leaf Chewing	Yes	19 (63.3%)	22 (73.3%)	0.405
Betel Leaf Chewing	Yes	22 (73.3%)	27 (90.0%)	0.095
Betel Nut Chewing	Yes	24 (80.0%)	26 (86.7%)	0.488
Family History of Cancer	Present	7 (23.3%)	5 (16.7%)	0.519
Tumor Stage	Stage III	22 (73.3%)	22 (73.3%)	1.000
	Stage IVA	8 (26.7%)	8 (26.7%)	
Tumor Grade	Well Differentiated	12 (40.0%)	14 (46.7%)	0.709
	Moderately Differentiated	13 (43.3%)	14 (46.7%)	
	Poorly Differentiated	5 (16.7%)	2 (6.6%)	
Lymph Node Level Involvement	Level II	8 (26.7%)	4 (13.3%)	0.596
	Level III	4 (13.3%)	2 (6.7%)	
	Level IV	2 (6.7%)	5 (16.7%)	
	Level V	1 (3.3%)	2 (6.7%)	
Bilateral Cervical Node	Present	2 (6.7%)	3 (10.0%)	—
Lymph Node Size	<3 cm	11 (36.7%)	11 (36.7%)	1.000
	3–6 cm	5 (16.7%)	4 (13.3%)	
	>6 cm	1 (3.3%)	1 (3.3%)	
Lymph Node Consistency	Hard	17 (56.7%)	16 (53.3%)	0.929

Both treatment arms were well-matched at baseline across demographic, personal habit, and tumor-related variables. There were no statistically significant differences in age, sex distribution, smoking or chewing habits, family history of cancer, tumor stage or grade, or lymph node characteristics between the two groups.

**Table-II***CT Scan Response at 1st Follow-Up (n=60)*

Response Type	Arm A (n=30)	Arm B (n=30)	P-value
Complete Response	14 (46.7%)	17 (56.7%)	1.00
Partial Response	13 (43.3%)	10 (33.3%)	
No Response	1 (3.3%)	2 (6.7%)	
Progressive Disease	2 (6.7%)	1 (3.3%)	

Table IV summarizes at the first follow-up, a complete response was observed in 56.7% of Arm B and 46.7% of Arm A ( $p = 1.00$ ). Partial responses occurred in 43.3% of Arm A and 33.3% of Arm B. No response and progressive disease were infrequent, with each accounting for less than 7% in both groups. There was no statistically significant difference in response rates between the two arms.

**Table-III**

Non-Hematologic Toxicities Across Follow-Ups (n=60)						
Site	Grade	Arm	1st Follow-Up	2nd Follow-Up	3rd Follow-Up	P-value
Skin	G1	A	16 (53.3%)	15 (50.0%)	6 (20.0%)	>0.05
		B	14 (46.7%)	14 (46.7%)	7 (23.3%)	
	G2	A	14 (46.7%)	—	—	
		B	16 (53.3%)	—	—	
Mucosa	G1	A	16 (53.3%)	15 (50.0%)	5 (16.7%)	>0.05
		B	16 (53.3%)	16 (53.3%)	6 (20.0%)	
	G2	A	13 (43.3%)	—	—	
		B	14 (46.7%)	—	—	
	G3	A	1 (3.3%)	—	—	
		B	0 (0.0%)	—	—	
Ear	G1	A	18 (60.0%)	—	—	>0.05
		B	23 (76.7%)	—	—	
	G2	A	8 (26.7%)	—	—	
		B	6 (20.0%)	—	—	
	G3	A	0 (0.0%)	—	—	
		B	1 (3.3%)	—	—	
Salivary Gland	G1	A	19 (63.3%)	11 (36.7%)	6 (20.0%)	>0.05
		B	20 (66.7%)	9 (30.0%)	6 (20.0%)	
	G2	A	11 (36.7%)	—	—	
		B	10 (33.3%)	—	—	
Esophagus	G1	A	17 (56.7%)	8 (26.7%)	5 (16.7%)	>0.05
		B	17 (56.7%)	9 (30.0%)	6 (20.0%)	
	G2	A	12 (40.0%)	—	—	
		B	13 (43.3%)	—	—	
	G3	A	1 (3.3%)	—	—	
		B	0 (0.0%)	—	—	
Larynx	No Chg.	A	4 (13.3%)	—	—	>0.05
		B	8 (26.7%)	—	—	
	G1	A	18 (60.0%)	9 (30.0%)	3 (10.0%)	
		B	17 (56.7%)	14 (46.7%)	4 (13.3%)	
	G2	A	8 (26.7%)	—	—	
		B	5 (16.6%)	—	—	

Table 5 shows, across all three follow-ups, non-hematologic toxicities affected multiple organ systems with no significant differences between treatment arms ( $p > 0.05$ ). Grade 1 skin and mucosal toxicities were initially common in both arms but decreased over time. Ear toxicity (Grade 1) was more frequent in Arm B (76.7% vs. 60.0%), while salivary gland toxicity peaked in Arm B at the first follow-up (66.7%) and then declined. Esophageal toxicity also decreased similarly in both groups. Laryngeal changes varied, with more patients in Arm B showing no change (26.7% vs. 13.3%). However, none of these differences were statistically significant.

**Table-IV**

Hematologic Toxicities Across Follow-Ups (n=60)					
Parameter	Follow-Up	Grade	Arm A: Concurrent CRT	Arm B: Sequential CRT	P Value
WBC	1st Follow-Up	G1	9 (30.0%)	7 (23.3%)	>0.05
		G2	1 (3.3%)	1 (3.3%)	
	2nd Follow-Up	G1	5 (16.7%)	4 (13.3%)	
		G2	0 (0.0%)	0 (0.0%)	
	3rd Follow-Up	G1	4 (13.3%)	4 (13.3%)	
		G2	0 (0.0%)	1 (3.3%)	
Neutrophils	1st Follow-Up	G1	9 (30.0%)	6 (20.0%)	>0.05
		G2	2 (6.7%)	2 (6.7%)	
	2nd Follow-Up	G1	3 (10.0%)	4 (13.3%)	
		G2	0 (0.0%)	0 (0.0%)	
	3rd Follow-Up	G1	4 (13.3%)	5 (16.7%)	
		G2	0 (0.0%)	0 (0.0%)	
Hemoglobin %	1st Follow-Up	G1	4 (13.3%)	4 (13.3%)	>0.05
		G2	1 (3.3%)	1 (3.3%)	
	2nd Follow-Up	G1	6 (20.0%)	5 (16.7%)	
		G2	0 (0.0%)	1 (3.3%)	
	3rd Follow-Up	G1	5 (16.7%)	5 (16.7%)	
		G2	0 (0.0%)	1 (3.3%)	
Platelet	1st Follow-Up	G1	3 (10.0%)	3 (10.0%)	>0.05
	2nd Follow-Up	—	—	—	
	3rd Follow-Up	—	—	—	
Hematocrit	1st Follow-Up	G1	1 (3.3%)	1 (3.3%)	>0.05
	2nd Follow-Up	—	—	—	
	3rd Follow-Up	—	—	—	

Table 6 illustrates Hematologic toxicities were comparable between the two arms throughout all follow-up periods, and no statistically significant differences were found ( $p > 0.05$ ). White blood cell (WBC) toxicity of Grade 1 was most commonly observed during the first follow-up, occurring in 30.0% of patients in Arm A and 23.3% in Arm B, with the incidence declining in later visits. Neutrophil toxicity at Grade 1 similarly peaked at the first follow-up and was slightly more common in Arm A (30.0%) than in Arm B (20.0%). Hemoglobin levels showed some fluctuations at Grade 1 toxicity but remained comparable between the two groups. Changes in platelet counts and hematocrit levels were minimal and consistent across both arms, with low-grade effects primarily observed only during the first follow-up period.

This prospective comparative study aimed to evaluate and compare the efficacy and toxicity profiles of concurrent chemoradiotherapy (Arm A) and sequential chemoradiotherapy following induction chemotherapy (Arm B) in patients with locally advanced base of tongue carcinoma. Our findings are particularly relevant in the context of limited-resource settings like Bangladesh, where balancing treatment effectiveness with toxicity and patient tolerability is crucial. This discussion contextualizes the study results with relevant regional and international research findings to assess consistency, divergence, and implications for future management<sup>9</sup>. The mean age in Arm A was  $49.97/\pm 9.53$  years and  $48.83/\pm 8.31$  years in Arm B, which reflects the general trend of oropharyngeal cancers affecting individuals in their 5th to 6th decades of life. A similar age distribution was observed in a study conducted at Chittagong Medical College, where the average age was 56.25 years, slightly older than our cohort, possibly due to regional lifestyle differences and healthcare-seeking behaviors. Both arms exhibited a male predominance (70%), in line with global epidemiological data showing higher prevalence of head and neck cancers in males due to greater exposure to carcinogenic risk factors like tobacco and betel nut use<sup>10</sup>. Personal habits analysis revealed that smoking was prevalent in 70% of Arm A and 60% of Arm B patients, and betel nut chewing was seen in 80% and 86.7% of patients, respectively. These rates are significantly higher than those reported in studies from developed nations but are consistent with findings from South Asian studies, including a study where 66.7% of oral cancer patients were smokeless tobacco chewers, and 24.4% used both smoking and smokeless tobacco. This emphasizes the critical role of preventive education and cessation support in reducing disease incidence in high-risk populations (11). The clinical staging was identical in both arms, with 73.3% of cases being Stage III and 26.7% being Stage IVA. This is consistent with findings by Lalango et al., where most patients presented with advanced-stage disease, underscoring the diagnostic delay common in developing countries<sup>12</sup>. In terms of tumor grade, 40% of Arm A and 46.7% of Arm B had well-differentiated tumors, while moderately differentiated tumors were present in 43.3% (Arm A) and 46.7% (Arm B), and poorly differentiated tumors in 16.7% (Arm A) and 6.6% (Arm B). These proportions are consistent with general patterns of squamous cell carcinoma differentiation reported in major head and neck oncology textbooks and reviews<sup>13</sup>. Nodal involvement was present in all patients, with Level II cervical nodes being the most

commonly affected (26.7% in Arm A and 13.3% in Arm B). Bilateral nodal involvement was slightly higher in Arm B (10%) compared to Arm A (6.7%). This pattern mirrors findings by Ferlito et al., where bilateral nodal involvement, particularly in base of tongue cancers, was common due to the midline anatomical location and lymphatic drainage pattern<sup>14</sup>. Response evaluation at the first follow-up showed a complete response (CR) in 46.7% of Arm A and 56.7% of Arm B patients, indicating a slight edge for the sequential approach. Partial response (PR) was observed in 43.3% (Arm A) and 33.3% (Arm B), while minimal cases in either group showed stable or progressive disease. These outcomes align with the Southwest Oncology Group (SWOG) trial by Urba et al., which reported a histological CR rate of 62% for induction chemotherapy followed by concurrent chemoradiation in head and neck cancers. Though our CR rates were slightly lower, the overall trend favors the use of induction chemotherapy in select cases, particularly where tumor burden is high or where there is a need to downstage disease before definitive local therapy<sup>15</sup>. Toxicity profiles were comparable across both arms, with manageable side effects. Grade 1 skin reactions were observed in 53.3% of Arm A and 46.7% of Arm B during the first follow-up. Mucosal toxicities were equally reported in both arms (53.3% each). In comparison, a study observed Grade 3 mucositis in 60% of patients undergoing similar treatment, suggesting that our cohort experienced milder mucosal reactions, possibly due to optimized supportive care or shorter follow-up duration<sup>16</sup>. Salivary gland toxicity peaked at the first follow-up in Arm B (66.7%) and was also notable in Arm A (53.3%), gradually declining in both arms. This trend aligns with findings by Deasy et al., who described early salivary gland dysfunction after radiotherapy with partial recovery over time<sup>17</sup>. Ear toxicity (Grade 1) was slightly higher in Arm B (76.7%) compared to Arm A (60%), which may be attributable to cumulative cisplatin dose or anatomical field overlap during radiotherapy. Hematologic toxicity remained largely within Grade 1 across both arms. WBC toxicity (Grade 1) was noted in 30% (Arm A) and 23.3% (Arm B), while neutrophil toxicity was similarly low. In contrast, Chakraborty et al. observed higher rates of Grade 3–4 neutropenia and thrombocytopenia with more intensive induction chemotherapy regimens, suggesting that our regimen was more tolerable and potentially safer in resource-limited settings with restricted access to growth factor support<sup>18</sup>.

### **Limitations of the Study:**

The limitations of this study include its quasi-experimental design with potential bias due to lack of randomization, small sample size, single-center setting, and absence of survival analysis.

### **Conclusion**

Concurrent and sequential chemoradiotherapy after induction chemotherapy showed similar treatment responses and manageable toxicity in patients with a locally advanced base of tongue carcinoma within a limited resource setting. Both modalities provide effective therapeutic options.

### **Recommendation**

Larger, multicenter studies with longer follow-up are recommended to validate these findings further and to assess long-term survival and quality of life outcomes. Treatment choices should be individualized based on the patient's condition, resource availability, and institutional expertise.

### **Conflict of interest:** None

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