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Original Research Article

Comparative study between sequential chemoradiotherapy with concurrent chemoradiotherapy for unresectable locally advanced esophageal cancer

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ABSTRACT

Background: Esophageal squamous cell carcinoma (ESCC) is a prevalent malignancy in South Asia with a high burden of unresectable cases at presentation. Chemoradiotherapy remains the mainstay of treatment, with concurrent chemoradiotherapy (CCRT) offering improved tumor control but at the cost of higher toxicity. The study aimed to compare the clinical efficacy and treatment-related toxicities of sequential chemoradiotherapy (SCRT) versus concurrent chemoradiotherapy (CCRT) in patients with unresectable locally advanced ESCC.
Methods: This quasi-experimental study was conducted at Khwaja Yunus Ali Medical College and Hospital, Sirajganj, from January 2020 to June 2021. A total of 62 patients with histologically confirmed unresectable ESCC were randomly assigned to two groups: Arm A (CCRT) and Arm B (SCRT), with 31 patients in each group.
Results: The baseline characteristics were comparable between the two arms. At 24 weeks, complete response rates were slightly higher in Arm A (51.61%) than in Arm B (41.93%), though not statistically significant ($p>0.05$). Toxicity analysis revealed a significantly higher incidence of Grade III esophagitis in the CCRT group (22.58% vs 3.23%; $p=0.001$). Hematologic and late radiation-related toxicities were also more frequent in Arm A. Weight loss and need for nutritional support (e.g., NG tube) were more common in the CCRT group, although not statistically significant.
Conclusions: While both treatment strategies showed similar tumor response rates, SCRT was associated with a more favorable toxicity profile. Thus, SCRT may serve as an effective and safer alternative for patients with unresectable locally advanced ESCC, especially in resource-constrained settings or among patients with borderline performance status.

Keywords: Cancer, Chemoradiotherapy, Survival, Therapy

INTRODUCTION

Esophageal cancer is a significant global health burden, ranking as the seventh most common cancer and the sixth leading cause of cancer-related deaths worldwide.[1] The two major histological types, esophageal squamous cell carcinoma (ESCC) and adenocarcinoma, show distinct epidemiological patterns, with ESCC predominating in

developing countries including Bangladesh, India and parts of East Asia and Africa.[2,3] In Bangladesh, ESCC accounts for a substantial proportion of esophageal malignancies, driven by high prevalence of risk factors such as tobacco smoking, betel nut chewing, alcohol consumption and nutritional deficiencies.[4,5] Despite advances in early detection and treatment, the prognosis remains poor, with five-year survival rates below 20%, particularly for patients presenting with unresectable locally advanced disease.[6,7] Surgical resection remains the primary curative approach for localized esophageal cancer. However, many patients present with disease that is unresectable due to tumor extent or medical comorbidities, necessitating alternative treatment modalities.[8]

Chemoradiotherapy has become the standard of care for such cases, combining systemic chemotherapy and localized radiotherapy to improve locoregional control and overall survival.[9,10] Two main strategies are employed: concurrent chemoradiotherapy (CCRT), in which chemotherapy is administered simultaneously with radiotherapy and sequential chemoradiotherapy (SCRT), where chemotherapy precedes radiotherapy.[11] The landmark Radiation Therapy Oncology Group (RTOG) 85-01 trial demonstrated the superiority of CCRT over radiotherapy alone, with significantly improved survival and local control, establishing CCRT as the preferred approach.[9]

However, CCRT is associated with increased acute toxicities, including esophagitis, hematologic side effects and nutritional compromise, which can limit patient compliance and quality of life.[11,12] These toxicities pose particular challenges in resource-limited settings like Bangladesh, where supportive care resources are constrained.[4] SCRT is considered a potential alternative with potentially reduced toxicity by avoiding overlapping treatment side effects, though concerns remain regarding its relative efficacy compared to CCRT.[11,13]

Several studies have compared SCRT and CCRT, yielding mixed results some report comparable survival outcomes with better tolerability in SCRT, while others favour the enhanced tumor control seen with concurrent treatment.[10,14] Given the heterogeneity in patient populations, treatment protocols and healthcare infrastructure, it is important to evaluate these approaches in local contexts.

In Bangladesh, data comparing SCRT and CCRT for unresectable locally advanced ESCC are sparse, limiting evidence-based decision-making. This study aims to fill this gap by comparing the efficacy, toxicity profiles and treatment tolerability of SCRT versus CCRT in a Bangladeshi cohort. The findings will provide crucial insights for clinicians balancing treatment intensity and patient safety in a resource-constrained environment.[5] Ultimately, optimizing chemoradiotherapy regimens for unresectable ESCC can improve survival outcomes and maintain patients' quality of life. By assessing these two established approaches in the context of local patient characteristics and healthcare capabilities, this research contributes valuable evidence toward more personalized, effective cancer care in Bangladesh and similar settings.

METHODS

This quasi-experimental study was conducted at the Department of Oncology, Khwaja Yunus Ali Medical College and Hospital (KYAMCH), Enayetpur, Sirajganj, from January 2020 to June 2021. A total of 62 patients with histologically confirmed, unresectable, locally advanced esophageal squamous cell carcinoma (ESCC) were enrolled. Patients were aged 18 to 70 years, with ECOG performance status up to 2 and had no prior history of surgery, chemotherapy or radiotherapy.

After obtaining written informed consent and IRB approval, patients were randomly assigned to two treatment arms Arm A (Concurrent Chemoradiotherapy, CCRT) and Arm B (Sequential Chemoradiotherapy, SCRT), each with 31 patients. In Arm A, patients received radiotherapy at a total dose of 50.4 Gy in 28 fractions (1.8 Gy/fraction) over 5 weeks along with concurrent chemotherapy cisplatin (75 mg/m² IV on Day 1) and 5-fluorouracil (1000 mg/m² continuous IV infusion, Days 1–4) every 4 weeks for four cycles. In Arm B, patients first received two cycles of the same chemotherapy regimen at 3-week intervals, followed by radiotherapy with identical fractionation.

Radiotherapy was delivered using 3D conformal techniques (3D-CRT) with a linear accelerator (Elekta Synergy) employing 6 MV and 15 MV photon beams. CT simulation and target volume delineation followed standard oncological protocols, incorporating GTV, CTV and PTV with appropriate margins. Baseline evaluation included clinical history, physical examination, blood tests, endoscopy with biopsy, CT imaging and cardiac assessment. Treatment response was assessed using RECIST 1.1 criteria, while toxicities were graded using CTCAE v3.0. Patients were followed up at 6, 12 and 24 weeks post-treatment. Statistical analysis was performed using SPSS v25.0, employing chi-square and t-tests where appropriate, with significance defined at $p<0.05$. Ethical standards were maintained throughout the study.

Inclusion criteria

Patients aged between 18 and 70 years. Histologically confirmed squamous cell carcinoma (SCC) of the esophagus. Clinical staging of T1 to T4 tumors with N1–N3 nodal involvement and no evidence of distant metastasis (as per AJCC 7th edition). ECOG Performance Status 0 to 2

Exclusion criteria

Patients with double primary malignancies. Pregnant or lactating women. Presence of severe uncontrolled comorbidities, including significant heart disease,

uncontrolled diabetes mellitus, uncontrolled hypertension or psychiatric disorders.

RESULTS

Table 1 shows both treatment arms were well matched in terms of demographic and clinical characteristics. The mean age was comparable between Arm A (55.7±9.9 years) and Arm B (54.8±8.9 years), with no statistically significant difference. Common risk factors such as tobacco smoking and betel leaf use were prevalent in both groups, although betel leaf use was higher in Arm B (87.1% vs 70.97%).

Alcohol use was negligible in both arms. Performance status was similar, with most patients in ECOG 1 (77.42% in Arm A vs 74.19% in Arm B). The primary tumor site was predominantly in the middle thoracic esophagus in both arms. Distribution of T and N stages, group stage and histological grade was largely balanced, though Arm B had more moderately differentiated tumors (51.6%) compared to none in Arm A. Comorbidities such as diabetes, hypertension and ischemic heart disease were more frequently reported in Arm B, though without statistical significance.

Figure 1 presents the gender distribution of the study population. Both arms demonstrated a male predominance, with males accounting for 81% in Arm A and 77% in Arm B. Female patients constituted 19% of Arm A and 23% of Arm B. This male predominance aligns with known epidemiological patterns of esophageal cancer, particularly in regions with high tobacco and betel nut use. The slight difference in gender distribution between the two arms is minor and unlikely to influence treatment outcomes or toxicity profiles.

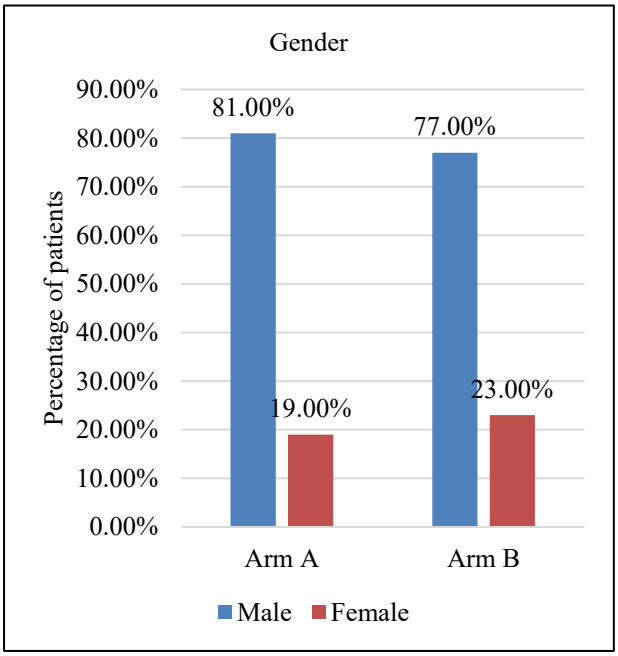

Figure 1: Distribution of the patients by gender(n=62).

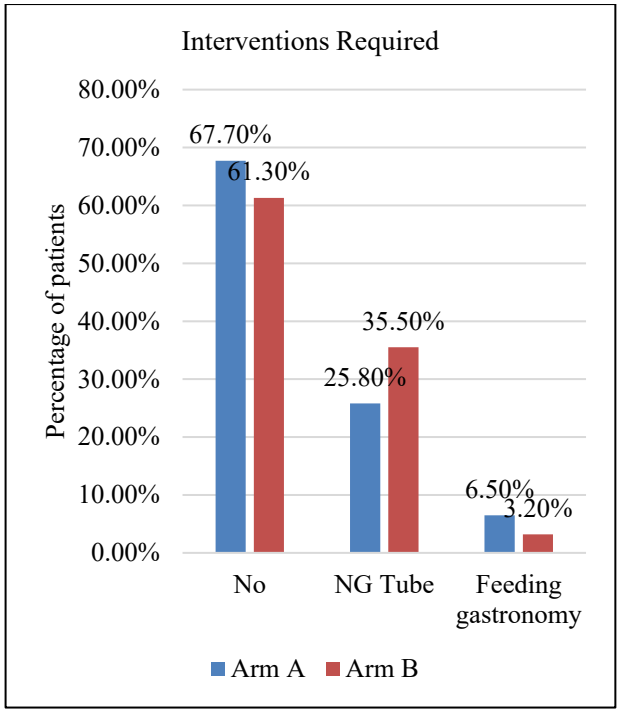

Figure 2: Distribution of the patients by interventions required (n=62).

Table 2 presents at all evaluation points (6th, 12th and 24th weeks), both arms demonstrated similar response profiles. At 6 weeks, complete response was slightly higher in Arm A (41.94%) than in Arm B (35.48%) and partial response was also comparable (48.39% vs 45.16%). A similar pattern persisted through the 12th and 24th weeks, with Arm A showing marginally higher complete responses at each interval. Progressive disease was observed in a small percentage of patients in both arms, slightly higher in Arm B. However, none of the differences reached statistical significance, indicating comparable efficacy between sequential and concurrent approaches in terms of tumor response.

Table 3 illustrates significant differences were noted in the incidence and severity of acute esophagitis. Arm B (sequential chemoradiotherapy) had a significantly higher rate of Grade I esophagitis (87.10% vs 29.03%, p=0.001), whereas Arm A (concurrent chemoradiotherapy) had higher proportions of Grade II (48.39%) and Grade III (22.58%) esophagitis compared to Arm B (9.68% and 3.23%, respectively). This suggests that while mild esophagitis was more common in the concurrent group, the sequential group experienced more severe forms of this toxicity.

Table 4 presents the hematological toxicities observed in both arms. In the case of anemia, mild cases (Grade I) were more common in Arm B (32.26%) than in Arm A (19.35%), while moderate cases (Grade II) were higher in Arm A (51.61%). Severe anemia (Grade III) was also slightly more frequent in Arm A (12.90%) than in Arm B (6.45%). For neutropenia, a similar pattern was seen, with

more cases in Arm A across all grades. However, none of these differences were statistically significant, as the p-values were 0.350 for anemia and 0.156 for neutropenia. This suggests that while Arm A showed a trend toward more side effects, the differences could be due to chance.

Table 5 shows both arms experienced nausea and vomiting, with Grade II being the most frequent (61.29% in Arm A vs 54.84% in Arm B). Grade I and Grade III incidences were also comparable and the differences were not statistically significant (p=0.644), indicating that gastrointestinal side effects were similar in both treatment modalities.

Table 6 shows late radiation-related toxicities affecting skin and lung were more frequent in Arm A. Grade I and II skin toxicities occurred more often in Arm A (58.06% and 22.58%, respectively) compared to Arm B (38.71% and 12.90%), whereas the incidence of no skin toxicity was higher in Arm B (48.39% vs 19.35%). Lung toxicities followed a similar trend, with Arm A showing more cases of Grade I and II toxicity. However, none of these differences reached statistical significance.

Table 7 illustrates neurotoxicity was more commonly observed in Arm A (58.07% combined Grade I and II) compared to Arm B (38.71%), though again without statistical significance (p=0.313). Dysphagia occurred at similar rates in both arms across all grades, with no significant difference (p=0.948), suggesting that the burden of swallowing difficulty was comparable during treatment.

In figure 1, the distribution of patients based on interventions required during treatment reveals that the majority in both arms did not need any form of nutritional support, with 67.7% in Arm A and 61.3% in Arm B managing without intervention. However, nasogastric (NG) tube insertion was more commonly required in Arm B (35.5%) compared to Arm A (25.8%), suggesting a relatively higher incidence of treatment-related dysphagia or nutritional compromise in the concurrent chemoradiotherapy group. Feeding gastrostomy was rarely needed in either group, but slightly more patients in Arm A (6.5%) required this intervention compared to Arm B (3.2%). Overall, while most patients tolerated treatment without the need for feeding support, the higher NG tube usage in Arm B indicates a possible trend toward increased acute toxicity affecting swallowing. Table 8 shows weight loss was more pronounced in Arm A, where 54.83% experienced Grade I and 32.25% Grade II weight loss, compared to 45.16% and 22.58% respectively in Arm B. Notably, more patients in Arm B reported no significant weight loss (32.25% vs 12.90%), indicating better nutritional preservation. However, the difference was not statistically significant (p=0.183).

Table 1: Baseline Characteristics of patients in Arm A and Arm B (n=62).

Variables	Category	Arm A (n=31)	Arm B (n=31)	P value
Age (years)	Mean±SD	55.7±9.9	54.8±8.9	>0.05
Risk factor	Tobacco smoking	61.29%	64.52%	>0.05
	Betel leaf use	70.97%	87.10%	
	Alcohol use	0.00%	3.23%	
	Multiple risk factors	51.61%	58.06%	
	No risk factors	9.68%	3.23%	
Performance status	ECOG 1	77.42%	74.19%	
	ECOG 2	22.58%	25.81%	
Site of primary tumor	Middle thoracic	54.8%	61.3%	>0.05
T stage	T3	29.03%	32.26%	>0.05
	T4a	16.13%	22.58%	
	T4b	6.45%	6.45%	
	Tx	48.39%	38.71%	
Nodal status	N0	29.0%	25.81%	>0.05
	N1	32.26%	-	
	N2	32.26%	38.71%	
	N3	6.45%	6.45%	
Group stage	I-II	16.13%	12.90%	>0.05
	III	54.84%	51.61%	
	IVA	29.03%	35.48%	
Histological grade	Well	45.2%	41.9%	>0.05
	Moderate	-	51.6%	
	Poorly	12.9%	9.7%	
Comorbidity	Diabetes mellitus	12.90%	19.35%	
	Hypertension	22.58%	16.13%	
	Ischemic heart disease	0.00%	6.45%	

Table 2: Treatment response at 6th, 12th and 24th weeks (n=62).

Response	Arm A (n=31)	Arm B (n=31)	Time Point	P value
Complete response	41.94%	35.48%	6th Week	>0.05
Partial response	48.39%	45.16%	6th Week	>0.05
Stable disease	9.68%	19.35%	6th Week	>0.05
Complete response	48.38%	41.93%	12th Week	>0.05
Partial response	41.93%	38.70%	12th Week	>0.05
Stable disease	6.45%	12.90%	12th Week	>0.05
Progressive disease	3.23%	6.45%	12th Week	>0.05
Complete response	51.61%	41.93%	24th Week	>0.05
Partial response	38.71%	45.16%	24th Week	>0.05
Progressive disease	3.23%	6.45%	24th Week	>0.05

Table 3: Acute esophagitis in study arms (n=62).

Grade	Arm A (n=31)	Arm B (n=31)	P value
Grade I	29.03%	87.10%	
Grade II	48.39%	9.68%	0.001
Grade III	22.58%	3.23%	

Table 4: Hematological toxicities in study arms (n=62).

Toxicity type		Grade I	Grade II	Grade III	P value
Anemia	(Arm A)	19.35%	51.61%	12.90%	0.350
	(Arm B)	32.26%	35.48%	6.45%	
Neutropenia	(Arm A)	32.26%	19.35%	9.68%	0.156
	(Arm B)	25.81%	6.45%	3.23%	

Table 5: Nausea/vomiting in study arms (n=62).

Grade	Arm A (n=31)	Arm B (n=31)	P value
Grade I	16.13%	25.81%	0.644
Grade II	61.29%	54.84%	
Grade III	22.58%	19.35%	

Table 6: Late skin and lung toxicity in study arms (n=62).

Toxicity type		Grade I	Grade II	Absent	P value
Skin	(Arm A)	58.06%	22.58%	19.35%	0.091
	(Arm B)	38.71%	12.90%	48.39%	
Lung	(Arm A)	48.39%	6.45%	45.16%	0.210
	(Arm B)	38.71%	0.00%	61.29%	

Table 7: Neurotoxicity and dysphagia in study arms (n=62).

Toxicity type		Grade I	Grade II	Absent	P value
Neurotoxicity	(Arm A)	48.39%	9.68%	41.94%	0.313
	(Arm B)	32.26%	6.45%	61.29%	
Dysphagia	(Arm A)	41.94%	19.35%	29.03%	0.948
	(Arm B)	45.16%	22.58%	22.58%	

Table 8: Weight loss in study arms (n=62).

Parameter	Grade I (%)	Grade II (%)	No issue (%)	P value
Weight loss (Arm A)	54.83%	32.25%	12.90%	0.183
Weight loss (Arm B)	45.16%	22.58%	32.25%	

DISCUSSION

This study aimed to compare the clinical efficacy and treatment-related toxicities of sequential chemoradiotherapy (SCRT) versus concurrent chemoradiotherapy (CCRT) in patients with unresectable, locally advanced esophageal squamous cell carcinoma (ESCC). While both arms showed comparable response rates, toxicity profiles significantly differed favoring SCRT.

The complete response (CR) rates in our study at 24 weeks were 51.61% for the CCRT group and 41.93% for the SCRT group. This aligns with findings from, which reported a CR rate of 62.2% in the CCRT arm for ESCC using cisplatin and 5-FU.[15] Although our study observed a higher CR rate with CCRT compared to SCRT, the difference did not reach statistical significance, suggesting that SCRT remains a clinically acceptable alternative when CCRT is contraindicated. In our study, the toxicity burden was significantly higher in the CCRT arm, particularly concerning acute esophagitis. Grade III esophagitis occurred in 22.58% of CCRT patients, compared to just 3.23% in the SCRT arm (p=0.001).

These findings are consistent with those reported by a study, where endoscopic grade 3 esophagitis was observed in 27.1% of patients undergoing CCRT, while none in the radiotherapy-alone group exhibited this severity (p=0.004).[16] The increased toxicity can be attributed to the radio sensitizing effect of concurrent chemotherapy, which, while enhancing tumor response, often compromises mucosal integrity.

Additionally, hematologic toxicities such as anemia and neutropenia were more pronounced in the CCRT arm. Though our study did not find statistically significant differences in hematologic parameters, the trend echoed that of, who reported grade≥3 leukopenia in 13.7% of CCRT recipients, compared to 4% in RT-alone or SCRT groups.[17] This higher toxicity profile of CCRT emphasizes the need for rigorous patient selection, particularly in populations with marginal performance status. Regarding nutritional impact, 35.5% of SCRT patients required nasogastric (NG) tube feeding, slightly higher than 25.8% in CCRT.

However, paradoxically, Grade II weight loss was more frequent in the CCRT group (32.25% vs 22.58%), reflecting the more severe esophagitis and systemic toxicity. Studies like that by Wang et al, (2022) emphasize early nutritional interventions to prevent treatment interruptions and maintain dose intensity.[18] Neurotoxicity and late skin/lung toxicities were also marginally higher in the CCRT group in our study, although not statistically significant.

This pattern has been noted in prior studies, where cisplatin-induced neuropathy was more prevalent with concurrent regimens.[19] Our findings suggest that although SCRT may result in longer overall treatment duration, it reduces cumulative toxicity a valuable consideration in resource-limited settings. The progression of disease during follow-up was comparable in both arms, with slightly higher progression in the SCRT group at 6.45% versus 3.23% in CCRT. This again supports data from RTOG 85-01, a landmark study that demonstrated superior local control with CCRT (5-years OS 26% vs 0% in RT alone) but also reported substantial treatment-related toxicity.[10]

The findings resonate with Vellayappan et al who in a meta-analysis, argued that although surgery after chemoradiation may offer marginal benefits in select cases, the addition of concurrent chemotherapy significantly enhances local control, albeit with greater toxicity.[20]

Thus, the decision between SCRT and CCRT should be individualized based on patient comorbidities, ECOG performance status and resource availability. The utility of SCRT may be particularly relevant in Bangladesh and similar low-resource settings, where treatment adherence, supportive care and nutritional support may be inconsistent.

For patients with borderline performance status or elderly individuals, SCRT offers a tolerable and logistically feasible regimen with comparable outcomes to CCRT. It is also noteworthy that the chemotherapy agents used in this study cisplatin and 5-FU remain the backbone of treatment in many centers worldwide.

However, newer agents such as paclitaxel or carboplatin and targeted therapies including PD-1 inhibitors, are currently under investigation and may shape future regimens for locally advanced EC.[21,22] In conclusion, this study underscores that while CCRT offers slightly superior tumor response, it is associated with higher acute and late toxicities. SCRT, though slightly less aggressive, is a viable, safer option for many patients, particularly in regions where patient tolerance and logistical barriers are of concern.

The limitations of this single-institution study include potential selection bias, a short study period that prevents survival analysis, a small sample size and limited generalizability to the broader population of Bangladesh.

CONCLUSION

This study demonstrated that both sequential chemoradiotherapy (SCRT) and concurrent chemoradiotherapy (CCRT) yield comparable tumor response rates in patients with unresectable locally advanced esophageal squamous cell carcinoma.

However, SCRT was associated with significantly lower incidence of severe acute toxicities, particularly esophagitis and had a more favorable overall toxicity profile. These findings suggest that SCRT may be a safer and more tolerable treatment option, especially for patients with compromised performance status or in resource-limited settings where managing treatment-related toxicities is challenging. Larger-scale studies with long-term follow-up are warranted to confirm these results and to further evaluate survival outcomes.

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