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Feasibility, Safety, and Factors Predicting Completion of CROSS Protocol–Based Neoadjuvant Chemoradiotherapy for Esophageal Squamous Carcinoma: Experience from an Indian Tertiary Care Cancer Center

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Abstract


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Background Neoadjuvant chemoradiotherapy (NACRT) using the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) protocol has improved esophageal cancer outcomes. This study reports the real-world experience of the CROSS regimen for esophageal squamous cell carcinoma (ESCC) regarding its feasibility, safety, and predictors of treatment completion from an Indian tertiary center.

Methodology A retrospective review was conducted for patients with ESCC receiving CROSS (radiation dose: 41.4 Gy) or a modified CROSS (mCROSS; radiation dose: 45 Gy) protocol NACRT between 2015 and 2022. We studied the treatment tolerability, factors predicting NACRT completion, and the effect of completion of its chemotherapy component on the pathological outcomes.

Results Of the109 patients (68.8% males; mean age, 56 ± 9 years; Charlson's comorbidity index [CCI] >2, 19.3%; stage III–IVA, 58%; mean tumor length, 5.5 ± 2.1cm; CROSS, 70.6%; mCROSS, 29.4%), all except 4 completed radiotherapy but only 58 (53.2%) patients completed ≥4 cycles of chemotherapy. Forty-nine patients belonged to the "extended" CROSS trial inclusion criteria. Among the 60 patients who fulfilled the CROSS inclusion criteria, only 51.7% were able to complete ≥4 chemotherapy cycles. The commonest reason for noncompletion of chemotherapy was the occurrence of neutropenia (60.8%). Pretreatment hemoglobin (≥12 vs. <12 g%;

Keywords
- CROSS
- esophageal squamous carcinoma
- feasibility

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odds ratio [OR]: 2.76; 95% confidence interval [CI]: 1.10–6.96; $p = 0.031$), a low CCI (≤ 2 vs. >2; OR: 2.98; 95% CI: 1.02–8.73; $p = 0.047$), and radiation therapy techniques (conformal vs. conventional; OR: 3.29; 95% CI: 1.14–9.50; $p = 0.028$) were associated with completion of chemotherapy (≥ 4 cycles). Although there was a trend toward improved R0 resection (95.7 vs. 91.4%), reduced node positivity (17.0 vs. 31.4%), and a high pCR (57.4 vs. 48.6%) in patients completing chemotherapy (≥ 4 cycles) compared with those not completing chemotherapy (<4 cycles), these differences were statistically nonsignificant.

Conclusion In this study, ESCC patients receiving the CROSS protocol NACRT could complete their radiotherapy component, but a significant proportion exhibited poor chemotherapy tolerance. Neutropenia was a major factor limiting chemotherapy delivery, but anemia, high CCI, and conventional radiation techniques were also associated with noncompletion of chemotherapy. The omission of a few chemotherapy cycles had no significant effect on the pathological response; however, its impact on cancer survival requires further evaluation.

- neoadjuvant chemoradiotherapy
- pathological outcomes
- treatment

Introduction

Esophageal cancer (EC) is the seventh most common cancer and ranks sixth in terms of cancer-associated mortality worldwide,[1] with developing countries accounting for approximately 80% of cases and deaths.[2] The mainstay of treatment for locally advanced EC is surgery, but the survival outcomes following surgery alone are dismal, with 5-year survival rates of approximately 25%.[3] Following the "Chemo-Radiotherapy for Oesophageal cancer followed by Surgery Study" (CROSS)[4] and the "NEOCRTEC5010"[5] trials, neoadjuvant chemoradiotherapy (NACRT) and surgery have become the standard trimodality therapy for locally advanced but resectable EC. However, a significant number of patients suffer from cancer-associated malnutrition and cachexia, which could lead to deterioration of their general well-being during the preoperative therapy, resulting in treatment interruption/poor tolerance and poor candidature for surgery. Additionally, there may be a general reluctance to practice this form of preoperative treatment due to the fear of increased postoperative complications and the lack of adequate infrastructure for its delivery, particularly in low-middle-income nations.[6] Furthermore, few reported literature from India and other South Asian countries often shows poor patient tolerability to NACRT, particularly to its chemotherapy component.[7,8] The advanced stage at presentation, poor baseline performance and nutritional statuses of the patients, and predominance of esophageal squamous cell carcinoma (ESCC) are common in Asian countries[2,9–11]; these factors may alter the behavior and response of the tumor to NACRT and could affect its effective delivery.

NACRT, as per the CROSS regimen, is the most accepted preoperative therapy for ESCC. However, real-world data from low-middle-income nations about the selection and outcomes of ESCC patients receiving NACRT as per the CROSS regimen in the standard care setting outside the scope of a clinical trial are scarce. Although there are a few studies from the Indian subcontinent that report the feasibility, safety, and outcomes of NACRT in operable EC,[7,8,10,12] data are scarce on the pretherapy factors that could influence the treatment tolerability[8] and the effect of the completion of NACRT on the pathological outcomes. Identifying these pretherapy factors could affect the choice of trimodality therapy or serve as a guide for its modifications. This can also help in better optimization of patients receiving NACRT and improve their treatment tolerance.

The purpose of this single-center study was to explore the feasibility, safety, and tolerability of NACRT (CROSS protocol [paclitaxel–carboplatin + 41.4 Gy] or its modification [45 Gy]) in patients with ESCC and to determine the pretherapy factors that could potentially affect the treatment completion. Additionally, we studied the impact of neoadjuvant treatment completion on the various pathological outcomes.

Patients and Methods

After obtaining the ethics committee approval (Min. No. 12998/2020), a retrospective review of patients with ESCC, who were discussed in the tumor board of our cancer center from January 2015 to May 2022, was performed. The relevant data were collected from a prospective database and the electronic medical records.

The clinico-demographic details collected included details of comorbidities, substance abuse, body mass index, baseline laboratory data, tumor location, staging, and treatment received. The comorbidities were graded using the Charlson comorbidity index (CCI),[13] and a CCI >2 was considered a "high" score. The patient's performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) score.[14] The diagnosis of EC was confirmed using esophagogastroscopy and biopsy. A contrast-enhanced computed tomography of the thorax/abdomen was used to stage the disease. ^{18}Fluorodeoxyglucose positron emission tomography was performed selectively. The Union for International Cancer Control TNM (tumor

node metastasis) classification (8th edition) was used for disease staging.[15]

The initial part of this study cohort includes patients who received 45-Gy radiation and concurrent paclitaxel/carboplatin × 5 cycles (defined as "modified" CROSS regimen [mCROSS]), which was followed in our center before the adaptation of the CROSS protocol. The remaining patients received NACRT as per the CROSS protocol (41.4 Gy in 23 fractions and concurrent 5 cycles of paclitaxel [50 mg/m^2] and carboplatin [area under the curve (AUC) = 2]).[4] Total radiation of 41.4 to 45 Gy is widely accepted as "low-dose radiation" in a neoadjuvant setting for EC; hence, we decided to include the former group in this study. Patients who received NACRT beyond the original CROSS trial inclusion criteria[4] were classified as an "extended" criteria group.

Radiation was planned to include the gross tumor and the nodal disease with appropriate margins. The adverse events were reported using Common Terminology Criteria for Adverse Events (CTCAE) v4.0.[16] Chemotherapy completion was defined as having received a minimum of four cycles.

The clinical reassessment was performed about 6 weeks after NACRT, and suitable patients underwent surgery. The reasons to defer the operation were documented, if any. The severity of 30-day postoperative complications was graded using the Clavien–Dindo grading.[17] The pathological (ypTNM) staging was defined as per UICC TNM (8th edition).[15] The completeness of the oncological resection and the tumor regression grading (TRG) was defined as per the College of American Pathologists criteria.[15]

Continuous variables were documented using mean with standard deviation (SD) or median with range or interquartile range (IQR). The frequencies and percentages were used to document the categorical variables, which were compared using an independent *t*-test or Mann–Whitney *U* test. The chi-squared test or Fisher exact test was used to find the association between completion of chemotherapy (≥4 vs. <4 cycles) and the pretherapy factors that could influence the treatment completion. The study variables that were significant at less than 0.05 levels in an unadjusted analysis were included in a multivariable logistic regression model. The model fit was assessed using the Hosmer and Lemeshow goodness fit test. A *p*-value less than 0.05 was considered significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM Corp., Armonk, NY, United States).

Results

Demography, Clinical, and Tumor Profile

The baseline clinico-demography and tumor profile are summarized in ►Table 1. In total, 109 patients (63.3% males; mean age, 55.9 ± 9.0 years) were included. Forty-one (37.6%) patients had at least one comorbid illness with a CCI >2 in 21 (19.3%) patients. The majority (94.5%) of patients had ECOG scores of 0 to 1, 20 (18.3%) patients were "underweight," and

Table 1 Demography, clinical profile, and tumor-related details

Variable	Value $N = 109$
Age (y)	55.9 ± 9.0
≤60	69 (63.3)
>60	40 (36.7)
Sex	
Male	75 (68.8)
Female	34 (31.2)
Ethanol consumption	21 (19.3)
Tobacco consumption	61 (56.0)
Domicile	
Northeast India	35 (32.1)
East India	24 (22.0)
South India	19 (17.5)
West India	1 (0.9)
Central India	1 (0.9)
Bangladesh	29 (26.6)
Comorbidities	
Yes	41 (37.6)
No	68 (62.4)
CCI	
≤2	88 (80.7)
>2	21 (19.3)
BMI (kg/m^2)	21.8 ± 4.3
<18.5	20 (18.3)
≥18.5	89 (81.7)
ECOG score	
0–1	103 (94.5)
2	6 (5.5)
Hemoglobin (g/dL)	12.9 ± 1.8
<12	32 (29.4)
≥12	77 (70.6)
Location of the tumor[a]	
Lower thoracic	50 (45.9)
Mid-thoracic	59 (54.1)
Length of the tumor[a] (cm)	5.5 ± 2.1
>5	51 (46.8)
≤5	58 (53.2)
Clinical stage of cancer[b]	
T stage	
T2	3 (2.8)
T3	80 (73.4)
T4a	26 (23.9)
N stage	
N0	56 (51.4)
N1	41 (37.6)
N2	12 (11.0)

(*Continued*)

Table 1 (*Continued*)

Variable	Value $N = 109$
TNM staging	
II	46 (42.2)
III	37 (33.9)
IVA	26 (23.9)
Nasogastric tube feeding	
Yes	37 (33.9%)
No	72 (66.1%)

Abbreviations: BMI, body mass index; CCI, Charlson's comorbidity index; ECOG, Eastern Cooperative Oncology Group.
Note: Values expressed as *n* (%) or mean ± standard deviation.
[a]The location and length of the tumor were determined by endoscopy. In the case of a stenotic lesion, the same was determined from the baseline computed tomography scan.
[b]Clinical staging as per the 8th edition of AJCC (TNM) staging for esophageal cancer.

61 (56%) patients consumed tobacco. The mean baseline hemoglobin was 12.9 ± 1.8 g/dL, and 29.4% of patients were anemic. The average tumor length was 5.5 ± 2.1 cm, and 57.8% of patients had clinical stage III or IVA disease.

Neoadjuvant Chemoradiotherapy

The details of NACRT and the reasons to suspend chemotherapy are elaborated in ►Table 2. NACRT was given as per the "CROSS" regimen in 77 (70.6%) patients and the "mCROSS" regimen in 32 (29.4%) patients. When the original CROSS trial inclusion criteria were applied,[4] 45% of patients belonged to the "extended" CROSS eligibility criteria. Although 105 (96.3%) patients completed the planned radiotherapy without interruption, the concurrent chemotherapy course (5 cycles) was completed by only 17 (15.6%) patients. Only 58 (53.2%) patients completed ≥4 cycles. There was no significant difference in the chemotherapy completion (≥4 cycles) rate between the CROSS (41.4 Gy) and mCROSS (45 Gy) groups (50.6 vs. 59.4%, $p = 0.406$) or between the CROSS "eligible" and "extended" eligibility groups (51.7 vs. 55.1%, $p = 0.721$). However, within the CROSS "eligible" group ($n = 60$), only 51.7% of patients could complete ≥4 chemotherapy cycles. The most common reason for noncompletion of the chemotherapy was neutropenia (60.8%).

Surgery, Perioperative Details, and Postoperative Complications

The details of the surgery and postoperative complications are elaborated in ►Table 3. Twenty-seven (24.8%) patients did not proceed to surgery. Among patients found "eligible" for NACRT as per the CROSS trial inclusion criteria ($n = 60$), 23.3% did not receive surgery. The most common reason for not receiving the surgery was patient refusal (29.7%), either due to symptomatic improvement or due to a lack of willingness to accept the operative morbidity. Local inoperability and worsening general condition/comorbidities lead to avoidance of surgery in 25.9% of patients each. All patients received McKeown's esophagectomy with a two-field lymphadenectomy. The overall and major complications rates were 54.9 and 23.2%, respectively.

Surgical Histopathology

The postoperative histopathological information is detailed in ►Table 4. The rate of R0 resection, pathological complete response (pCR), and node-negative disease were 93.9, 53.7, and 76.8%, respectively, and nearly 63% of patients were downstaged to stage I.

Factors Influencing Completion of Chemotherapy (≥4 vs. <4 Cycles)

As detailed in ►Table 5, a low CCI (odds ratio [OR]: 2.98; 95% confidence interval [CI]: 1.02–8.73; $p = 0.047$), absence of anemia (hemoglobin ≥ 12 g/dL; OR: 2.76; 95% CI: 1.10–6.96; $p = 0.031$), and conformal techniques of radiotherapy (OR: 3.29; 95% CI: 1.14–9.50; $p = 0.028$) were associated with completion of (≥4 cycles) chemotherapy.

Effect of Chemotherapy Completion on the Pathological Outcomes

As detailed in ►Table 6, there was a trend toward improved R0 resection (95.7 vs. 91.4%), reduced node positivity (17.0 vs. 31.4%), and a high pCR (57.4 vs. 48.6%) in patients completing ≥4 chemotherapy cycles, compared with those who did not complete, but these differences were statistically nonsignificant.

Discussion

In the CROSS trial,[4] which had randomized patients with operable EC to receive either NACRT followed by surgery or surgery alone, the treatment adherence was excellent, with chemotherapy and radiotherapy being tolerated by 91 and 92% of patients, respectively. Although patients in this trial tolerated the paclitaxel–carboplatin regimen well, adapting this regimen in a real-life scenario needs caution, as not every patient of operable EC is medically fit to receive the combined modality treatment. Toxopeus et al[18]compared the outcomes of patients receiving the CROSS protocol NACRT outside the trial with those within the CROSS trial. There were older patients with frequent comorbidities, poor performance status, and advanced "N" stage in the post-CROSS cohort. Despite these differences, greater than 95% of patients in each group tolerated the entire chemotherapy course, and there was no significant difference in adverse events or survival between the groups. Another study by de Heer et al[19] assessed the impact of the "extended" CROSS eligibility criteria in patients with EC. Although there was no effect on the NACRT-associated toxicity and postoperative safety, the prognosis was adversely affected by the application of the "extended" criteria. In another study by Paireder et al,[20] among the 56 patients receiving the mCROSS protocol (46 Gy), 64% of patients progressed to surgery, and 83% of them could complete ≥4 chemotherapy cycles, with grade 3 leukopenia (34%) being the foremost reason for noncompletion of chemotherapy.

Table 2 Details of neoadjuvant chemoradiotherapy

Variable	*N* = 109
Eligible for CROSS protocol?[a]	
Yes	60 (55.0)
No (extended criteria)	49 (45.0)
Type of NACRT	
Pacli/Carbo × 5 + 41.4 Gy (CROSS)	77 (70.6)
Pacli/Carbo × 5 + 45 Gy (mCROSS)	32 (29.4)
Technique of radiation	
Conventional (Cobalt-60)	22 (20.2)
Conformal	87 (79.8)
3D-CRT	42 (38.5)
IMRT/VMAT	45 (41.3)
Completion of radiotherapy	
Yes	105 (96.3)
No	4 (3.7)
No. of chemotherapy cycles received	
0	2 (1.8)
1	7 (6.4)
2	11 (10.1)
3	31 (28.4)
4	41 (37.6)
5	17 (15.6)
Duration of NACRT (d)	34 (31–35.5)
Chemotherapy completed? (≥4 cycles)	
Yes	58 (53.2)
No	51 (46.8)
Chemo completion for *CROSS* (41.4 Gy) vs. *mCROSS* (45 Gy) groups	39/77 (50.6) vs. 19/32 (59.4), $p = 0.406$
Chemo completion for CROSS "*eligible*" vs. "*extended*" eligibility groups	31/60 (51.7) vs. 27/49 (55.1), $p = 0.721$
Reasons to stop chemotherapy	(***n*** = **92**)
Neutropenia	56 (60.8)
Fatigue	10 (10.9)
Diarrhea and/or vomiting	3 (3.2)
Mucositis	2 (2.2)
Worsening of comorbid illness[b]	7 (7.6)
Bacterial pneumonia	2 (2.2)
Reason not documented	10 (10.9)
Defaulted	2 (2.2)

Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; IMRT/VMAT, intensity-modulated radiation therapy/volumetric modulated arc therapy; mCROSS, "modified" CROSS; NACRT, Neoadjuvant chemoradiotherapy; Pacli-Carbo, paclitaxel and carboplatin.
Note: Values expressed as *n* (%) or median (interquartile range [IQR]).
[a]For assessment of patient eligibility as per CROSS trial inclusion criteria, those receiving 45 Gy were also included.
[b]Systemic illnesses included exacerbation of chronic obstructive airway disease, cardiac complications, and acute on chronic kidney injury.

It must be noted that the dominant histology of EC in the CROSS trial and the above post-trial cohort studies was adenocarcinoma (>70% of patients). In contrast, squamous carcinoma is the dominant histology in Asian countries.[2,9,10] Patients with poor performance, comorbidities, significant weight loss, and locally advanced, long-segment diseases are frequent in low-middle-income countries.[2,6,7] In the NEO-CRTEC5010 trial,[5] comparing upfront surgery versus NACRT and surgery for ESCC, 40 Gy of radiotherapy and two cycles of concurrent vinorelbine and cisplatin were given to patients in the NACRT arm; 87% completed the chemotherapy, and all except two patients received the planned radiotherapy. Although the study had significant (grade 3/4) hematological complications (neutropenia [45.7%], leucopenia [48.9%]), chemotherapy was withheld only if the complication persisted for 2 weeks. Chemotherapy cycles being fewer and 3 weeks apart are the probable reasons that patients were able to recover from cytopenia and complete their chemotherapy cycles.

The published literature on real-life experience with NACRT for ESCC is limited, particularly concerning the factors affecting its completion. Wong et al[11] observed that among

Table 3 Surgery, perioperative details, and postoperative complications

Variable	Value
Esophagectomy	***N* = 109**
Yes	82 (75.2)
No	27 (24.8)
CROSS "eligible" and no surgery vs. "extended" CROSS eligibility and no surgery	14/60 (23.3) vs. 13/49 (26.5), $p = 0.700$
Reasons for deferring surgery	***N* = 27**
Refusal	8 (29.7)
Locally inoperable on reassessment	7 (25.9)
Progression to metastatic disease	1 (3.7)
Medically unfit/worsened performance	7 (25.9)
Lost to follow-up	4 (14.8)
Variable	***N* = 82**
Interval between NACRT and surgery (d)	46.5 (30–113)
Type of esophagectomy	
McKeown's	82 (100)
Surgical approach	
Thoraco-laparoscopic	65 (79.3)
Hybrid[a]	10 (12.2)
Open	7 (8.5)
Postoperative complications	
Overall complications	45 (54.9)
Pulmonary complications	17 (20.7)
Anastomotic leak	7 (8.5)
Superficial surgical site infection	9 (11.0)
Vocal cord palsy	6 (7.3)
Chylothorax	1 (1.2)
Hemothorax	1 (1.2)
Intra-abdominal bleed	1 (1.2)
Acute coronary event/arrhythmias	5 (6.1)
Postoperative seizure	1 (1.2)
Severity of complications[b]	
Minor (CDG 1–2)	26 (31.7)
Major (CDG 3–5)	19 (23.2)
Postoperative hospital stay (d)	**10 (6–33) d**
30-d postoperative mortality	0 (0.0)
90-d postoperative mortality	1 (1.2)

Abbreviations: CDG, Clavien–Dindo grade; CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; NACRT, neoadjuvant chemoradiotherapy.

Note: Values expressed as *n* (%) or mean ± standard deviation or median with range.

[a]Hybrid means thoracoscopy and laparotomy.

[b]In patients with more than one complication, Clavien-Dindo grading was done based on the most severe complication.

ESCC patients receiving the CROSS protocol chemoradiotherapy, 91% of patients could complete ≥4 cycles of chemotherapy. Krishnamurthy et al[7] and Bajwa et al[10] analyzed the outcomes of patients from the Indian subcontinent with EC (SCC dominant cohorts) receiving NACRT as per the CROSS regimen; ≥4 chemotherapy cycles were completed by 80 and 97% of patients, respectively. However, the authors did not report the proportion of patients who were "eligible" or "extended" as per the CROSS trial inclusion criteria. Strict adherence to patient inclusion criteria in these studies likely led to the high chemotherapy tolerance seen in their experience. It should also be noted that these studies included patients with adenocarcinoma, whereas, in our study, only patients with ESCC were included.

This study aimed to analyze the real-world experience concerning the feasibility and tolerability of NACRT for the CROSS/mCROSS regimen in patients with ESCC. It also evaluated the factors predicting the completion of NACRT. In our experience, radiotherapy was well tolerated without treatment breaks; however, the tolerability of chemotherapy was poorer, with neutropenia being the commonest reason for the omission of chemotherapy in 61% of patients. The application of patient inclusion criteria for the CROSS trial in our cohort showed that nearly 45% of patients would have been

Table 4 Surgical histopathological details

Variable	$N = 82$
Completeness of resection	
R0 R1/R2	77 (93.9) 5 (6.1)
Lymph node yield	8 (5–12.3)
Pathological response (TRG)	
TRG: 0 (pCR) TRG: 1 TRG: 2 TRG: 3	44 (53.7) 13 (15.9) 15 (18.3) 10 (12.2)
Nodal response	
ypN0 ypN+	63 (76.8) 19 (23.2)
Pathological staging (ypTNM)	
I II III IVA	52 (63.4) 12 (14.6) 17 (20.7) 1 (1.2)

Abbreviations: pCR, pathological complete response; TRG, tumor regression grade; ypTNM, yp tumor node metastasis; ypN0, complete pathological response in the lymph nodes after neoadjuvant chemoradiation; ypN+, incomplete pathological response in the lymph nodes after neoadjuvant chemoradiation.
Note: Metastasis as per the Union for International Cancer Control (UICC), 8th edition.

Table 5 Univariate and multivariate analysis of the factors affecting completion (≥4 cycles) of chemotherapy

Variable	≥4 chemotherapy cycles		Univariate analysis		Multivariate analysis	
	Yes; $n = 58$	No; $n = 51$	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (y)						
≤60 >60	39 (67.2) 19 (32.8)	30 (58.8) 21 (41.2)	1.44 (0.66–3.14) 1.00	0.364	–	–
Sex						
Male Female	43 (74.1) 15 (25.9)	32 (62.7) 19 (37.3)	1.70 (0.75–3.85) 1.00	0.202	–	–
Tobacco use						
No Yes	25 (43.1) 33 (56.9)	23 (45.1) 28 (54.9)	1.00 1.08 (0.51–2.31)	0.834	–	–
BMI (kg/m^2)						
<18.5 ≥18.5	10 (17.2) 48 (82.8)	10 (19.6) 41 (80.4)	1.00 1.17 (0.40–3.09)	0.750	–	–
CCI						
≤2 >2	51 (87.9) 7 (12.1)	37 (72.5) 14 (27.5)	2.76 (1.01–7.50) 1.00	0.047	2.98 (1.02–8.73) 1.00	0.047
ECOG score						
0–1 2	53 (91.4) 5 (8.6)	50 (98.0) 1 (2.0)	1 4.72 (0.53–41.79)	0.163	–	–
Hemoglobin[a] (g/dL)						
<12 ≥12	10 (17.2) 48 (82.8)	22 (43.1) 29 (56.9)	1.00 3.64 (1.51–8.76)	0.004	1.00 2.76 (1.10–6.96)	0.031
Albumin (g/dL)	4.2 ± 0.41	4.1 ± 0.45	2.17 (0.88–5.36)	0.094	–	–

(*Continued*)

Table 5 (*Continued*)

Variable	≥4 chemotherapy cycles		Univariate analysis		Multivariate analysis	
	Yes; $n = 58$	No; $n = 51$	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Location of the tumor						
Lower thoracic Mid-thoracic	26 (44.8) 32 (55.2)	24 (47.1) 27 (52.9)	1.00 1.09 (0.51–2.33)	0.816	–	–
Tumor length (cm)						
≤5 >5	28 (48.3) 30 (51.7)	30 (58.8) 21 (41.2)	1.00 1.53 (0.72–3.27)	0.272	–	–
cT stage						
2 and 3 4	44 (75.9) 14 (24.1)	39 (76.5) 12 (23.5)	1.00 1.03 (0.43–2.50)	0.941	–	–
cN stage						
cN0 cN+	27 (46.6) 31 (53.4)	29 (56.9) 22 (43.1)	1.00 1.51 (0.71–3.23)	0.283	–	–
Overall stage (cTNM)						
II III IVA	21 (36.2) 23 (39.7) 14 (24.1)	25 (49.0) 14 (27.5) 12 (23.5)	1.00 1.96 (0.81–4.73) 1.39 (0.53–3.65)	0.136 0.505	–	–
Eligible as per CROSS study inclusion criteria?						
No (extended eligibility) Yes	27 (46.6) 31 (53.4)	22 (43.1) 29 (56.9)	1.00 0.87 (0.41–1.86)	0.721	–	–
Nasogastric tube feeding						
No Yes	39 (67.2) 19 (32.8)	33 (64.7) 18 (35.3)	1.00 0.89 (0.40–1.98)	0.780	–	–
Technique of radiation						
Conventional (cobalt-60) Conformal	7 (12.1) 51 (87.9)	15 (29.4) 36 (70.6)	1.00 3.04 (1.12–8.20)	0.028	1.00 3.29 (1.14–9.50)	0.028

Abbreviations: BMI, body mass index; CCI, Charlson's comorbidity index; CI, confidence interval; CROSS, ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; TNM, tumor node metastasis (as per UICC, 8th edition).
Note: The Hosmer and Lemeshow test chi-squared value is 1.48 ($p = 0.830$), which indicates that the model is a good fit.
[a]Baseline hemoglobin before the initiation of chemoradiotherapy.

Table 6 Effect of completion of chemotherapy on the completeness of resection, node positivity, and pathological response

Pathological outcomes	Overall ($N = 82$)	Completed (≥4 cycles) $n = 47$	Not completed (<4 cycles) $n = 35$	*p*-value
Completeness of resection				
R0 R1/R2	77 (93.9) 5 (6.1)	45 (95.7) 2 (4.3)	32 (91.4) 3 (8.6)	0.646
Node positivity				
ypN0 ypN +	63 (76.8) 19 (23.2)	39 (83.0) 8 (17.0)	24 (68.6) 11 (31.4)	0.126
Pathological response				
TRG: 0 (pCR) TRG: 1/2/3	44 (53.7) 38 (46.3)	27 (57.4) 20 (42.6)	17 (48.6) 18 (51.4)	0.425
Pathological response				
TRG: 0 and 1 (major) TRG: 2 and 3 (minor)	57 (69.5) 25 (30.5)	32 (68.1) 15 (31.9)	25 (71.4) 10 (28.6)	0.309

Abbreviations: pCR, pathological complete response; R0, no macroscopic or microscopic evidence of tumor; R1, microscopic evidence of tumor alone; R2, macroscopic evidence of tumor; TRG, tumor regression grade; ypN0, complete pathological response in the lymph nodes after neoadjuvant chemoradiation; ypN+, incomplete pathological response in the lymph nodes after neoadjuvant chemoradiation.
Note: Values are expressed as *n* (%).

"ineligible" for receiving NACRT as per the original trial protocol. We had to include these patients since many presented with locally advanced/long-segment disease in our population. Although there was no statistically significant difference in the tolerance to chemotherapy between the CROSS "eligible" and "extended" criteria groups (51.7 vs. 55.1%, $p = 0.721$), it has to be noted that nearly 50% of patients even within the CROSS "eligible" group failed to complete at least four cycles. Although there were no significant differences in the baseline demographic factors, compared with the CROSS trial, our study had patients with ESCC alone, and the tumors were relatively more advanced with longer tumor length (mean tumor length: 5.5 cm), necessitating a larger radiotherapy target volume. These factors perhaps contributed to a high risk of bone marrow toxicity/myelosuppression within the CROSS "eligible" group, thereby leading to a higher incidence of neutropenia.

Leukopenia and thrombocytopenia are frequent adverse effects encountered during NACRT.[21] Drug dose modifications, chemotherapy interruptions, and early treatment discontinuation are frequent in patients developing neutropenia, and this emerged as the leading cause of chemotherapy discontinuation in this study. In a few of our patients, the occurrence of neutropenia after the fourth chemotherapy pushed us to avoid the last cycle of chemotherapy, although the patient might have recovered from neutropenia. Such a decision was taken in patients in whom there were frequent interruptions in the treatment or severe neutropenia after the fourth cycle, which could potentially delay the surgery, which is considered the key cancer treatment. Although PEGylated recombinant human granulocyte colony-stimulating factor can be considered judiciously in patients developing neutropenia,[22] its routine use to prevent or treat chemotherapy-associated myelosuppression is not advocated in patients with EC receiving NACRT. We do not use this agent in our routine practice.

Radiation-induced esophagitis often interrupts treatment in patients with EC.[8,21] Although radiation-induced esophagitis did occur in our patients, it led to treatment interruption only in 2% of our patients. Patients with dysphagia to solids often have a nasogastric tube placed for feeding prior to NACRT to ensure nutritional maintenance during therapy and to manage radiation esophagitis–related dysphagia. In this study, 34% of patients alone had a nasogastric tube placed before or during NACRT. Despite our advice for tube feeding in all patients with significant dysphagia and/or weight loss, patients' acceptability was poor due to their general reluctance to have a nasal tube for a prolonged duration and due to local social taboos.

As the tolerability of chemotherapy was poor in this study, we studied the pretherapy factors that could influence the completion of chemotherapy. Multivariate analysis showed that patients with anemia had a lower chance of completing chemotherapy. Although the extent of anemia leading to treatment interruption needs future validation, anemia needs timely correction before and during NACRT. In our study, nearly a third of patients had at least one medical comorbidity, and a high CCI (>2) predicted chemotherapy discontinuation. These findings demonstrate that CCI may be a potential indicator for pretreatment patient stratification and periodic assessment, and timely optimization of the patient's medical diseases and functional status can improve treatment tolerance. Additionally, those with a high CCI can be offered alternate treatment options, for instance, radical chemoradiotherapy for ESCC. However, the findings from our study concerning the role of CCI need validation from future large-sized studies. Conventional radiotherapy delivery techniques, particularly when combined with a relatively more toxic chemotherapy regimen, can lead to poor patient tolerance to NACRT.[8] The newer techniques of radiation delivery, mainly intensity-modulated radiation therapy (IMRT), can minimize collateral tissue damage, including bone marrow and cardiopulmonary toxicity.[23] In our study, the application of image-guided conformal techniques resulted in superior tolerability of concurrent chemotherapy compared with conventional techniques. However, despite our study's frequent use of the conformal IMRT technique, chemotherapy tolerance was still poor compared with the CROSS trial, which utilized the three-dimensional conformal radiation therapy (3D-CRT) technique alone.[4] However, in a study by Innocente et al,[24] utilizing radiation doses of 52.5 to 54 Gy (IMRT technique) along with five cycles of concurrent paclitaxel and carboplatin to patients with EC (SCC, 58%), 54% of patients could complete at least four cycles of chemotherapy, despite receiving a higher intensified dose than reported in our study. This study's findings demonstrate that the treatment toxicity and, hence, the chemotherapy component's tolerability could be improved by better tumor targeting using newer radiation delivery techniques. Although shown to be beneficial in improving the tolerability of NACRT[24] and reducing postoperative morbidity,[23] the lack of wide availability and the increased cost of advanced radiation techniques are significant limiting factors for their routine application in low-middle-income countries.

The real-life incidence of planned surgery cancellations after neoadjuvant therapies for EC can be 16 to 22%.[25] In our experience, nearly 25% of our patients did not receive esophagectomy, which is higher than the figure of 6% reported from the CROSS trial[4] but better than the figure of 57% reported by Anap et al[12] among patients with EC. In the study by Krishnamurthy et al, 78% of patients received operation and 14% were deemed inoperable on-table.[7] In the NEOCRTEC5010 trial, the most common reason for deferring surgery was patient refusal (12.9% of patients), whereas disease progression or poor performance precluded surgery in 0.8% of patients alone.[5] Unresectability, patient refusal, mainly due to complete clinical response, and poor general condition are reported to be frequent reasons for not performing surgery in patients with ESCC treated with NACRT.[25] In our experience, among those who did not reach surgery, patient refusal (30%), disease progression/inoperability (30%), and lack of fitness due to comorbid illnesses or poor performance (26%) were the frequent reasons for deferring surgery. Low socioeconomic background[2] and lack of socioeconomic support are common contributing factors for deferring surgery in patients from the Indian subcontinent.[12] Hence, cancer care providers in a low-middle-income

countries should also consider the patients' socioeconomic support before finalizing their decision regarding multimodality treatment, and the patients who decide to defer surgery due to clinical improvement must be thoroughly counseled about the pros and cons of such decisions.

In the neoadjuvant settings, concurrent chemotherapy acts primarily as a radiosensitizer. Through its radiosensitizing effect, it is shown to reduce the locoregional and distant metastasis in EC, compared with radiotherapy alone.[26] Hence, completing the chemotherapy component is vital to improve EC's pathological and survival outcomes. In our experience, the rate of R0 resection, pCR, and node positivity rates were similar to that reported in the literature.[4,5,10,27] Although there was a trend toward better pathological outcomes in patients completing chemotherapy, these differences were statistically insignificant. The omission of a few cycles of concurrent chemotherapy did not affect various pathological outcomes, particularly the histological response; however, we feel that there is an actual positive effect, which we were unable to demonstrate, perhaps due to small individual samples, and hence this needs further prospective evaluation. Whether a survival advantage exists for the chemotherapy completion group (vs. the noncompletion group) also needs careful exploration through further long-term follow-up of our cohort and future prospective studies. Additionally, should we be looking at adjuvant therapy for patients in whom the preoperative chemotherapy cycles could not be completed, particularly if the pathological tumor response is suboptimal? This question gains relevance and importance in the current era of possible immunotherapy options.

Our study had a few limitations. First, it was a retrospective, single-center study with inherent biases. Second, the psychosocial issues limiting the completion of preoperative treatment are not studied, considering most patients were from low socioeconomic backgrounds. "Prehabilitation" programs, including dietary interventions, can help improve overall treatment compliance and reduce treatment-associated morbidity in esophagogastric cancer patients.[28] However, data on baseline nutritional assessment and degree of weight loss were lacking for most of our patients; hence, the effect of pretherapy nutritional inadequacy and weight loss or its improvement after nutritional interventions on the treatment completion could not be studied in our cohort. This was the third limitation of this study. Fourth, since the proportion of patients who received five cycles of chemotherapy was low, completion of a minimum of four cycles was taken as the cutoff to study the oncological effects of chemotherapy completion. Furthermore, the superiority of various conformal radiation delivery techniques in terms of their tolerability and toxicity could not be established due to the small individual sample size. Finally, the long-term oncological effects of chemotherapy completion and the oncological outcomes of patients who never reached surgery need to be explored. Despite these limitations, our study is one of the largest studies from the subcontinent, which has explored the pretherapy factors contributing to chemoradiotherapy completion in a cohort of ESCC patients.

Conclusion

Tolerability to the CROSS regimen or its modification is poor among the Indian subcontinent patients with esophageal squamous cancer. Although radiotherapy is well tolerated, chemotherapy is often associated with hematological toxicity, which leads to suspension or omission of therapy. Anemia at presentation and a high CCI are strongly associated with noncompletion of the planned chemotherapy cycles, and these indicators can guide us in better case selection for NACRT or its modification. Conformal radiation delivery techniques can help reduce toxicity and improve treatment tolerance. Although the completion of chemotherapy has no significant effect on the various pathological outcomes, its impact on long-term survival in squamous carcinoma needs to be prospectively studied.

Data Availability

Data are unavailable for public access.

Ethical Approval

Ethical approval was obtained from the institutional review board (IRB Min. No.12998/2020).

Consent to Participate

Waiver was obtained from the Ethics Committee considering the retrospective nature of the study.

Consent for Publication

All the authors gave consent to the publication of the manuscript in the *South Asian Journal of Cancer* should the article be accepted by the editor-in-chief upon completion of the refereeing process.

Author Contributions

Conception and design were done by S.S., G.M., R.I., and I.S. Acquisition of data was done by S.S. and G.M. Data analysis and interpretation were done by all the authors. Drafting of the manuscript was done by S.S., G.M., and T.M. Critical appraisal and revision were done by S.S., M.M., R.I., N.P., M.Y., B.K.S., S.P., S.C., V.A., S.J., and I.S. Overall guarantors of the work are B.K.S. and I.S. All the author approved the final version of manuscript to be published.

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Conflict of Interest

None declared.

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