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RESEARCH

Outcomes of Neoadjuvant Chemoradiotherapy Using Volumetric Modulated Arc Therapy in Locally Advanced Squamous Cell Oesophageal Cancers

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Abstract

Purpose Neoadjuvant chemoradiotherapy has been established as the standard of care for locally advanced oesophageal cancers. Most of the evidences on neoadjuvant chemoradiotherapy (NACTRT) comes from the Western world where the predominant histology is adenocarcinoma. This study aimed to study the outcomes of neoadjuvant chemoradiotherapy using CROSS protocol and volumetric modulated arc therapy (VMAT) in locally advanced squamous cell oesophageal cancers.
Case Presentation.
We report a multicentric abdominal inflammatory myofibroblastic tumor in a 6-year-old girl who presented with massive abdominal distention. The sheer size of the mass, coupled with multicentric presentation and absent mobility on clinical examination, would have led to a very morbid surgical exploration. This patient was treated with initial chemotherapy, which led to a dramatic response in both symptoms and size of masses, facilitating a complete surgical resection with negligible postoperative morbidity.
Methods This was a single-institute retrospective analysis utilizing a prospectively collected database where all patients with locally advanced operable oesophageal cancers with squamous histology diagnosed between 2021 and 2022 were screened and included. All patients received neoadjuvant chemoradiotherapy in accordance with the CROSS protocol with all patients receiving radiotherapy using VMAT technique.
Results A total of 102 patients with locally advanced oesophageal cancers with squamous histology were included in the study. The median follow-up for the cohort was 29 months. The 3-year overall survival (OS), disease-free survival (DFS), and local control (LC) were 72%, 59.1%, and 72%, respectively. Pathological complete response was 59.4%. The major Clavien–Dindo classification (≥ class 3) of surgical complications was 32%. Lower incidence of pulmonary (17.7%) and cardiac (5.2%) complications was observed in this cohort.
Conclusions NACTRT using the CROSS protocol enhances the pathological complete response rates and the survival outcomes in locally advanced oesophageal cancers with squamous histology. The utilization of VMAT has been associated with a reduction in postoperative cardiopulmonary toxicities. However, further prospective randomised studies are required to validate the technique's superiority.

Keywords Neoadjuvant chemoradiotherapy · Squamous cell oesophageal cancers · Volumetric modulated arc therapy

Introduction

Oesophageal cancer is the 11 th most commonly diagnosed malignancy in the world and the seventh leading cause of cancer mortality worldwide [1]. In the late 1960 s, oesophageal squamous cell carcinoma (ESCC) was the dominant histological type in both Western and Eastern regions [2]. However, since the late 1990 s, there has been a notable shift in the predominant histology from the Orient to the Occident with the incidence of oesophageal adenocarcinoma (EAC) rising in the Western world [3]. Beyond the histopathological and epidemiological distinctions between EAC and ESCC, molecular differences were also noted in the pathogenesis of both histologies [4–7]. While ESCC was similar to squamous carcinoma occurring in the other parts of the

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body, EAC resembled an unstable chromosomal variant of gastric cancer. A sound understanding of the inherent differences in the epidemiology, pathology, and genomics of these two histologies will aid in rationalising the differences in response to cancer-directed therapy, and patterns of failures and provide a foundation for newer treatment approaches in the management of oesophageal cancers [8]

A meta-analysis of 24 trials by the Australasian Gastrointestinal Trial Group revealed a significant reduction in all-cause mortality when patients were treated with neoadjuvant chemoradiotherapy (CRT) followed by surgery compared to those who underwent surgery alone (HR 0.77; CI 0.69–0.86) [9]. The "CROSS trial" established neoadjuvant CRT as the standard of care in locally advanced oesophageal or junctional cancers with 10-year outcomes showing a consistent absolute overall survival benefit of 13% [10–12]. Most of the randomised controlled trials (RCT) evaluating the role of neoadjuvant therapy in oesophageal cancer were conducted in the Western population, predominantly involving EAC and junctional cancers. These trials exhibited heterogeneity in radiotherapy dose—fractionation and chemotherapy regimens [13–17]. The "NEOCRTEC$_{50}$10 trial," a multicentric, open-labelled randomised control study among patients with locally advanced ESCC, demonstrated a 5-year OS benefit of 10.8% for patients treated with neoadjuvant CRT followed by surgery (HR 0.7; $p = 0.03$) [18, 19]. While in CROSS protocol, neoadjuvant CRT consisted of concurrent weekly platinum–taxane doublet with radiotherapy to a cumulative dose of 41.4 Gy, the NEOCRTEC$_{50}$10 trial employed concurrent three weekly regimens of Vinorelbine-cisplatin doublet with radiotherapy dose of 40 Gy delivered in 20 fractions as the neoadjuvant CRT protocol. In addition to the survival benefits, these trials demonstrate higher rates of R0 resections after trimodality treatment (92–98%) [11, 18]. A meta-analysis comparing postoperative outcomes between neoadjuvant chemoradiotherapy (NACTRT) and surgery alone for oesophageal squamous cell carcinoma found no significant differences in overall postoperative morbidity ($p = 0.17$; 95% CI 0.91–1.67) or anastomotic complications ($p = 0.71$; 95% CI 0.60–2.12) [20]. Another noteworthy finding from these NACTRT trials is the higher pathological complete response (pCR) rates observed in ESCC compared to EAC, suggesting greater radiosensitivity in squamous histology.

Volumetric modulated arc therapy (VMAT) enables highly conformal dose distributions, enhancing target volume coverage while minimising exposure to normal tissues, thereby reducing both acute and chronic toxicities compared to conventional radiotherapy techniques [21]. Most NACTRT trials have utilised three-dimensional conformal radiotherapy (3DCRT). In this retrospective study, we evaluated the outcomes of neoadjuvant chemoradiotherapy using VMAT for locally advanced squamous cell carcinoma of the oesophagus. Additionally, we assessed treatment tolerance, surgical morbidity, failure patterns, and factors contributing to improved survival.

Materials and Methods

This was a single institute retrospective analysis utilising a prospectively collected database. All patients with locally advanced operable oesophageal cancers with squamous histology diagnosed between 2021 and 2022 were screened and included. The baseline evaluation of the patient (see Fig. 1) included upper GI endoscopy (for disease mapping and biopsy confirmation), positron emission tomography–computed tomography (PET–CT) (for metastatic workup), and fibreoptic bronchoscopy (for lesions above carina). The neoadjuvant chemoradiotherapy regimen followed the "CROSS protocol." Radiotherapy was delivered to a dose of 41.4 Gy in 23 fractions at 1.8 Gy per fraction, administered five times a week over 4.5 weeks. All patients were treated using VMAT. The gross tumour volume (GTV-primary) was delineated using upper GI endoscopy and PET–CT findings. It was then expanded by 3 cm craniocaudally along the oesophageal wall and 1 cm radially, with adjustments made for anatomical barriers to define the clinical target volume (CTV-primary) [22]. A 5-mm margin was applied to the GTV-node to create the CTV-N. The bilateral supraclavicular region was treated prophylactically if the oesophageal disease extended above the level of the carina, and gastrohepatic ligament nodes were treated prophylactically in case of disease involving gastroesophageal junction. The dosimetric constraints for organs at risk (OAR) included lung constraints of $V_{2000cGy} < 20\%$ and $V_{500cGy} < 60\%$; heart constraints of $V_{4000cGy} < 30\%$, $V_{3000cGy} < 40\%$, and $D_{mean} <$

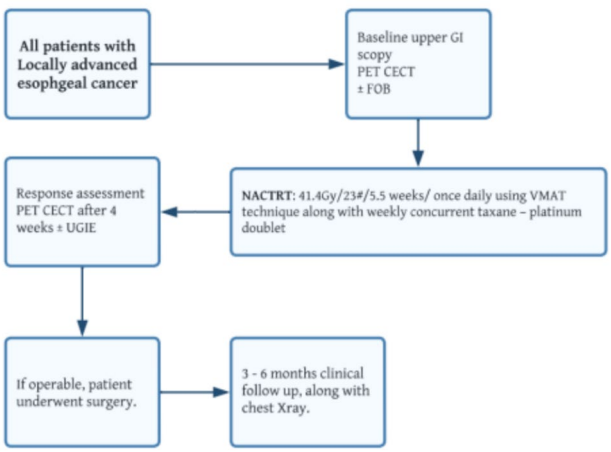

Fig. 1 Institutional work flow

3000 cGy; and left ventricle constraints of $V_{1000cGy} < 50\%$. The eligible patients received concurrent chemotherapy with a platinum-taxane doublet, with paclitaxel administered weekly at a dose of 50 mg/m^2 and carboplatin at an AUC of 2. After completing the planned neoadjuvant CRT, response assessment PET–CT was done at 4 weeks along, with upper gastrointestinal endoscopy if clinically warranted. Patients deemed operable proceeded to surgery. The follow-up protocol included three monthly clinical follow-ups with chest X-rays. Cross-sectional imaging was conducted when clinically indicated.

Descriptive analyses were conducted for patient, tumour, and treatment-related factors. The data that appeared missing or incorrect was either corrected when possible or excluded from the study. Continuous variables were expressed as the mean ± standard deviation or as median (maximum–minimum) depending on the normality of the respective data.

Categorical variables were expressed as absolute (number) and relative frequency (percentage). The chi-squared test was performed for categorical variables. For independent samples, the Student's *t*-test or Mann–Whitney *U* test was performed depending on the normality of the continuous variable to compare between groups. One-way analysis of (ANOVA) variance or Kruskal–Wallis test was used for the comparison of more than two groups depending on the normality.

For all statistical tests, a *p*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (the statistical package for social sciences) IBM Corp. released in 2017, IBM SPSS Statistics for Windows, Version 25.0 Armonk, NY: IBM Corp.

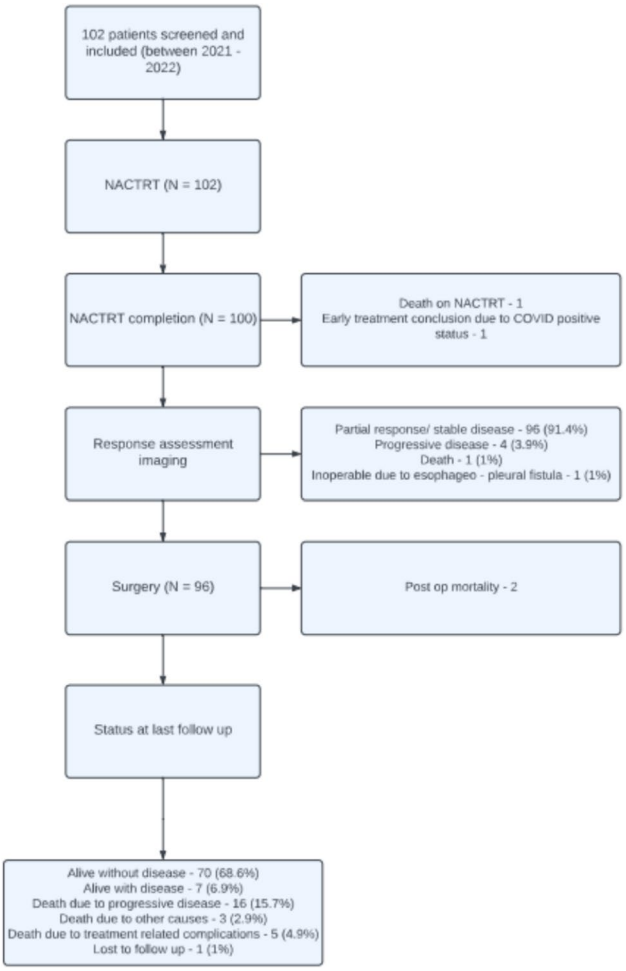

Fig. 2 Consort diagram

Results

A total of 102 patients with locally advanced ESCC were screened and included in the study (Fig. 2). All patients underwent PET–CECT as part of staging workup and upper GI endoscopy for histopathological confirmation and disease mapping.

The demographic details of this cohort of patients are summarised in Table 1.

This cohort consisted of patients with stage IIB or III mid-lower thoracic ESCC. All patients were treated using VMAT to a cumulative dose of 41.4 Gy in 23 fractions (98%). The mean duration of radiotherapy was 33 days. Of the 102 patients, 100 completed planned NACTRT. One patient died during NACTRT due to febrile neutropenia, septic shock, and acute renal failure. CTCAE v5.0 Grade 3 mucositis requiring nasogastric tube placement was observed in 16.7% of cases. Grade 3/4 neutropenia occurred in 8.82% of patients. Additional reported toxicities included 8% experiencing Grade ≥ 2 chemotherapy–induced nausea and vomiting (CINV), 7% with Grade ≥ 3 hyponatremia, 6% with Grade ≥ 2 thrombocytopenia, 2% with Grade ≥ 2 transaminitis, and 1% experiencing hypersensitivity to paclitaxel. All patients underwent PET CECT 4–6 weeks after radiotherapy to assess their response. During this evaluation, progressive disease was observed in four patients (3.9%). Additionally, one patient was deemed inoperable due to a oesophageo-pleural fistula.

Patients with non-progressive disease were scheduled for surgery, with the mean interval between radiotherapy completion and surgery being 8.2 weeks. The most common surgical technique was McKeowen esophagectomy (77%). VATS and robotic approaches were used in 32 (33%) and 18 (19%) patients, respectively. Complete resection (R0) was achieved in 98% of patients, and pCR was observed in 57 patients (59.4%). 68.8% (64/96) patients had pCR at primary, and 78% (75/96) had pCR at the nodes. The mean duration of ICU stay was 1.5 days, and the median intraoperative blood loss was 350 mL. The major Clavien Dindo classification [23] (≥ class 3) of surgical complications

Table 1 Demographics

Patient-related factors	
Age	Mean: 55 years IQR: 51–62 years
Sex	Male: 50 (49%) Female:52 (51%)
Comorbidities	27 (26.5%) Most common: hypertension—18 (17.6%) and Pulmonary disease—7 (6.9%)
Tobacco use	Smoking—19 (18.6%) Chewable forms—38 (37.3%) Both—3 (2%) Nil—43 (42.2%)
Performance status	ECOG 0.1: 98 (96%) ECOG 2 or more: 4 (4%)
PFT	Median FEV1%—75.5% (IQR 67.6–82.87) Median DLCOsb%—77% (IQR 69–89)
Tumour-related factors	
Histology	Squamous carcinoma—101 (99%) Adenosquamous—1 (1%)
Grade	Well-differentiated—1 (1%) Moderately differentiated—50 (49%) Poorly differentiated—30 (29.4%) Unknown—21 (20.6%)
Location	Mid—52 (51%) Lower—50 (49%)
AJCC 8th edition T staging (cT)	T2—2 (2%) T3—100 (98%)
AJCC 8th edition N staging (cN)	N0—64 (62.7%) N1—35 (34.3%) N2—3 (2.9%)
Craniocaudal disease extent	Median—5.42 (range 2–12 cm)
Tumour thickness	Median—1.6 cm (range 0.4–3.7 cm)
Treatment details	
Radiotherapy dose	$\leq$ 40 Gy—3 (3%) 41.4 Gy—99 (97%)
Radiotherapy technique	VMAT
Mean radiotherapy treatment duration	33 days
Concurrent chemotherapy	All patients received concurrent chemotherapy
Concurrent chemotherapy agent	Paclitaxel + Carboplatin—101 (99%) Single-agent carboplatin—1 (1%)
Concurrent chemotherapy cycles	Less than four cycles—3 (2.9%) 4–5 cycles—93 (91.2%) 6 cycles—6 (5.9%)
Completion of planned NACTRT	Completed—98 (98%) Treatment-related death—1 (1%) Early termination due to COVID—1 (1%)
The mean interval between radiotherapy completion and surgery	8 weeks
Type of surgery	Mc Keowns—74 (77%) Ivor Lewis—18 (18.8%) Transhiatal esophagectomy—4 (4.2%)
Surgical approach:	Open—44 (45.8%) Video-assisted thoracoscopic surgery (VATS)—32 (33.3%) Robotic—18 (18.7%) Hybrid—2 (2.2%) Conversion to open—4 out of 50 (8%)
Median blood loss during the surgery	350 mL
Median duration of surgery	5.5 h

Table 1 (continued)

Dosimetry	
PTV (mean, IQR)	275 cc (181.75–352 cc)
Lung (mean, IQR)	V_{500cGy}: 52.55% (46.34–58.75) $V_{1000cGy}$: 33.46% (27.95–38.53) $V_{2000cGy}$: 8.48% (4.73–10.25) $V_{3000cGy}$: 1.31% (0.67–1.37) D_{mean}: 7.96 Gy (6.83–8.85)
Heart (mean, IQR)	$V_{3000cGy}$: 12.98% (9.08–16.62) $V_{4000cGy}$: 5.56% (3.72–7.15) D_{mean}: 16.12 Gy (13.84–18.77)

Table 2 Surgical complications

Complications	Number	Percentage
Anastomotic leak	17	17.7
Vocal cord palsy	13	16.7
Pulmonary complications	17	17.7
Cardiac complications	5	5.2
Chyle leak	5	5.2
Gastric dilatation	11	11.5

was 32% (31/96). Anastomotic leaks occurred in 17.7% of patients. Cardiac and pulmonary complications were seen in 5.2% and 17.7% of patients, respectively. Table 2 summarises post-operative complications. Post-operative mortality was seen in two patients (2%). One patient developed acute myocardial infarction in the immediate postoperative period. Another patient developed mediastinitis, and septic cardiomyopathy and died in the ICU secondary to multi-organ failure. In long-term follow-up, the incidence of tube dependency and gastric dumping was 2.1% and 1%, respectively.

The median follow-up for the cohort was 29 months, with two patients (2%) lost to follow-up. The 2-year and 3-year overall survival (OS) rates were 78% and 72%, respectively (Fig. 3). The 2-year and 3-year disease-free survival (DFS) was 72.2% and 59.1%, respectively. Treatment-related deaths (from both NACTRT and surgical) occurred in 5% of patients. Additionally, three patients died due to other non-oncological causes.

The 2-year and 3-year local control rates were 84.4% and 72%, respectively. 15% (14/96) of patients had locoregional failure (Table 3). Anastomotic recurrence was seen in four out of 96 patients (4.1%). The supraclavicular region was the most frequent site of nodal failure (6/11). Out of the 11 patients who had only locoregional failure, one patient (9%) had failure inside the radiation portals, eight patients (73%) had out-of-field failure, and two patients (18%) had combined infield and out-of-field failures. Distant failure occurred in eight patients, with nodal, bone, and liver metastasis being the most common sites of recurrence. One patient developed brain metastasis. Five patients with isolated out-of-field nodal recurrence, good performance status, and longer disease-free intervals underwent salvage chemoradiotherapy. Surgical salvage was not feasible in this cohort. Patients not eligible for salvage therapy were started on palliative chemotherapy or radiotherapy. Additionally, one patient developed a second primary lung cancer.

Univariate analysis (see Table 4) indicated that poorly differentiated (grade III) disease, ≤ 6 weeks' interval between radiotherapy completion and surgery, skip lesions, and poor tolerance to concurrent chemotherapy were associated with poorer local control rates. Multivariate analysis showed that poorly differentiated histology ($p = 0.035$) and skip lesions ($p = 0.001$) were associated with inferior outcomes.

Discussion

Oesophageal cancers rank as the fifth most commonly diagnosed cancer in India [24]. Unlike the Western world, squamous cell carcinoma is the predominant histology in the Asian belt [25]. The CROSS trial demonstrated the benefit of neoadjuvant chemoradiotherapy in oesophageal cancers [10]. However, similar to the other NACTRT trials from the West, only a minority of patients in this trial had squamous histology (23%). Here, we report the outcomes for patients with locally advanced operable oesophageal cancers with squamous histology treated with neoadjuvant chemoradiotherapy followed by surgery.

Most patients in our cohort presented with locally advanced oesophageal cancer. More than half (51%)of the patients in our cohort had midthoracic oesophageal cancer, unlike in the CROSS trial where the most common site was the lower thoracic and gastroesophageal junction (82%), with squamous histology being predominant [10]. The median cranial-caudal disease extent and tumour thickness were 5.42 cm and 1.6 cm, respectively. Unlike other Asian countries with robust screening mechanisms where oesophageal cancers tend to be detected at an earlier stage, most of our patients present with cT3 disease, which adds complexity to treatment planning and delivery.

Studies evaluating neoadjuvant CTRT in squamous oesophageal cancers have used varying radiotherapy doses between 35 and 40 Gy in 1.8–2 Gy per fraction [20]. At our

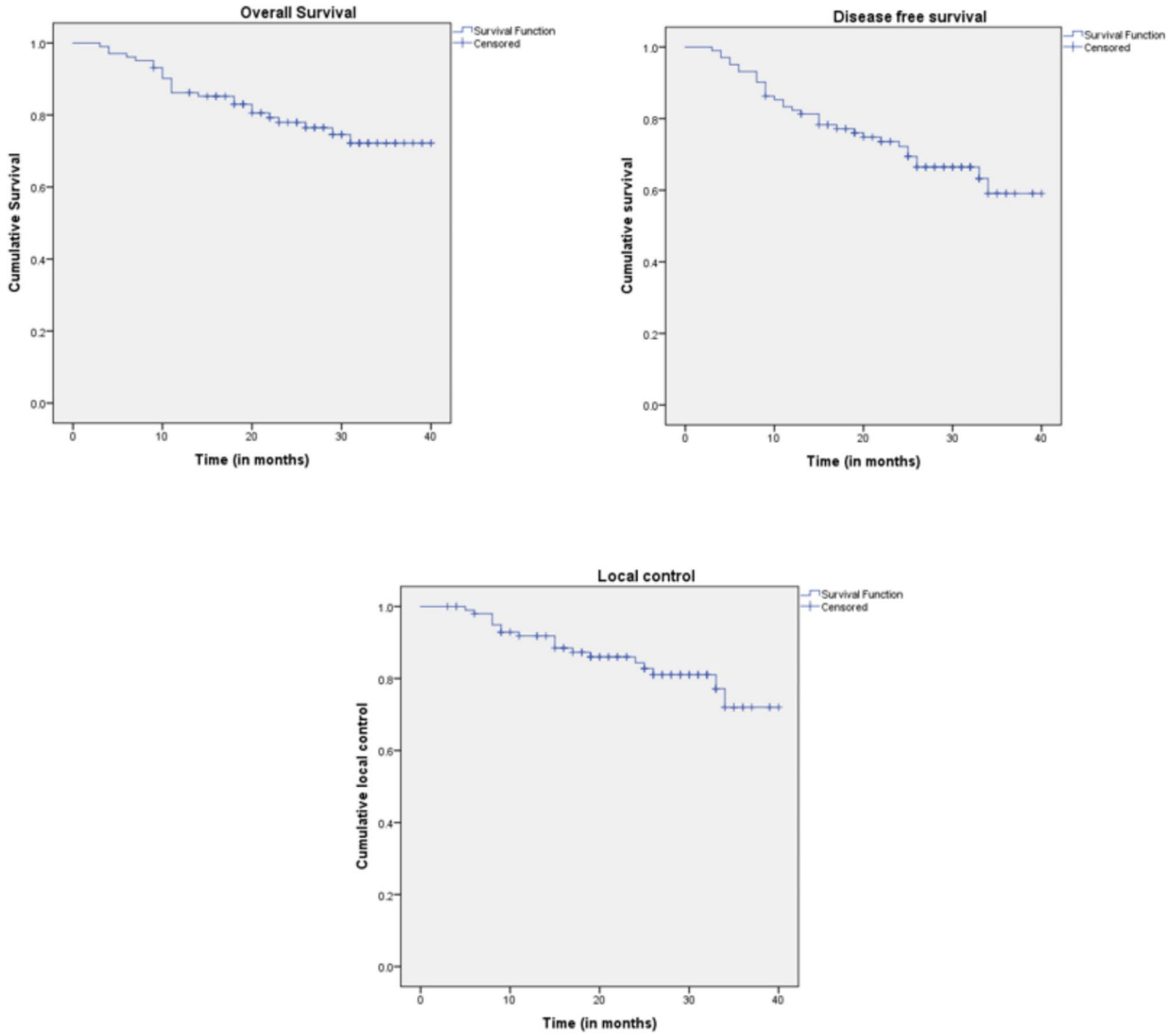

Fig. 3 Survival outcomes

Table 3 Patterns of failure

Patterns of failure and cause of death in the entire cohort	
Total treatment failures in the cohort	19
Locoregional failure (LRF) only	11
Distant metastasis (DM) only	5
Combined failure (LRF + DM)	3
Anastomotic recurrence	4
Death due to disease progression	16
Treatment-related death	5
Death due to other causes	3

centre, we used the standard 41.4 Gy in 23 fractions at 1.8 Gy per fraction. All patients were treated using VMAT. In contrast, the CROSS and NEOCRTEC 5010 studies used 3 CDRT technique for all patients [10, 18]. Pulmonary function tests (PFT) and the diffusing capacity of the lungs for carbon monoxide (DLCO) were conducted pre-treatment to assess pulmonary function and evaluate the risk of perioperative pulmonary morbidity. Using the VMAT technique, we successfully achieved lower heart and lung doses, staying below the planned dose constraint targets. This may have translated to lower perioperative pulmonary (17.7%) and cardiac (5.2%) complication rates [11, 18, 26]

The chemotherapy was administered according to the CROSS trial protocol, with the majority of patients

Table 4 Univariate analysis

Variable	Number	3-year OS	*p*-value
Age ≥ 55 years	62	67.1%	0.09
Age < 55 years	40	80.9%	
Poorly differentiated			0.07
Yes	30	65.3%	
No	51	82.3%	
Variable	Number	3-year LC	*p* value
Poorly differentiated			0.042
Yes	30	46.5%	
No	51	86.2%	
≥ 4 cycles of concurrent chemotherapy			0.017
Yes	99	73.5%	
No	3	33.3%	
Completion of concurrent chemotherapy			0.034
Yes	97	73.5%	
No	5	33.3%	
The interval between radiotherapy completion and surgery ≤ 6 weeks			0.05
Yes	21	72.9	
No	75	82.9	

completing four to five cycles of concurrent platinum–taxane doublet. This was in contrast with other NACTRT studies/trials with predominant squamous histology where the most common chemotherapeutic combination that was used was 5 Fluorouracil and platinum doublet. The NEOCRTEC$_{50}$10 study utilised a three-weekly cisplatin-vinorelbine doublet [18]. The weekly taxane-platinum doublet chemotherapy was well tolerated, with only three patients (2.9%) receiving fewer than four cycles. The treatment was delivered in an outpatient setting, eliminating the need for hospitalisation.

The meta-analysis by Qin et al. demonstrated that increasing the interval between the end of NACTRT and surgery to 7–8 weeks resulted in better pathologically complete response rates [27]. In our study, the mean interval between radiotherapy completion and surgery was 8 weeks, likely contributing to an improved pathological complete response without compromising the survival outcomes. However, the meta-analysis also indicated that further delays in surgery could lead to detrimental outcomes. In the NeoRes II study, the investigators cautioned delaying surgery beyond 6 weeks after NACTRT [28]. However, in our study, patients with ≤ 6 weeks of radiotherapy had poorer local control (72.9 vs 82.9, $p = 0.05$). Prolonging the interval between surgery and radiotherapy beyond 8 weeks did not translate into any survival or local control benefit ($p = 0.95$).

Postoperative surgical morbidity rates in this study were consistent with those observed in other RCTs of NACTRT [10, 18, 29]. In this cohort, the incidence of anastomotic leak was 17.7%. In our cohort, pulmonary complications occurred in 17.7% of patients, and cardiac complications were seen in 5.2%, likely due to the use of advanced conformal techniques and sparing of organs at risk [30]. Other acute and chronic toxicities were similar to those reported in other studies. NACTRT did not increase the risk of surgical morbidities.

The pathological complete response (pCR) rate in the cohort was 59.4%, which is higher than the rates reported in the CROSS trial (49% in SCC histology) and the NEOCRTEC5010 trial (43%). However, this did not translate into any significant benefit in overall survival (3-year OS in responders 81.6% vs 69.9% in non-responders; $p = 0.36$), disease-free survival (3-year DFS in responders 62.5% vs 63.5% in non-responders; $p = 0.56$), or local control (3-year LC in responders 72.5% vs 78.6% in non-responders; $p = 0.79$) [31].

The outcomes of using the CROSS protocol in NACTRT indicated promising survival rates and local control. The 3-year OS in this cohort was 72%. This was marginally higher than reported data for squamous oesophageal cancers, where RT doses ranged from 35 to 40 Gy and 5 Fluorouracil–platinum doublets were commonly used. NACTRT using the CROSS protocol appears tolerable and feasible in low-income and middle-income countries, where hospital admission for chemotherapy and access to optimal supportive care can be challenging.

Locoregional failure was the most common type of failure in this cohort, with the supraclavicular nodal region being the most common site of local relapse. Most failures occurred outside the radiation field. There was no statistical difference between the location of disease and supraclavicular nodal recurrence ($p = 0.652$). There was a significant difference in overall survival between patients who had disease relapse and those who did not (3-year OS 85.4 vs 41.8%; $p = 0.002$). Only five out of 19 patients who had disease recurrence (26.3%) were feasible for salvage therapy. Surgical salvage was not feasible in this cohort. Given the failure patterns and low salvage rates, intensifying local therapy or considering prophylactic irradiations should be explored while maintaining an acceptable toxicity profile.

This study presents one of the largest real-world data on NACTRT using the CROSS protocol for locally advanced resectable squamous oesophageal cancers treated with VMAT [28, 32]. All patients were treated with a homogenous protocol. The use of NACTRT in this cohort of patients improved pathological complete response rates, local control, and survival outcomes, with acceptable acute toxicity profiles compared to the available literature [33]. Findings from the ongoing prospective randomised controlled studies assessing various neoadjuvant strategies will offer deeper insights into enhancing outcomes in locally advanced oesophageal cancers [34].

One of the main limitations of this study is that it is a single-centre retrospective analysis without a comparison arm. While the study indicates a reduction in pulmonary and cardiac morbidities with the use of VMAT, further prospective randomised studies are needed to establish definitive conclusions regarding the technique's superiority. Additionally, we were unable to assess long-term toxicities and their impact on quality of life.

Conclusion

NACTRT using the CROSS protocol enhances the survival outcomes in locally advanced oesophageal cancer with squamous histology. The safety profile is acceptable, particularly in LMICs where access to optimum supportive care is limited. Poorly differentiated histology is associated with poorer local control and overall survival. The utilisation of VMAT has been associated with a reduction in postoperative cardiopulmonary toxicities. However, further prospective randomised studies are required to validate the technique's superiority.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection, analysis and initial draft was prepared by Dr Sam David. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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