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Chemoradiotherapy using Volumetric Modulated Arc Therapy for Locally Advanced Esophageal Cancer: A Single Institute Experience

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Abstract

Objective: Locoregional failure after trimodailty treatment is a crucial problem for locally advanced esophageal carcinomas. The goal of this study is to assess outcomes of preoperative chemoradiation followed by esophagectomy in locally advanced esophageal carcinomas.

Material and Methods: Patients with cT3-T4 or node+ esophageal carcinomas receiving trimodality treatment (2017-2020) were analyzed retrospectively. Demographics, histology, grade, stage, dose, fractionation, chemotherapy, surgery and resection margins were analyzed. Primary end points were Disease Free Survival (DFS) and Overall Survival (OS).

Results: 122 patients were included, mean follow-up of 13.4 months. 99 (82%) patients had cT3 and 58(47.5%) had cN1 disease. Most common histology was Squamous Cell 102 (83.6%), grade was moderate 92 (75.4%) and most patients received chemotherapy, induction (n=99, 81%) *vs*. concurrent (n=116, 95%). Chemoradiation 50 Gy in 25 fractions with platinum-based chemotherapy was the most common regimen. 65 patients were treated with definitive intent; and 57 patients with pre-operative intent, of whom 56 (98%) underwent surgery. Most common surgery was 3-stage esophagectomy. In the pre-operative group, R0 resection was achieved in 38 patients (66.7%). 2-year OS was better in pre-operative group compared to definitive group (72% *vs*. 32%, p=0.001). Similarly, 2-year DFS was better in pre-operative group compared to definitive group (78% *vs*. 52%, p=0.03). R0 resection and radiation dose of 50Gy were associated with better overall survival on MVA. Disease recurrence was seen in 34 (27.9%) with local recurrence in 10 (8.2%), distant metastasis in 20 (16.4%) and both in 4 (3.3%) patients.

Conclusion: Trimodality treatment with standard preoperative radiation dose and chemotherapy yielded a high pathologic complete response rate and better 2-year DFS and OS. R0 resection and 50 Gy radiation dose were associated with better OS.

Keywords: Esophageal carcinoma • Volumetric modulated arc therapy • VMAT • Locally advanced

Introduction

Esophageal cancer is a major global health concern, ranking as the eighth most common cancer and the sixth leading cause of cancer-related deaths worldwide. Over 500,000 new cases are diagnosed annually, with a 5-year survival rate of less than 20%, largely due to lack of screening thus advanced stage diagnoses [1]. Geographic disparities exist in incidence and prognosis, driven by factors such as population aging, rising obesity rates, tobacco and alcohol use and poor dietary habits. In the U.S., the SEER database reports over 17,000 new cases and nearly 16,000 deaths annually [2].

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In Pakistan there are many challenges to collect correct estimates of incidence and mortality associated with esophageal or any other cancer. The reasons being lack of optimal resources for cancer care including the limited number of cancer centers for such a huge population, limited infrastructure within hospitals, high rate of illiteracy, poverty, social practices, lack of awareness of cancer screenings and many others. Most of the patients with cancer go to Quacks, Hakeems, religious or spiritual guides for alternative medicine, amulets, spiritual waters and special manipulations etc. instead of using proper cancer care. These patients do not reach any record systems. Most of the hospitals do not have electronic medical record systems or sophisticated cancer registries, causing the loss of important statistical data [3,4]. Well established cancer centers like Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH&RC) which is a trust hospital providing cancer care free of charge accepts patients with early-stage cancer patients only and other robust cancer centers like Agha Khan University Hospital, Karachi and Shifa International Hospital, Islamabad are too expensive for general population. For all these reasons the stats about cancer epidemiology are just estimates, true numbers can be very different. According to Global Cancer Observatory, esophageal cancer is the 5th most common cancer in Pakistan accounting for about 5% of total cancer population [5].

Two main histologic subtypes Squamous Cell Carcinoma (SCC) and adenocarcinoma differ in location, risk factors and epidemiology. SCC,

predominant globally, typically arises in the upper/mid-esophagus and is linked to tobacco and alcohol, whereas adenocarcinoma, increasing in Western countries, is found in the lower esophagus and associated with obesity and Barrett's esophagus [3,4]. Both types are more common in males, with SCC having a ratio of 2.7:1 and adenocarcinoma having a ratio of 7:1, with distinct ethnic variations, emphasizing the need for effective targeted interventions [2]. Management involves a multidisciplinary approach, with chemoradiotherapy (CHT-RT) followed by surgery or definitive CHT-RT for inoperable cases. Radiation therapy plays a pivotal role, especially in locally advanced or cervical esophageal cancers and is more effective when combined with chemotherapy [6]. Although surgery improves local control, it does not significantly enhance overall survival in advanced SCC. Preoperative chemoradiotherapy is an established treatment for operable esophageal or esophagogastric junctional cancer. In the CROSS trial, using preoperative chemoradiotherapy significantly increased R0 resection rates (92% *vs*. 69%, P value <0.001) and improved median overall survival (48.6 *vs*. 24.0 months, P value=0.003) [7].

Advances in radiotherapy from conventional 2D to 3D-CRT, IMRT and most recently Volumetric Modulated Arc Therapy (VMAT) aim to improve tumor targeting while sparing normal tissue. VMAT offers advantages over static IMRT, including better dose conformity, homogeneity, shorter treatment times and reduced exposure to lungs, heart and spinal cord. Studies suggest VMAT for esophageal cancer treatment in both definitive and neoadjuvant settings is well-tolerated, with mild toxicity and consistent dosimetry, particularly partial arc VMAT auto-planning significantly improved lung dose, target coverage and dose homogeneity [8]. Reduced lung V20, shorter delivery times and reduced monitor units, suggesting potential for high-dose treatment in esophageal cancer [9]. However, in a comparison with fixed-field intensity-modulated radiotherapy for middle-thoracic esophageal cancer, VMAT showed better coverage for the boost region but less dose homogeneity for the planning target volume compared to IMRT, prompting further clinical investigation [10]. Thus, VMAT can improve treatment precision and minimize side effects.

This study evaluates the clinical outcomes of VMAT-based CHT-RT for locally advanced esophageal cancer in a setting where such data is lacking. Through retrospective analysis of patients treated at a single institution, we assess understanding of the efficacy and safety of this treatment modality, tumor response, survival outcomes, treatment toxicities and factors influencing treatment outcomes, such as patient characteristics, tumor stage, treatment protocols and adherence.

Materials and Methods

This single-institution retrospective study was conducted at the Department of Clinical and Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan. Institutional review board approval was obtained; informed consent was waived due to the retrospective nature of the study. Patients aged ≥18 years with locally advanced esophageal cancer (regardless of histology), clinical stage T3–T4 or node-positive and ECOG performance status 0-1 were included. All received definitive Chemoradiotherapy (CHT-RT) or neoadjuvant CHT-RT followed by surgery, with radiotherapy delivered *via* VMAT. Patients with performance status ≥2, metastatic disease, prior malignancies, or re-irradiation were excluded. A total of 122 patients treated between January 2017 and December 2020 met the inclusion criteria.

All patients underwent staging with EGD, biopsy, endoscopic ultrasound and FDG-PET. Multidisciplinary tumor board discussions guided treatment planning. Based on staging and tumor location, patients were offered either definitive CHT-RT (for medically inoperable or cervical tumors) or neoadjuvant CHT-RT followed by surgery. Some received induction chemotherapy.

Chemotherapy typically involved platinum-based regimens combined with fluoropyrimidines or taxanes based on institutional protocols and guidelines. Radiation therapy planning used contrast-enhanced CT simulation in the supine position, with VMAT applied for all patients as the radiation delivery technique. Treatment plans were generated using advanced treatment planning system, considering the tumor location, size and adjacent critical structures.

Data collected included demographics, clinical characteristics, treatment details, toxicity and outcomes. Tumor response was evaluated *via* imaging and clinical exam using RECIST criteria. Adverse events were graded per CTCAE v5. Survival outcomes (overall survival and progression-free survival) were calculated from the start of CHT-RT. Kaplan-Meier curves were used for survival analysis. Descriptive statistics were used to summarize patient characteristics, treatment parameters and treatment outcomes. Patterns of failure were recorded based on clinical and imaging follow-up. This study adhered to ethical principles and guidelines, including patient confidentiality, as per the regulations of the institutional review board or ethics committee.

Table 1. Patient's baseline and tumor-related characteristics.

Variable	Categories	Definitive Intent 65 (53.3%)	Pre-operative Intent 57 (46.7%)
Age (years)	Mean ± SD	48.1 ± 12.6	45.3 ± 10.5
Sex	Male	35 (53.8)	20 (35.1)
	Female	30 (46.2)	37 (64.9)
Histology	SCC	58 (89.2)	44 (77.2)
	Adeno CA	5 (7.7)	12 (21.1)
	Others	2 (3.1)	1 (1.8)
Grade	Well	6 (9.2)	6 (10.5)
	Moderate	50 (76.9)	42 (73.7)
	Poor	9 (13.8)	9 (15.8)
Tumor location	Upper thoracic	9 (13.8)	2 (3.5)
	Middle thoracic	21 (32.3)	20 (35.1)
	Lower thoracic	20 (30.8)	35 (61.4)
	Cervical	15 (23.1)	-
Clinical tumor stage T	I	1 (1.5)	1 (1.8)
	II	1 (1.5)	1 (1.8)
	III	49 (75.4)	50 (87.7)
	IV	14 (21.5)	5 (8.8)
Clinical tumor stage N	0	16 (24.6)	14 (24.6)
	I	27 (41.5)	31 (54.4)
	II	20 (30.8)	12 (21.1)
	III	2 (3.1)	-
Clinical tumor stage M	0	62 (96.9)	56 (100.0)
	I	2 (3.1)	-

Results

Demographic and tumor-related characteristics

Our study enrolled patients with locally advanced esophageal cancer, stratifying them into two distinct treatment intents: "Definitive Intent" and "Pre-operative Intent." Mean age was 47 years (Range 23-81). Analysis of baseline characteristics including age, gender, histology, tumor grading and location revealed notable differences between the two intent groups as shown in Table 1. Mean age, male gender, cervical location and moderate grade tumor were more prevalent in definite intent group. Clinical staging was fairly equivalent.

Treatment modalities and associated parameters

Table 2 presents various treatment modalities and characteristics of two groups. All patients in the preoperative group and most of the patients (92.3%) in definitive group were treated with conventional fractionation while 4 (7.7%) patients in the definite intent group received higher daily doses of 216, 217 and 220 cGy. Fractionation was 25 treatments in 84.6% of patients in the Definitive Intent group and 100% in the Pre-operative Intent group. Induction chemotherapy was prevalent in both groups as was concurrent chemotherapy. No surgical interventions were done in the Definitive Intent group, while in the Pre-operative Intent group, 70.2% underwent 3-stage esophagectomy, 26.3% Left Thoracoabdominal Esophagectomy (LTE) and 1.8% Iver Lew is Esophagogastrostomy (ILE). Baseline weight and weight after XRT showed slight differences. Mean follow-up duration for Definitive Intent was 12.6 months and Pre-operative Intent was 14.4 months.

Dose constraints

The dose constraints as shown in Table 3 for the "Definitive Intent" and "Pre-operative Intent" groups are as follows: Mean PTV coverage of 95% and 110% were similar in both groups. Mean lung V20, spinal cord point Dmax, right kidney mean doses were higher in the Definitive intent group compared to the Pre-operative group while lung V5, heart mean dose and left kidney mean doses were higher in Pre-operative group. Lung mean dose and conformity index were similar for the two groups.

Toxicities

Assessment of toxicities experienced by patients revealed differences in the incidence and severity of radiation-induced toxicities between the two intent groups. Radiation-induced toxicity was common in both groups, with a slightly

Table 2. Treatment modalities.

Variable	Categories	Definitive Intent 65 (53.3%)	Pre-operative Intent 57 (46.7%)
Highest prescribed dose (XRT)	180 cGy	22 (33.8)	20 (35.1)
	200 cGy	38 (58.5)	37 (64.9)
	216 cGy	1 (1.5)	-
	217 cGy	3 (4.6)	-
	220 cGy	1 (1.5)	-
Fractions (XRT)	25	55 (84.6)	57 (100.0)
	27	1 (1.5)	-
	30	7 (10.8)	-
	35	2 (3.1)	-
Induction chemotherapy	No	8 (12.3)	15 (26.3)
	Yes	57 (87.7)	42 (73.7)
Concurrent chemotherapy	No	6 (9.2)	-
	Yes	59 (90.8)	57 (100.0)
Surgical types	None	65 (100.0)	1 (1.8)
	3-stage esophagectomy	-	40 (70.2)
	LTE	-	15 (26.3)
	ILE	-	1 (1.8)
Baseline weight (kg)	Mean ± SD	50.9 ± 11.2	54.0 ± 12.3
Weight after XRT (kg)	Mean ± SD	52.5 ± 11.3	55.0 ± 14.6
Follow-up (months)	Mean	12.6	14.4
	Standard deviation	12.5	7.2
	Median	8	13
	Range	1-61	1-39

LTE: Left Thoracoabdominal Esophagectomy
ILE: Iver Lewis Esophagectomy

Table 3. Dose constraints.

Variable	Categories	Definitive Intent 65 (53.3%)	Pre-operative Intent 57 (46.7%)
Lung V20	Mean ± SD	12.8 ± 6.71	10.9 ± 6.04
Lung V5	Mean ± SD	51.7 ± 28.9	58.7 ± 20.6
Lung mean	Mean ± SD	9.6 ± 5.4	9.5 ± 3.4
Spine Dmax	Mean ± SD	35.2 ± 9.5	29.6 ± 7.4
Heart mean	Mean ± SD	13.4 ± 11.2	16.8 ± 7.5
Right kidney mean	Mean ± SD	1.1 ± 2.6	0.92 ± 1.3
Left kidney mean	Mean ± SD	2.1 ± 4.3	2.7 ± 2.6
PTV 95	Mean ± SD	93.9 ± 17.2	97.6 ± 1.3
PTV 110	Mean ± SD	0.02 ± 0.17	0.02 ± 0.13
Conformity index	Mean ± SD	1.05 ± 0.11	1.04 ± 0.14

higher incidence in the Pre-operative Intent group (96.5%) compared to the Definitive Intent group (90.8%). While skin reactions, dysphagia and mucositis were prevalent in both groups, skin reactions were less common in the Pre-operative Intent group, with the majority of patients reporting no reactions (Table 4). The Definitive Intent group had a larger proportion of Grades I and II skin reactions. Dysphagia was more pronounced in the Definitive Intent group, especially Grade II and Grade III while Pre-operative Intent group showed a higher proportion of Grade I dysphagia. Mucositis was also more pronounced and severe in Definitive Intent group (Table 4).

Table 5 presents the changes in weight before and after Radiotherapy (XRT). The mean pre-XRT weight was 52.4 kg (SD 11.8), while the mean post-XRT weight was 53.7 kg (SD 13.0) with minimal changes before and after radiotherapy treatment.

Table 4. Toxicities.

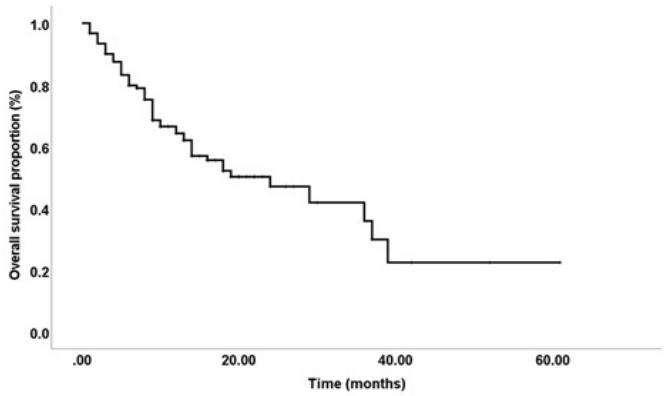
Variable	Categories	Definitive Intent 65 (53.3%)	Pre-operative Intent 57 (46.7%)
Radiation-induced toxicity	No	6 (9.2)	2 (3.5)
	Yes	59 (90.8)	55 (96.5)
Skin reaction	Grade 0	43 (66.2)	50 (87.7)
	Grade I	21 (32.3)	7 (12.3)
	Grade II	1 (1.5)	-
Dysphagia	Grade 0	6 (9.2)	4 (7.0)
	Grade I	16 (24.6)	24 (42.1)
	Grade II	24 (36.9)	15 (26.3)
	Grade III	19 (29.2)	13 (22.8)
	Grade IV	-	1 (1.8)
Mucositis	Grade 0	27 (41.5)	33 (57.9)
	Grade I	34 (52.3)	22 (38.6)
	Grade II	3 (4.6)	2 (3.5)
	Grade III	1 (1.5)	-

Table 5. Pre and post-radiotherapy weight.

Variable	Categories	Pre XRT	Post XRT	
Pre and post-XRT weight (kg)	Mean ± SD	52.4 ± 11.8	53.7 ± 13.0	0.003

Table 6. Disease recurrence and metastasis with location.

		Location			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Local	10	8.2	29.4	29.4
	Distant	20	16.4	58.8	88.2
	Both	4	3.3	11.8	100
	Total	34	27.9	100	-
Missing	System	88	72.1	-	-
Total		122	100		

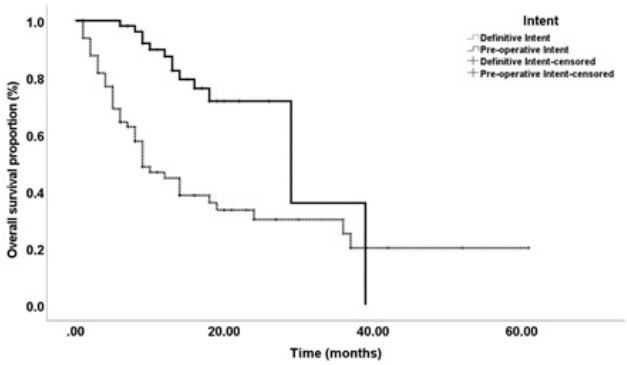


Means and Medians for Survival Time

Mean				Median			
Estimate	Std. error	95% Interval Lower Bound	Confidence Upper Bound	Estimate	Std. Error	95% Interval Lower Bound	Confidence Upper Bound
27.575	3.054	21.589	33.56	24	5.585	13.052	34.948

a. Estimation is limited to the largest survival time if it is censored.

Figure 1. Overall survival proportion.

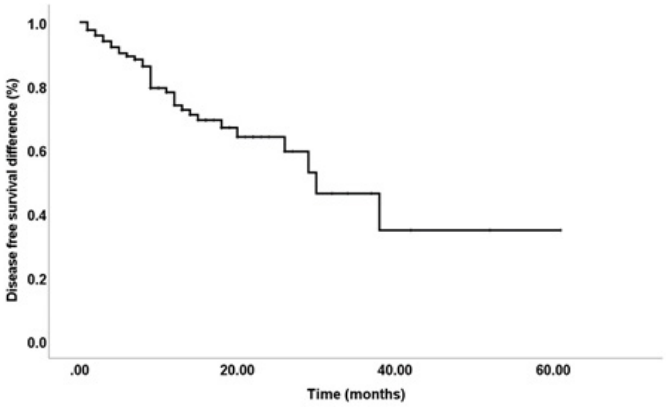


Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Intent	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Definitive Intent	21.476	3.236	15.133	27.819	9.000	1.982	5.116	12.884
Pre-operative Intent	27.920	3.119	21.807	34.033	29.000	7.868	13.579	44.421
Overall	27.575	3.054	21.589	33.560	24.000	5.585	13.052	34.948

a. Estimation is limited to the largest survival time if it is censored.

Figure 2. Overall survival with respect to intents.



Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
34.100	3.924	26.408	41.792	30.000	4.791	20.609	39.391

a. Estimation is limited to the largest survival time if it is censored.

Figure 3. Disease-free survival proportion.

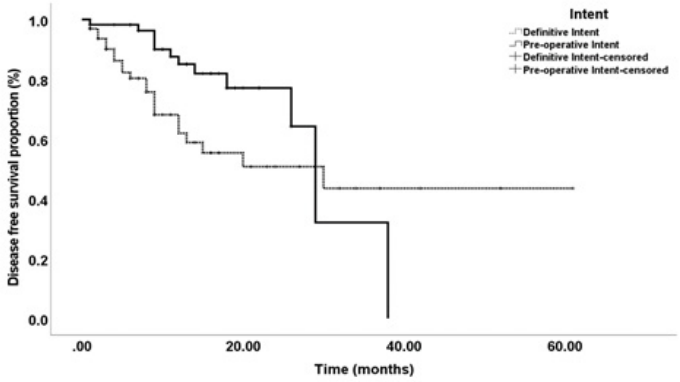
Survival outcomes

Analysis of overall survival rates demonstrated a statistically significant difference between the Definitive Intent and Pre-operative Intent groups. At 2-years, the overall survival significantly improved in pre-operative group compared to definitive group (72% *vs.* 32%, p=0.001), underscoring the potential benefits of a neoadjuvant treatment approach in improving long-term survival outcomes in esophageal cancer. Figure 1 shows overall survival, demonstrating a median survival period of 24 months. Figure 2 shows the overall survival rates in relation to two distinct intents with a statistically significant difference in survival rates between two intent groups, with a notable divergence in median survival time: 9 months for definitive intent compared to 29 months for pre-operative intent. R0 resection and radiation dose of 50 Gy were associated with better overall survival on MVA.

Figure 3 shows overall disease-free survival with a median disease-free survival of 30 months while Figure 4 shows disease free survival curves for both groups showing the disease-free survival was significantly improved in pre-operative group compared to definitive group (78% *vs.* 52%, p=0.03) at 2-years. Disease recurrence was seen in 34 (27.9%) with local recurrence in 10 (8.2%), distant metastasis in 20 (16.4%) and both in 4 (3.3%) patients.

Discussion

Esophageal cancer remains a major global health challenge, with low survival rates and high geographic variability in incidence and outcomes. Our study highlights real-world data from a single institution in Pakistan, showcasing the feasibility and clinical outcomes of Chemoradiotherapy (CHT-



Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Intent	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Definitive Intent	33.039	4.450	24.316	41.761	30.000	12.559	5.384	54.616
Pre-operative Intent	27.461	2.770	22.032	32.890	29.000	2.209	24.670	33.330
Overall	34.100	3.924	26.408	41.792	30.000	4.791	20.609	39.391

a. Estimation is limited to the largest survival time if it is censored.

Figure 4. Disease-free survival proportion with respect to intents.

RT) using Volumetric Modulated Arc Therapy (VMAT) for locally advanced esophageal cancer. Our analysis demonstrates that VMAT-based treatment is feasible, well-tolerated and associated with acceptable toxicity and promising clinical outcomes, particularly in the neoadjuvant (pre-operative) setting.

In our cohort, patients treated with neoadjuvant CHT-RT followed by surgery had significantly better overall and disease-free survival compared to those receiving definitive CHT-RT. The 2-year Overall Survival (OS) in the pre-operative group (72%) was significantly higher compared to the definitive group (32%, p=0.001), with a median survival of 29 months versus 9 months, respectively. This is in line with the CROSS trial and subsequent studies, which demonstrated improved R0 resection rates and survival outcomes in patients receiving neoadjuvant therapy compared to surgery or chemoradiation alone [7,11]. The improved outcomes in our pre-operative group may reflect better local control due to tumor down staging, more favorable surgical outcomes and patient selection with better performance status.

VMAT allowed for excellent PTV coverage and conformity in both treatment groups, while maintaining acceptable Organ-At-Risk (OAR) doses. Previous studies have demonstrated VMAT's superiority over conventional 3D conformal radiotherapy and static IMRT in achieving better dose conformity, reduced treatment times and lower doses to the heart, lungs and spinal cord [12-14]. Our findings further support the use of VMAT as a favorable modality for esophageal cancer, especially in resource-constrained settings.

Toxicity profiles in our study were comparable to those reported in similar series. Skin reactions, mucositis and dysphagia were the most common adverse effects. These toxicities were more severe in the definitive intent group, likely due to higher radiation doses, lack of surgical resection and prolonged tumor exposure to radiotherapy. This trend mirrors findings from studies comparing definitive and neoadjuvant CHT-RT [15,16]. The preoperative group showed a higher incidence of skin sparing and less severe mucositis, possibly due to improved patient selection and earlier stage tumors amenable to resection. Although not all patients in the neoadjuvant group underwent surgery due to medical inoperability or disease progression, those who did had favorable R0 resection rates and better survival outcomes, which align with previous evidence that R0 resection is an independent predictor of improved survival [17].

The dose distribution analysis demonstrated satisfactory Planning Target Volume (PTV) coverage and organ-at-risk sparing, affirming VMAT's ability to deliver conformal radiation with acceptable dose constraints. While lung V20 and spinal cord Dmax were slightly higher in the definitive group, the mean heart and kidney doses remained within acceptable limits. The conformity index remained consistent between groups, indicating comparable treatment plan quality. Our multivariate analysis identified R0 resection and a total radiation dose of 50 Gy as independent predictors of improved survival. The importance of achieving complete resection underscores the need for accurate pre-treatment staging and multidisciplinary decision-making in determining surgical candidacy. Furthermore, while radiation dose escalation beyond 50 Gy has been explored in various studies, our results reinforce 50 Gy as an effective and safe standard dose when used with concurrent chemotherapy.

Our cohort was relatively young (mean age 47 years) and had a male predominance, consistent with regional epidemiological trends for Squamous Cell Carcinoma (SCC), which was the dominant histology in both groups. Most tumors were located in the mid and lower thoracic esophagus; however, a notable proportion of cervical tumors (23.1%) were observed in the definitive group, explaining the non-surgical management in this subset. The recurrence pattern showed a predominance of distant metastases (16.4%), followed by local recurrence (8.2%) and combined recurrence (3.3%). This emphasizes the need for improved systemic disease control and may support the consideration of induction chemotherapy or novel systemic agents such as immunotherapy in future treatment protocols [18,19].

One of the major strengths of this study is the real-world insight into esophageal cancer management in a low-resource setting, where data is sparse due to lack of national cancer registries and inadequate health infrastructure [20]. Our results validate the utility of VMAT as a viable option that balances efficacy and toxicity, especially when combined with appropriate systemic therapy and surgery. Limitations of this study include its retrospective design, single-center data, the inherent selection bias, a relatively small cohort and limited follow-up duration, which may limit generalizability. Nonetheless, our results provide valuable evidence supporting the role of VMAT in the management of esophageal cancer and highlight the need for more robust, prospective studies in South Asian populations.

Conclusion

This study demonstrates that VMAT-based chemoradiotherapy, particularly in the neoadjuvant setting, is a safe and effective treatment for locally advanced esophageal cancer in a developing country context. With

favorable toxicity profiles, good target coverage and improved survival in surgical candidates, VMAT represents a technically advanced, clinically viable option in modern esophageal cancer care. Larger, prospective studies and long-term follow-up are warranted to confirm these findings and explore potential improvements with integration of novel systemic agents.

Acknowledgement

None.

Conflict of Interest

None.

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