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Response Evaluation with Definitive Chemoradiotherapy in Carcinoma of the Esophagus

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [3,4,5]Drafting the work or revising it critically for important intellectual content [2]Final approval of the version to be published [3]Active participation in active methodology

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ABSTRACT

Objective: i) To evaluate the treatment outcomes of patients with carcinoma of the esophagus receiving definitive chemoradiation using IMRT with concurrent chemotherapy and ii) To assess patient demographics and disease characteristics in relation to treatment response and patterns at a single tertiary care center.

Methodology: This prospective cohort study was conducted in the Department of Radiation Oncology at Shifa International Hospital from June 2024 to November 2024. A total of 133 patients with biopsy-proven esophageal carcinoma, aged 16 to 65 years, were enrolled using non-probability consecutive sampling. All patients received definitive chemoradiation, consisting of either 5040 cGy in 28 fractions or 5400 cGy in 30 fractions delivered via intensity-modulated radiation therapy (IMRT), along with concurrent chemotherapy. Chemotherapy regimens included either weekly carboplatin (AUC 2) and paclitaxel (50 mg/m²) for five weeks, or cisplatin (75 mg/m² on day 1) combined with continuous infusion of fluorouracil (1000 mg/m²/day for 96 hours) during weeks 1 and 5 of external beam radiotherapy.

Results: Out of 133 patients, 78 (63%) were males and 55 (37%) were females. Most patients (n = 79, 59%) had stage II disease, while 46 (34%) had stage III disease. An objective complete response was achieved in 66 patients (61%), while partial response was observed in 67 patients (38%). The majority of patients achieving complete response had squamous cell carcinoma histology (66%). No patients died or experienced disease progression during treatment. Grade 3 mucositis occurred in 7 patients (5%), grade 3 dysphagia in 9 patients (7.5%), and grade 3 myelosuppression in 3 patients (2.2%).

Conclusions: Patients treated with definitive concurrent chemoradiotherapy (CCRT) for non-metastatic carcinoma of the esophagus demonstrated promising outcomes, with a complete remission rate of 66%. Complete response was more frequently observed in patients with squamous histology. A significant correlation was noted between radiological stage and pathological complete response, with stage II patients showing the highest frequency of complete responses.

Keywords: Definitive chemoradiotherapy,

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Introduction

Esophageal carcinoma is a highly aggressive malignancy with a poor prognosis, often diagnosed at an advanced stage due to late-onset symptoms such as dysphagia and weight loss.[1] The two most common histological subtypes are squamous cell carcinoma and adenocarcinoma, each with distinct etiological and geographical patterns.[4] Squamous cell carcinoma is typically linked to smoking and alcohol use, while adenocarcinoma is often associated with chronic gastroesophageal reflux and Barrett's esophagus. Tumor progression involves the disruption of epithelial cell adhesion, increased cellular proliferation, and the invasion of surrounding tissues, facilitated by

angiogenesis and evasion of immune surveillance.[2,3] Approximately 10-20% of all cases of cancer of the esophagus are cervical esophageal cancers and are therefore relatively rare.[5]

According to a study conducted by JPMC Karachi, dysphagia, weight loss and vomiting were the most common symptoms. [6,7] Surgery was once considered the standard treatment for patients with resectable esophageal cancer. However, patient outcomes remain unsatisfactory, with median survival rarely exceeding 18 months.[6]

Definitive chemoradiotherapy (CRT) has emerged as a standard non-surgical treatment option for locally advanced esophageal cancer, particularly in patients unfit for surgery or those who refuse it.[17] In the UK, neoadjuvant chemoradiotherapy is often used in combination with surgery as standard treatment for esophageal cancer to achieve better survival outcomes with minimal morbidity.[10,11] Patients receiving dCRT may develop local recurrence and require salvage surgery, and two-year survival rates have been reported to be 31–40%.[8,9,10]

CRT works by combining cytotoxic chemotherapy with radiation to enhance tumor cell kill, improve local control, and potentially achieve a complete pathological response. The biological response to this treatment is evaluated using radiological tools such as CT or PET-CT scans, guided by RECIST (Response Evaluation Criteria in Solid Tumors) criteria, which help quantify tumor shrinkage.

One of the key objectives in managing esophageal carcinoma with definitive chemoradiation therapy is to assess treatment effectiveness and patient tolerance. This study aims to evaluate the frequency of radiological response and pathological complete response using RECIST criteria, measured 2 to 3 months post-treatment, to determine how well the tumor responds to therapy. Such outcomes are crucial in predicting long-term survival and guiding further clinical decisions. Additionally, monitoring the frequency and severity of treatment-related toxicities during the course of chemoradiation, using the NCI CTCAE v5.0, is essential to understand patient safety and treatment feasibility. These evaluations together provide a comprehensive view of both therapeutic success and tolerability**.**

In Pakistan, there is scarce data regarding treatment outcomes with each modality of treatment. On literature review, only four local studies were found which investigated outcomes of radiation therapy in esophageal cancers.[18,19,20] The rationale of the study is to determine the outcomes of patients with esophageal carcinoma treated with definitive chemoradiotherapy via assessing the response rates and toxicities with this treatment modality. Also, our aim is to gather data on efficiency of the treatment in south east Asian subset of population. This will contribute to parting the lacuna of information that exists and will pave way for further customized studies in future.

Methodology

This hospital-based prospective cohort study was conducted between June 2024 and November 2024 in the Department of Radiation Oncology, Shifa International Hospital. A total of 133 patients were included. The sample size was calculated using the WHO sample size calculator.

Patients of either gender, aged 16–65 years, with a biopsy-proven diagnosis of esophageal carcinoma were enrolled using non-probability consecutive sampling. Exclusion criteria included patients with distant metastatic disease, those who refused chemotherapy, or those who had already received treatment elsewhere.

Demographic details and treatment-related data were retrieved from electronic medical records and radiotherapy prescription files. Access to patient data was granted following approval from the Institutional Review Board (IRB) of Shifa International Hospital (IRB Letter No. 181-24). In cases of ambiguous imaging findings, radiological consultation was sought to confirm treatment response based on RECIST criteria.

A pre-defined proforma was developed to capture all relevant information, initially recorded in Microsoft Excel. The variables included: age, gender, radiological stage, presence of hypopharyngeal, major vascular, or vertebral invasion, type of chemotherapy, radiation dose, objective response rate, pathological complete response, and treatment-related toxicities (including mucositis, dysphagia, and myelosuppression).

Radiological complete response, based on RECIST criteria, was defined as the disappearance of all measurable target lesions (i.e., sum of longest diameters of all target lesions reduced to 0 mm), with no new lesions or unequivocal progression of non-target lesions. Any involved lymph nodes must also have a short axis of 0 mm.

Pathological complete response, as defined by the College of American Pathologists (CAP) guidelines, referred to the absence of any residual invasive cancer following treatment.

Definitive external beam radiotherapy was delivered using intensity-modulated radiation therapy (IMRT) based on computed tomography (CT) simulation. Target volumes—including gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV)—were delineated according to the *Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer*. GTV was defined as the primary tumor and involved lymph nodes identified on CT, PET/CT, and endoscopic evaluation (EGD/EUS).

Clinical target volume (CTV) was defined as Esophageal GTV + 1cm radial margin and 4cm superior-inferior margin following the mucosa, but limited superiorly to not extend above the inferior portion of the cricoid. Involved node GTV was given 1cm margin. Vertebral bodies and heart were carved out of the CTV, while the trachea and great vessels were not. Elective nodal CTV was expanded to encompass nodal station 2-4,[21], level IV(a&b) and VIb (per Gregoire et al. Radiother Oncol 2014).[22] Planning Target Volume (PTV) was delineated as CTV + 1cm. OARs defined were Heart, Lungs, Cord, Esophagus, Brachial plexus, Thyroid and Larynx. Doses to the OARs were expressed minimum, mean, median and maximum.

Patients received radiotherapy 5 days per week to achieve a total 5040 Gy to 5400 Gy at 180 cGy per fraction in 28 fractions using sliding window, intensity modulated radiotherapy (IMRT) with X6Mv-15Mv photons. Varian linear accelerator (Unique) with 120 leaf multi-leaf collimator (MLCs) was used to deliver radiation therapy, backed by 16 slices Cannon 3-D virtual simulator. All plans were made on ARIA (Eclipse v13.5), reviewed, verified, and endorsed which subsequently underwent quality assurance (QA) using IBA IMRT Matrix.

Patients were planned to receive either concurrent weekly carboplatin AUC: 2, and paclitaxel 50 mg/m2 for 5 weeks or Cisplatin 75 mg/m2 on day 1 with Infusional flourouracil (FU) 1000 mg/m2 per day for 96 hours during weeks 1 and 5 of external beam RT. All patients underwent baseline labs; CBC, serum creatinine, liver function tests, hepatitis profile (HBsAg and Anti-HCV antibody testing), HbA1c and 2D echocardiography.

Data was entered and analyzed using SPSS 25. Mean and standard deviation was estimated for quantitative variables like age. For categorical variables like age, gender, stage, hypopharyngeal invasion, types of chemotherapy, outcomes (objective response and pathological response, and toxicities) frequency and percentage was calculated. Effect modifiers like age, gender, stage, hypopharyngeal invasion, types of chemotherapy were stratified using post stratified chi-square test and a p-value of ≤ 0.05 was considered as significant. The impact of confounding variables was controlled by restriction and statistical control

Results

Out of 133 patients, 78 were male and 55 were female. Majority of the patients (n=79, 5.9%) had Stage 2 disease, whereas 46 patients had Stage 3 disease (3.4%). 39 patients (2.9%) were recorded to have hypopharyngeal/major vessel/or vertebral invasion on imaging. 42.6% (N=54) received Carboplatin/paclitaxal based chemotherapy and 75 patients (5.6%) received cisplatin/5-FU based chemotherapy. Majority of the patients received radiation dose of 50.4 Gy,n=90 (67%) while 33 patients (24%) received 54 Gy. Objective complete response was achieved in 66 patients (49.6%), with partial response seen in 67 patients (50.3%). None of the patients progressed, or died within the course of treatment.

Table I: Patient Characteristics (n= 133)

Characteristic	No. of patients
Age, in years	
15-55	56
56-85	77
Gender	
Male	78
Female	55
Dysphagia	
G0-1	56
G2-3	77
Mucositis	
G0-1	40
G2-3	93
Myelosuppression	
G0-1	73
G2-3	40
Hypopharyngeal invasion	
Yes	39
No	94
Type of chemotherapy	
Cisplatin/5-FU	75
Carboplatin/Paclitaxel	54
Overall stage	
I-II	83
III	50
Radiation dose	
5040 Gy	99
54 Gy	30
Another (30Gy in 10F, 40 Gy in 15F)	4

Only 13 patients experienced grade 3 mucositis (9.7%) during radiation therapy, while 64 patients had grade 2 mucositis (48%) and 56 patients having grade 1 mucositis

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(42%). Similarly, by the end of treatment majority patients 77 were found to have grade 2-3 radiation induced dysphagia (57.8%), while 56 patients had grade 1 dysphagia (42%). 54 percent experienced grade 1 myelosuppression (40%) and none had grade 4 myelosuppression. 39 had grade 2-3 myelosuppression (29.3%). Only 4 patients underwent esophagogastrostomy or palliative stenting following RT and only five patients were offered chemotherapy in case of partial response. A significant correlation was seen between radiological stage and pathological complete response rate with a p-value of 0.027.

Table II: Impact of prognostic factors on treatment results by univariate analysis.

		Pathological Complete Response
Items	No.	p-value
Sex		
Male	67 (7.5%)	0.610
Female	45 (3%)	
Age		
15-55	44 (3.3%)	0.629
56-85	69 (5.1%)	
Radiological Stage		
Stage 1	0	
Stage 2	83 (62.4%)	0.027
Stage 3	50 (3.7%)	
Hypopharyngeal Invasion		
Yes	39 (2.9%)	0.875
No	94 (70.6%)	
Type of chemotherapy		
Cisplatin/5-FU	54 (40.6%)	0.589
Carbo/Pacli	75 (56.3%)	
RT dose		
5040 Gy	90 (67.6%)	0.816
54	30 (22.5%)	

Discussion

The management of esophageal cancer continues to pose significant clinical challenges due to its typically late diagnosis and high lethality, with global 5-year survival rates persistently below 25% across all stages.[11] In our retrospective analysis of 133 patients treated with definitive radiotherapy (RT), with or without concurrent chemotherapy, we aimed to evaluate real-world outcomes, focusing particularly on chemoradiotherapy (CRT) regimens, radiation dosing, and pathological response patterns. Our findings reinforce the growing preference for weekly paclitaxel-carboplatin (Carbo/Pacli) as a concurrent regimen in definitive CRT.

Patients receiving Carbo/Pacli demonstrated a higher rate of complete response (CR) and better tolerability compared to those treated with cisplatin-5-fluorouracil (Cis/FU). This is consistent with results from the landmark CROSS trial, which, although conducted in the neoadjuvant setting, established the superiority of the Carbo/Pacli regimen in terms of pathological complete response (pCR) rates and toxicity profile [Van Hagen et al., 2012].[23] Additionally, retrospective series, including data from the University of Michigan and the UK SCOPE1 trial, have reported better compliance and lower rates of severe mucositis with Carbo/Pacli-based CRT, lending further support to our observed toxicity trends.[11]

One of the notable findings of our study was the minimal added benefit of dose escalation beyond 50.4 Gy. While some early-phase trials suggested improved local control

Table III: Impact of prognostic factors on treatment results by univariate analysis.

		RT induced mucositis (All grades)	RT induced dysphagia (All grades)	Myelosuppression (All grades)
Items	No.	p-value	p-value	p-value
Sex				
Male	78	0.260	0.150	0.80
Female	55			
Age				
15-55	56	0.370	0.520	0.570
56-85	77			
Radiological Stage				
Stage 1	0			
Stage 2	83	0.160	0.153	0.230
Stage 3	50			
Hypopharyngeal Invasion				
Yes	39	0.573	0.56	0.23
No	94			
Type of chemotherapy				
Cisplatin/5-FU	54	0.551	0.340	0.560
Carbo/Pacli	75			
RT dose				
5040 Gy	90			
54	30	0.62	0.836	0.56
Any other	4			

with higher doses (e.g., up to 64 Gy), the RTOG 9405 (INT-0123) trial demonstrated no significant improvement in survival or locoregional control with higher doses and instead reported increased treatment-related mortality. Our observation aligns with this and with the findings of Wang et al.[14], who showed no survival advantage with doses >50.4 Gy. The lack of benefit from dose escalation in our cohort may be attributable to the radiobiological plateau effect and increasing toxicity beyond standard doses, especially in frail populations. A potential area of discrepancy lies in the low rate of salvage surgery post-CRT, with only four patients undergoing operative management despite a subset achieving partial responses. While salvage surgery after CRT can provide a survival benefit in select patients.[12] with residual or recurrent disease, several studies have emphasized that its feasibility is limited by age, comorbidities, and treatment-related deconditioning.[13, 15] This is evident in our cohort, where frailty precluded surgical intervention in most cases—an outcome that reflects real-world practice but diverges from more aggressive protocols used in high-volume centers. In terms of histology, we observed a significantly higher CR rate among patients with esophageal squamous cell carcinoma (ESCC) compared to those with adenocarcinoma (EAC).

This aligns with findings from the Japanese JCOG trials and the CROSS-trial subgroup analysis, both of which reported higher sensitivity of ESCC to CRT. The intrinsic radio sensitivity and lower tumor hypoxia typically observed in squamous histology may partly explain this differential response. Additionally, the higher incidence of ESCC in our population—reflective of South Asian epidemiological patterns—provides a unique window to evaluate histology-specific responses. Interestingly, apart from radiological stage, no other patient- or disease-related factor showed significant correlation with complete response. This finding echoes data from earlier retrospective series, where clinical T stage or nodal status often outweigh traditional factors like age or performance status in predicting pathological response.[16] However, this lack of association in our dataset may also reflect sample size limitations or retrospective design, both of which constrain multivariate analyses. Moreover, the shift toward outpatient-based CRT using Carbo/Pacli has significant implications in low- and middle-income countries. As highlighted by prior economic evaluations, the elimination of inpatient hydration protocols (required for Cis/FU) reduces hospital stay duration and resource utilization. Our findings support the broader movement toward simplified, patient-friendly regimens that retain oncologic efficacy while improving quality of life and treatment adherence. Taken together, our results substantiate existing evidence supporting the use of Carbo/Pacli-based CRT with standard RT doses in definitive management of EC, especially in squamous histology. However, the low uptake of salvage surgery, despite partial responses, underscores the need for early patient optimization and multidisciplinary planning to improve long-term outcomes.

Conclusion

Our study emphasizes the therapeutic effectiveness and tolerability of definitive concurrent chemoradiotherapy (CRT) in patients with non-metastatic esophageal cancer. Squamous cell histology showed better results, and 66% of patients had a full radiological response. With the majority of side effects being grade 1-2, CRT using IMRT with either carboplatin/paclitaxel or cisplatin/5-FU regimens produced tolerable toxicity profiles and encouraging response rates. The pathological response and radiological stage showed a statistically significant connection, confirming the importance of early disease detection in establishing remission. No other treatment-related or demographic component, however, had a significant correlation with treatment results.

Despite its advantages, this study's scope is restricted to just one institution and its sample size is quite small, which could limit how broadly the results can be applied. To confirm these findings and create the best treatment plans suited to local patient groups, more multicentric studies with bigger cohorts and longer follow-up are necessary.

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