DOI: 10.7860/JCDR/2024/71336.19673

Original Article

Oncology Section

Toxicity and Local-regional Control of Two Fractionation Schedules with Concurrent Chemotherapy and Intraluminal Brachytherapy for Oesophageal Carcinoma: A Pilot Study

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ABSTRACT

Introduction: Oesophageal cancer is the seventh most common cancer worldwide and the sixth highest cause of cancer-related mortality. Radiation plays an important role in the multimodality treatment of carcinoma of the oesophagus.

Aim: To compare locoregional control and toxicity of two External Beam Radiation Therapy (EBRT) fractionation schedules of concurrent chemoradiotherapy and high-dose intraluminal brachytherapy in patients with oesophageal carcinoma at a single institute.

Materials and Methods: The present study was a pilot study including a total of 33 participants with histologically confirmed oesophageal cancer. Patients were prospectively randomised into two groups. Arm I: EBRT with a total dose of 46 Gy delivered in 23 fractions at a rate of 2 Gy per fraction over 4.3 weeks, along with Concurrent Injection of Cisplatin (CDDP) 100 mg/m^2 on days 1 and 22, followed by Intraluminal Radiation Therapy (ILRT) with 6 Gy per session weekly. Arm II: EBRT with a total dose of 30 Gy delivered in 10 fractions at a rate of 3 Gy per fraction over two weeks and CDDP 100 mg/m^2 on day 1 only. The primary endpoint of this study was to compare the locoregional response and toxicities (both acute and late) in the two arms at the end of radiotherapy and six months.

Results: At the end of the two-month follow-up, no statistically significant difference was found in the response between the two arms (p-value=0.2697). Dysphagia relief was comparable in both arms; however, this difference was not statistically significant (p-value=0.9235).

Conclusion: The responses in both arms were comparable, and further randomised trials with larger sample sizes should be encouraged.

Keywords: Brachytherapy, Conventional, Hypofractionation, Oesophagus, Radiation

INTRODUCTION

Oesophageal cancer is the seventh most common cancer worldwide and the sixth highest cause of cancer-related mortality [1]. Adenocarcinoma and squamous cell carcinoma of the oesophagus collectively cause a significant number of deaths, with a mortality rate of 5.6 deaths per 100,000 individuals. The survival rate for these types of cancer is rather low, with less than 20% of patients surviving for five years or more [2]. According to the findings of the Radiation Therapy Oncology Group's (RTOG) 85-01 study, incorporating platinum-based chemotherapy alongside radiation therapy demonstrates a positive impact on the survival rates of patients diagnosed with locally advanced oesophageal cancer [3].

Conventional Fractionated Radiotherapy (CFRT) has traditionally been considered the standard neoadjuvant treatment option for patients with oesophageal cancer. However, Preoperative Hypo-Fractionated Radiation Therapy (HFRT) has been studied for its efficacy and safety in a few oesophageal cancer patients, which administers a higher dose of more than 2 Gray (Gy) per fraction but with a lower total dose [4]. These trials [4,5] have shown that preoperative HFRT can increase the rate of local control of oesophageal cancer and potentially improve patient survival when compared to surgery alone. Nevertheless, previous studies [5] have only compared the outcomes of surgery alone to the combination of preoperative HFRT and surgery.

For the neoadjuvant treatment of oesophageal cancer, little literature exists to substantiate comparisons between HFRT and CFRT, and the ideal dose-fractionation plan remains undetermined [6]. Thus, this study was executed prospectively to evaluate the efficacy of HFRT in comparison to the standard CFRT regimen, along with intraluminal brachytherapy, for treating oesophageal cancer. This study aimed to assess the locoregional control and toxicities, both acute and late, associated with these treatments.

MATERIALS AND METHODS

This was a pilot study where patients with a recent diagnosis of primary adenocarcinoma or squamous carcinoma of the oesophagus, with no prior treatment history, were recruited from the Oncology Outpatient Department (OPD) of the JK Cancer Institute in Kanpur, Uttar Pradesh, India, between July 2021 and June 2022. The Institutional Ethics Committee approved the study protocol (EC/NEW/INST/2021/1634). All participants provided signed informed consent, fulfilling the inclusion criteria.

Inclusion criteria: 1. Individuals aged between 18 and 60 years, 2. Eastern Cooperative Oncology Group (ECOG) score [7] of 1 or 2, 3. Advanced local disease, which included Stage II and III tumours that could not be surgically removed due to age or health factors. 4. Patients had to have good haematology and biochemistry for radiotherapy or chemotherapy.

Exclusion criteria: 1. Patients with tracheoesophageal fistula, 2. Any prior chest irradiation, chemotherapy, or definitive surgery in the past, not have any other primary cancer, and not have any severe co-morbid conditions. 3. Patients with distant metastases or cervical oesophageal carcinomas.

As part of the pilot study, patients who visited our OPD and met the inclusion and exclusion criteria, totaling 33 individuals were included in the study. These patients had not received any prior therapies and were deemed suitable for participation in the study. The patients were assigned to two arms, Arm I and Arm II, in a

random 1:1 ratio and were analysed as per the Intention-to-Treat Protocol (ITT).

The current study was limited to individuals aged between 18 and 60 years, with an Eastern Cooperative Oncology Group (ECOG) score [7] of 1 or 2, and advanced local disease, which included Stage II and III tumours that could not be surgically removed due to age or health factors. Patients had to have good haematology and biochemistry for radiotherapy or chemotherapy, not have a tracheoesophageal fistula, not have had chest irradiation, chemotherapy, or definitive surgery in the past, not have any other primary cancer, and not have any severe co-morbid conditions. The present investigation did not take into account the existence of remote metastases or cervical oesophageal carcinomas in its evaluation.

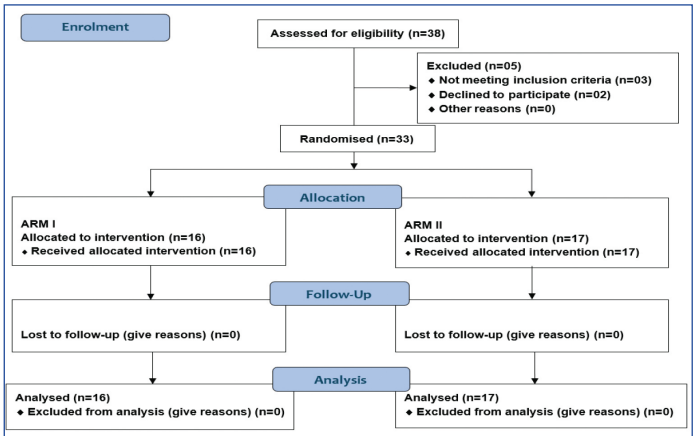
Before treatment, the evaluation included a detailed review of the patient's medical history, an examination of dysphagia severity, a clinical assessment, a symptom check, a nutritional evaluation, and a psychosocial assessment. Patients were evaluated for dysphagia before the treatment started, during the treatment period, and in subsequent follow-up. Any lower grade observed following treatment was considered an improvement in dysphagia compared to the pretreatment grade. Dysphagia was graded as per the Common Terminology Criteria of Adverse Events (CTCAE) dysphagia grading [8].

Desired laboratory values include Hb >10 g/dL, White Blood Cells (WBC)>4000/cu.mm, platelets >1,00,000/cu.mm, and normal liver and kidney function tests. Each patient had a barium swallow, upper Gastrointestinal (GI) endoscopy, chest X-ray, and Contrast-Enhanced Computed Tomography (CECT) scans of the abdomen and chest before treatment.

Participants were prospectively randomised into two arms: Arm I (Conventional fractionation radiotherapy arm or CFRT arm): EBRT with a total dose of 46 Gy delivered in 23 fractions at a rate of 2 Gy per fraction over 4.3 weeks [9], along with CDDP 100 mg/m^2 on days 1 and 22, followed by ILRT with 6 Gy per session weekly.

Arm II (Hypofractionation radiotherapy arm or HFRT arm): EBRT with a total dose of 30 Gy delivered in 10 fractions at a rate of 3 Gy per fraction over 2 weeks and concurrent injection of cisplatin 100 mg/m^2 on day 1 only [10]. [Table/Fig-1] shows CONSORT flow diagram.

Subsequently, there was an administration of High-Dose-Rate (HDR) Interstitial Brachytherapy (ILBT) with a dosage of 6 Gy divided into two portions, one week apart. The treatment started two weeks after finishing EBRT. Radiotherapy was administered



[Table/Fig-1]: Consort's flowchart.

using EBRT delivered by a Cobalt-60 teletherapy system at high energy levels. The patient's positioning was maintained using a thermoplastic mould. A diagnostic Computed Tomography (CT) scan was performed with the patient in the treatment position, lying down, and with the arms positioned overhead. The scan involved taking images in 3 mm thick slices, starting from the throat area (cricoid cartilage) and moving down to the upper abdomen. Oral and intravenous contrasts were supplied to enhance the delineation of the oesophagus and the tumour. The treatment used a traditional two-dimensional radiation approach. Radiotherapy was given with front and back fields initially, each receiving a daily dose of 2 Gy, totaling 46 Gy in Arm I, and each receiving a daily dose of 3 Gy, totaling 30 Gy in Arm II. The treatment portal covered the visible extent of the disease seen in the CT and barium swallow tests, with a minimum margin of 5 cm on each side and a 1 cm border. The spinal cord dose was respected and kept below 46 Gy. Patients in both groups had two sessions of HDR ILBT, with a week between each session, starting two weeks after finishing EBRT. Two days before beginning ILBT, a barium swallow procedure was done for treatment planning.

The location of the tumour was determined based on the preliminary results from the endoscopy and CT scan. Metal clips were used to mark the upper and lower boundaries of the treatment area on the patient's chest for ILBT planning. After administering local anaesthesia using lidocaine spray and sedating with midazolam, a flexible guide wire was inserted into the oesophagus. The applicator's outer diameter was 1 cm, and it was made by Mallinckrodt Medical in Petten, the Netherlands. Subsequently, it was inserted into the oesophageal lumen along the guide wire and secured in position with a mouth guard or tape. The insertion of a radiopaque dummy source into the applicator was utilised to confirm the proper placement of the applicator, as demonstrated by the orthogonal chest X-rays taken subsequently. The treatment was administered using an HDR (Microselectron, Elekta AB, Stockholm, Sweden) remote after-loading device. The Gross Tumour Volume (GTV) borders for brachytherapy were determined by using endoscopic measurements to determine the distance between the teeth and the starting and ending points of the tumour at the time of diagnosis. According to the American Brachytherapy Society standard, a 2 cm margin was added to the superior and inferior borders of the GTV to ensure that the overall length of the treated area does not exceed 10 cm. The cumulative prescription radiation dose was 6 Gy, administered in two fractions with a one-week interval between each administration. The dose prescription was based on a reference point located 1 cm from the central axis. After the completion of the planning phase, the patient was relocated to the treatment room. Ultimately, the after-loading machine was linked using transfer tubes to carry out the brachytherapy treatment.

The main objective was to evaluate the treatment response eight weeks after completing treatment in both groups. The assessment of tumour response was conducted according to RECIST (Response Evaluation Criteria in Solid Tumours) Criteria 1.1 [11]. Additionally, the patient's progress was assessed six months after completing radiation treatment. The patients were assessed every week for toxicity evaluation during irradiation, utilising the RTOG guidelines [12]. The assessment of acute toxicity was also conducted at six months following the final radiation treatment. Throughout the follow-up period, patients were evaluated to monitor the occurrence of any delayed adverse effects. Patients underwent evaluation eight weeks after therapy completion using clinical tests, blood tests, and imaging scans of the chest and abdomen. Follow-up throughout the study duration included clinical assessments, blood tests, and biochemical analyses. Endoscopic examinations were conducted every three months, and CT scans of the chest and abdomen were performed every six months for response assessment. The study had a median follow-up period of 12 months.

STATISTICAL ANALYSIS

The statistical analysis was carried out utilising Statistical Package for the Social Sciences (SPSS) version 28.0 The t-test, Chi-

square test, and Fisher's exact test were deployed to evaluate initial characteristics, response to treatment rates, and adverse consequences among patients in two separate therapy groups. A p-value <0.05 was considered to have statistical significance.

RESULTS

There were 16 patients in arm I and 17 patients in arm II. [Table/Fig-2] presents the baseline demographic and clinical features of the patients, including age, gender distribution, co-morbidities, and tumour staging. Baseline characteristics were similar in both study groups.

Complete Response (CR) + Partial Response (PR) was seen in 12 (75%) patients in arm I and 12 (70.58%) patients in arm II (χ^2=0.3765, p-value=0.2697). One patient in arm I (6.25%) and one patient in arm II (5.88%) were diagnosed with a progressing illness. The interrupted treatment was seen in 2 (12.5%) patients in arm I and 2 (11.76%) patients in arm II [Table/Fig-3].

This study found that 10 (76.92%) patients in arm I and 10 (71.428%) patients in arm II experienced improvement in dysphagia. 3 (23.07%) patients in CFRT and 4 (28.57%) patients in HFRT arm continued to complain of dysphagia with decreased severity in follow-up at the end of 12 months (p-value=0.9235) [Table/Fig-4].

Baseline characteristics	EBRT (46 Gy/23# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm I (n=16)	EBRT (30 Gy/10# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm II (n=17)	p-value
Age (years)			
Range	30-64	29-65	0.73
Median	60	60	
Sex	**n (%)**	**n (%)**	
Male	9 (56.25)	9 (52.94)	The Chi-square statistics with yates' correction is 0.0253. p=0.8736
Female	7 (43.75)	8 (47.06)	
Site of primary			
Upper thoracic	2 (12.50)	2 (11.77)	0.5995
Middle thoracic	9 (56.25)	10 (58.82)	
Lower thoracic	5 (31.25)	5 (29.41)	
Stage			
I	0	0	Fisher's exact test statistic value is 0.688.
II	4 (25)	3 (17.65)	
III	12 (75)	14 (82.35)	
Duration of dysphagia (months)			
≤6	12 (75)	14 (82.35)	Fisher's exact test statistic value is 0.6012, p value-: 0.9755
>6	4 (25)	3 (17.65)	
Degree of dysphagia			
I	0	0	Fisher's exact test statistic value is 0.6012.
II	2 (12.50)	1 (5.88)	
III	14 (87.50)	16 (94.12)	

[Table/Fig-2]: Comparison of baseline demographic and clinical characteristics of the study arms.

Response to treatment at two months	EBRT (46Gy/23# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm I n=16 (%)	EBRT (30Gy/10# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm II n=17 (%)	p-value
CR+PR*	12 (75)	12 (70.58)	χ^2=0.3765, p=0.2697
SD	0	1 (5.88)	
PD	1 (6.25)	1 (5.88)	
Death	1 (6.25)	1 (5.88)	
Interrupted treatment	2 (12.5)	2 (11.76)	

[Table/Fig-3]: Tumour response evaluation by Response Evaluation Criteria in Solid Tumours (RECIST).
*CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

Dysphagia response at twelve months	EBRT (46Gy/23# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm I n=13 (%)	EBRT (30Gy/10# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm II n=14(%)	
Complete Response (CR)	10 (76.92)	10 (71.43)	p=0.9235
Partial Response (PR)	3 (23.08)	4 (28.57)	

[Table/Fig-4]: Dysphagia response at twelve months.

[Table/Fig-5] displays the acute toxicity profile, detailing the adverse effects observed during the study, including skin toxicity, mucositis, and oesophageal toxicity. The acute grade 1 and grade 2 skin toxicity were comparable in both arms (p-value=0.303). The incidence of acute oesophageal toxicity in grades 2 and 3 was greater in arm I (11, 84.62%) compared to arm II (09, 64.29%) (p-value=0.2284).

Acute toxicities at six months	EBRT (46Gy/23# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm I (n=13) (%)	EBRT (30Gy/10# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm II (n=14) (%)	p-value
Skin			
Grade 1	9 (69.23)	12 (85.71)	0.303
Grade 2	4 (30.77)	2 (14.29)	
Pharynx			
Grade 1	8 (61.54)	12 (85.71)	0.152
Grade 2 and above	5 (38.46)	2 (14.29)	
Oesophagus			
Grade 1	2 (15.38)	5 (35.71)	0.2284
Grade 2 and 3	11 (84.62)	9 (64.29)	

[Table/Fig-5]: Acute treatment-related toxicities in the two arms.

Long-term oesophageal issues were similar in both study arms (p-value=0.9415) [Table/Fig-6]. Only one patient in arm A had significant scarring that needed oesophageal dilation for symptom relief due to stricture formation. After 12 months of follow-up, recurrence was observed in four out of 12 patients with an overall response in arm I, leading to the need for salvage therapy, and in five out of 12 patients with an overall reaction in arm II, resulting in disease progression.

Late toxicities after treatment completion	EBRT (46Gy/23# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm I (n=13) (%)	EBRT (30Gy/10# with CDDP 100 mg/m² + ILRT (6Gy/2#) Arm II (n=14) (%)	p-value
Late oesophageal toxicity			
Ryles tube dependency	1 (7.69)	1 (7.14)	0.9415
Feeding jejunostomy	11 (84.62)	10 (71.43)	
Stricture formation	1 (7.69)	03 (21.43)	

[Table/Fig-6]: Late treatment-related toxicities in the two study arms.

DISCUSSION

Oesophageal carcinoma accounts for approximately 6% of all GI malignancies, with a male-to-female ratio of 3.7:1 [13,14]. The majority of cases occur in elderly males, with those under the age of 55 years being rarely affected. Dysphagia is the most common presenting symptom, occurring in more than 90% of patients [13,14]. These findings were comparable in this study population.

CFRT has become the mainstay of preoperative radiotherapy in oesophageal cancer. However, the extension of the preoperative treatment time and the increase in treatment costs are issues that must be considered. HFRT may provide us with the benefit of higher

doses per fraction (more than 2 Gy) but a lower total dose, which can result in better tumour control, a shorter treatment time, better compliance due to fewer hospital visits, and also spare healthy tissue from damage [15,16]. HFRT in lung cancer [17,18], prostate cancer [19,20], breast cancer [21,22], advanced head and neck cancer [23,24], and locally advanced inoperable oesophageal cancer [25,26] are well documented in the literature. In rectal cancer, studies suggest that preoperative HFRT (also known as short-course radiotherapy) is equally effective as conventional radiotherapy (also known as long-course radiotherapy) in ensuring long-term survival [27-29].

Perhaps this was the first study of its kind to compare conventional radiotherapy with HFRT followed by brachytherapy in carcinoma of the oesophagus in radical settings. However, there have been studies investigating the use of preoperative HFRT followed by surgery in oesophageal cancer. Walsh TN et al., conducted a prospective, randomised trial comparing surgery alone and a combination of HFRT, chemotherapy, and surgery [5]. Patients undergoing multimodal therapy received two rounds of chemotherapy and a single session of radiotherapy, consisting of 40 Gy delivered in 15 fractions over three weeks before undergoing surgery. The study indicated that 25% of patients treated with multimodal therapy achieved a partial Clinical Response (pCR) rate. Patients receiving multimodal therapy had a median Overall Survival (OS) of 16 months, whereas those undergoing surgery alone had a median OS of 11 months, with a statistically significant difference (p-value<0.01). Studies in the past showed that combining HFRT with surgery was better for patients with resectable oesophageal cancer than surgery alone, with acceptable rates of side-effects. The study exclusively compared surgery alone with the combination of preoperative HFRT and surgery; it did not include a comparison between HFRT and CFRT. Furthermore, it is worth noting that all of these trials were published more than 20 years ago, and in the 20 years that have passed since then, advances in chemotherapy, radiotherapy, and surgery have occurred. This study has also shown how combining chemotherapy with HFRT or CFRT can effectively treat Stage-II or III oesophageal squamous cell cancer. The response rate of HFRT (75%) was similar to that of CFRT (70.5%). Due to the oesophagus's structure, HFRT may lead to severe side-effects like narrowing, bleeding, tears, or the formation of abnormal passages called strictures. Determining the correct total and daily radiation doses is crucial for the safe administration of HFRT [30].

Studies [25,26] have demonstrated that a daily radiation dose of up to 5 Gy is suitable and well-tolerated in HFRT for oesophageal cancer. Typically, a daily dose of 3 Gy is frequently used in HFRT for locally advanced oesophageal cancer. Ma JB et al., presented important results from a study involving 150 patients with thoracic oesophageal squamous cell carcinoma at specific cancer stages (T2, N0, and M0). A prospective study was done on 74 patients who had Moderate HFRT (MHFRT) with a total dose of 54-60 Gy given in 18-20 fractions over 3.5-4 weeks and on 76 patients who had CFRT. Both groups had about the same number of grade 3 or higher acute toxicities (66.3% in MHFRT vs. 50.0% in CFRT) and late complications (27.0% in MHFRT vs. 22.4% in CFRT; p>0.05). Within the MHFRT group, there were six treatment-related deaths linked to haematological toxicity, oesophageal fistulas, pneumonia, or cardiotoxicity. No treatment-related deaths occurred in the CFRT group. Only two treatment-related deaths occurred in the CFRT arm recently. Both the MHFRT and CFRT groups had about the same number of late oesophageal complications (18.9% vs. 21.1%, respectively) [26]. These included stenosis, fistula, or bleeding at a grade 3 or higher. Present study found no significant differences in radiation therapy toxicities between the HFRT and CFRT groups [6,26].

Limitation(s)

This study is vulnerable to specific restrictions. The smaller sample sizes in this study should be kept in mind when interpreting any data gathered from the statistics in this particular study. The study was performed in a single institution and utilised conventional 2-D planning for both EBRT and ILBT. Consequently, the results cannot be extrapolated to the entire population. However, in developing countries like India, where the majority of centres operate tele-cobalt machines and practice two-dimensional planning, present study information could be beneficial. Owing to the dearth of endoscopic ultrasonography, precise T-staging was not feasible for most patients. The shorter follow-up period is also a limitation of this study.

CONCLUSION(S)

This study found that the two different fractionation arms followed by brachytherapy had similar treatment outcomes for patients with locally advanced oesophageal cancer, as well as there were no additional side-effects. This observation will need to be confirmed by future research using a larger sample size, more conformal radiation techniques, and a longer follow-up time.

Acknowledgement

Authors would like to acknowledge the staff of JKCI, Kanpur, and colleagues for their support and for providing data.

Contribution of authors: MA contributed to the concept, design, and definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, and manuscript review. DKY and AKY were involved in the concept, design, the definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. RK and SNP helped in the definition of intellectual content, data acquisition and manuscript review.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 17, 2024
- Manual Googling: Apr 29, 2024
- iThenticate Software: Jun 12, 2024 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Apr 16, 2024**
Date of Peer Review: **Apr 25, 2024**
Date of Acceptance: **Jun 13, 2024**
Date of Publishing: **Jul 01, 2024**