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Intraluminal Brachytherapy with EBRT in Unresectable Esophageal Carcinoma: A Prospective Study

Shyamji Rawat[1], Ekta Kotwal[2*], Pinky Sarahiya[3], Laxmi Singotia[1], Lalit Mohan Patel[4], Garima Uikey[5]

[1]Professor, Department of Radiation Oncology, State Cancer Institute, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

[2]Third-year Resident, Department of Radiation Oncology, State Cancer Institute, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

[3]Senior Resident, Department of Radiation Oncology, Chirayu Medical College and Hospital, Bhopal, Madhya Pradesh, India

[4]Associate Professor, Department of Radiation Oncology, State Cancer Institute, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

[5]Assistant Professor, Department of Radiation Oncology, State Cancer Institute, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India

***Address for Correspondence:** Dr. Ekta Kotwal, Third-year Resident, Department of Radiation Oncology, State Cancer Institute, Netaji Subhash Chandra Bose Medical College, Jabalpur, Madhya Pradesh, India
E-mail: ektakotwal@gmail.com **& ORCID ID:** https://orcid.org/0009-0006-7245-9787

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ABSTRACT

Background: Esophageal cancer remains a significant global health concern, with a poor prognosis for patients diagnosed at an advanced stage. For those with locally advanced unresectable disease, intraluminal brachytherapy (ILRT) boost after external beam radiotherapy may improve treatment outcomes.

Methods: This prospective study, conducted from February 2020 to December 2022, included 53 histologically confirmed cases of locally advanced unresectable esophageal squamous cell carcinoma treated with high-dose-rate intraluminal brachytherapy (ILRT) boost after external beam radiotherapy (EBRT). Patients received 50 Gy in 25 fractions of EBRT followed by an ILRT boost of 8 Gy in two fractions, 4Gy/fraction, 1 fraction/week. Treatment response and toxicities were evaluated using clinical examination, upper gastrointestinal endoscopy, and computed tomography scans.

Results: Out of 53 patients, 31(58.49%) were male, and 22(41.5%) were female; the median age at presentation was 60 years. Four weeks post-treatment, 58.49% of patients achieved a complete response, 26.41% had a partial response, and 15.09% exhibited stable disease (p=0.001). These response rates remained stable at three and six months. The median progression-free survival was six months. Dysphagia was relieved in 75.4% of patients. The incidence of mucositis was 28.3%, and late complications were 5.6%.

Conclusion: The combination of chemoradiation with an ILRT boost is a safe and effective treatment approach for locally advanced unresectable esophageal cancer. It offers good local control, manageable toxicity, and improved swallowing function. So, intraluminal brachytherapy can be used as a curative approach in the treatment of locally advanced unresectable carcinoma esophagus.

Key-words: Dysphagia, Esophageal cancer, HDR boost, Intraluminal brachytherapy, Radiotherapy.

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INTRODUCTION

According to GLOBOCAN 2020, esophageal cancer accounted for 604,100 (3.1%) new cases and 544,076 (5.5%) deaths globally, making it the ninth most common cancer worldwide [1]. It is the fifth most common cause of cancer-related deaths in India [2]. Surgery remains the preferred curative option for patients with early-stage esophageal cancer. However, many cases are diagnosed

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at an advanced stage, often presenting as a locally advanced disease. For these patients, neoadjuvant chemotherapy followed by surgery is a viable treatment approach [4].

As the esophagus lacks a serosa covering with a vast and extensive lymphatic drainage network, direct invasion to nearby structures and lymph node involvement occurs early, resulting in a poor prognosis despite advances in treatment options [3]. In patients who are unfit for surgery or in whom surgical resection is not feasible, concurrent chemoradiation remains the standard treatment. RTOG 85-01, in its trial, has established the role of concurrent chemoradiation [5].

When treated with EBRT alone, there is an increased chance of loco-regional failure. To overcome this aspect, systemic or targeted chemotherapy can be added. However, this can lead to higher toxicity and treatment-related complications without any improvement in loco-regional control rates and survival outcomes. To improve the outcome, dose escalation can be done either by external beam radiotherapy or by ILRT.

Dose escalation with external radiotherapy is difficult to achieve because of proximity to vital structures such as the lungs, heart, great vessels, and spinal cord. Utilizing the principle of inverse square law, dose escalation is achieved by Intraluminal brachytherapy along with external radiotherapy by acting as a boost to deliver the highest dose to the local tumor tissue with rapid fall off to the nearby surrounding vital structures [6-8].

Thus, the ILRT boost may be used alone or with EBRT. Multiple studies have demonstrated the clinical superiority of combined EBRT plus ILRT compared to EBRT alone. Research by Sharan et al. and Tamaki et al. indicated improved local control and better disease-free survival [9,10]. Brachytherapy has proven to be a valuable option in both curative and palliative settings, helping achieve local control, alleviate symptoms, and improve quality of life.

Although studies have been conducted in the northeastern and southern parts of India, no such research has been carried out in central India. Therefore, we undertook this study to evaluate the safety and efficacy of ILRT boost after EBRT as a curative approach in locally advanced unresectable carcinoma esophagus in the Central India population.

MATERIALS AND METHODS

A total of 53 histologically confirmed cases of locally advanced unresectable oesophageal cancer, intended to be treated with an ILRT boost after completion of 50 Gy/25 fractions of EBRT, were included in this prospective study. This study was conducted at a central Indian tertiary care hospital, the State Cancer Institute, Jabalpur, from February 2020 to December 2022. Baseline investigations such as clinical examination, complete blood count, upper gastrointestinal (GI) endoscopy, and contrast-enhanced computed tomography (CECT) of the thorax and abdomen were performed before initiating the treatment. The patient has provided informed consent for the use and publication of the image.

Inclusion criteria- Only locally advanced unresectable cases involving upper-lower and middle third, biopsy-proven esophageal cancer with squamous cell carcinoma histology, age 18 years or older, and tumor length ≤10cm were included in the study.

Exclusion criteria- Patients with tumors at the cervical region within 5cm from the cricopharyngeus muscle, tumors involving gastroesophageal junction or cardia, and with metastatic disease at presentation, adenocarcinoma histology were excluded from the study.

Methodology- Patients were planned for ILRT 1 week after the completion of EBRT. Using a remote after-loading high-dose-rate (HDR) brachytherapy machine, Gamma Med with Ir-192 source, a total dose of 8 Gy in 2 fractions, 4 Gy in each fraction was delivered 1 week apart in 2 settings. No concurrent chemotherapy was given along with intraluminal brachytherapy. To administer the treatment, the patient was first positioned as per their comfort in lying or in a semi-recumbent position, and then local anesthesia was administered to the oral cavity using 2% viscous xylocaine. An oesophageal bougie is then inserted through the mouth and fixed. Figure 1 shows the esophageal applicator, and Figure 2 shows the placement of the brachytherapy source inside the esophagus, delivering a high dose of radiation directly to the tumor while minimizing exposure to surrounding healthy tissues.

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Fig. 1: Esophageal Applicator

Fig. 2. Patient undergoing esophageal brachytherapy with esophageal applicator connected to HDR Brachytherapy source.

Treatment length was determined by adding a 1 cm margin to the superior and inferior length of the tumor as in the initial CT scan finding. The reference point for dose calculation was 0.5 cm away from the surface of the applicator. CT imaging was done during the treatment to confirm the applicator position and the total dose was planned using Eclipse treatment planning software as shown in Fig. 3.

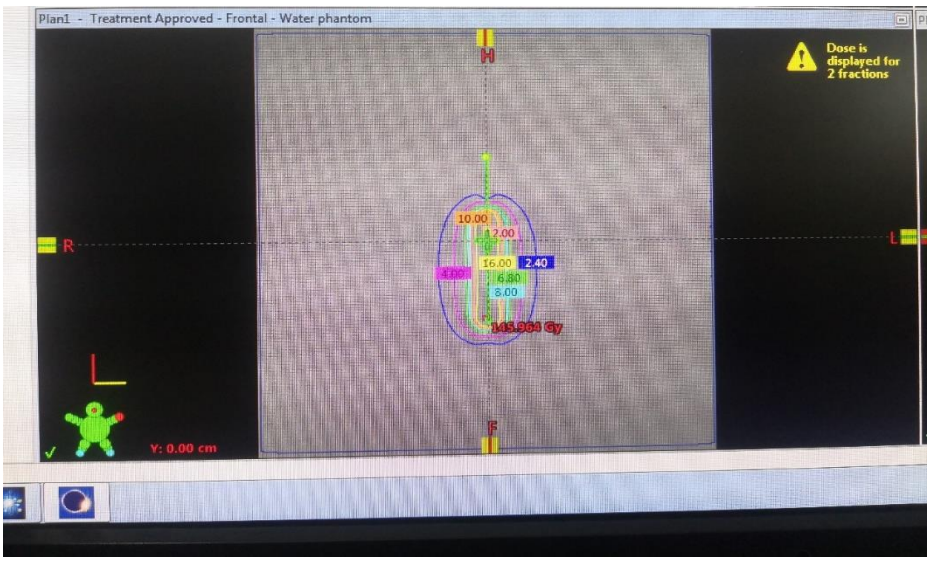

Fig. 3: CT-based treatment planning for intraluminal brachytherapy showing dose distribution using Eclipse treatment planning system

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All patients were initially treated using external beam radiation therapy with a total dose of 50Gy/25 fractions, 2Gy/fraction, 5 fractions per week, delivered in a 5 to 6-week period, using the appropriate portal. Treatment length includes the gross tumor volume with a 5 cm craniocaudal margin and a 2cm lateral margin along the esophagus. Concurrent chemotherapy was given to all the patients undergoing EBRT with weekly paclitaxel and carboplatin. On completion of the treatment, patients were advised for the first follow-up after 4 weeks of completion of treatment and then every 3 months thereafter. The response was assessed per Response evaluation criteria in solid tumors (RECIST Criteria 1.1), clinical examinations at each visit, upper gastrointestinal endoscopy, and CT scan performed when indicated. All complications and toxicities were reviewed carefully.

Statistical Analysis- The treatment outcomes were tabulated in MS Excel, and the percentage was generated manually. A chi-square test was performed, and a $p<0.05$ was considered statistically significant.

Ethical Approval- The study was approved by the Institutional Ethical Committee of Netaji Subhash Chandra Bose Medical College, and all subjects were provided informed consent before enrolment.

RESULTS

Among the 53 patients treated, 31 (58.49%) were male, and 22 (41.5%) were female. The median age at presentation was 60 years (43- 77 years). Geographically, the distribution was nearly equal, with 30 patients (56.6%) from rural areas and 23 (43.39%) from urban regions. Tumor location varied, with 23 patients (43.39%) having tumors in the middle third of the esophagus, followed by 17 (32.07%) in the lower third, and 13 (24.52%) in the upper third. At presentation, most patients had T4A disease (33 cases, 62.26%), while 20 (37.73%) had T3 disease. Patient characteristics are detailed in Table 1.

Table 1: Baseline characteristics of patients

Variables	Frequency
Sex	
Male	31 (58.49%)
Female	22 (41.5%)
Addiction History	
Yes	27 (50.94%)
No	26 (49.05%)
Geography	
Rural	30 (56.60%)
Urban	23 (43.39%)
Site of Tumor	
Middle-third	23 (43.39%)
Lower third	17 (32.07%)
Staging T	
T3	20 (37.73%)
T4A	33 (62.26%)
Staging N	
N0	12 (22.64%)
N1	32 (60.37%)
N2	09 (16.98%)
N3	0
Stage III	18 (33.96%)
Stage IVA	35 (66.03%)
Dysphagia	
Grade I	18 (33.96%)
Grade II	23 (43.39%)
Grade III	12 (22.64%)

Four weeks after completing treatment, 31 patients (58.49%) achieved a complete response, 14 (26.41%) had a partial response, and 8 (15.09%) showed stable disease ($p=0.001$). Three months after completion of treatment, 31 patients (58.49%) maintained a complete response, 16 (30.18%) had a partial response, and 6 (11.32%) exhibited stable disease ($p=0.001$). After six months, 29 (52.8%) continued to show a complete response, 19 (35.84%) had a partial response, and 4 (7.54%) had stable disease ($p=0.001$). The response evaluation is summarized in Table 2.

Table 2: Response Evaluation at Follow-Up Intervals

Response Evaluation	4 Weeks	3 months	6 months
CR	31 (58.49%)	31 (58.49%)	29 (54.71%)
PR	14 (26.41%)	16 (30.18%)	19 (35.84%)
SD	08 (15.09%)	06 (11.32%)	04 (7.54%)
Chi-Square	16.113	17.925	18.151
p-value	0.001	0.001	0.001

[1]*CR: Complete Response, PR: Partial Response, SD: Stable Disease*

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During treatment, 15 patients (28.3%) developed acute mucositis, which was managed symptomatically. Two patients developed benign stricture 3 months post-radiation and underwent dilatation. One patient developed a tracheo-esophageal fistula at the end of 5 months, likely due to disease progression. The initial CT scan showed locally advanced disease abutting the trachea, and he died eventually due to aspiration pneumonitis. The toxicity profile is shown in Table 3.

Table 3: Toxicity Profile at Follow-Up Intervals

Toxicity	4 weeks	3 months	6 months
Acute Mucositis	15	-	-
Stricture	-	1	1
Fistula	-	-	1

During follow-up, the swallowing function was assessed by the ability to take a normal diet, and dysphagia was graded based on WHO Criteria. Those who presented with dysphagia were evaluated with upper gastrointestinal endoscopy, and when required, a CT scan was performed. Dysphagia was relieved in 40(75.4%) of patients. With a median follow-up of 8 months, the progression-free survival (PFS) was 6 months. The patients with local recurrence and residual disease were considered for palliative chemotherapy for symptomatic relief and to improve their quality of life.

DISCUSSION

Several randomized trials have demonstrated the clinical benefits of combining EBRT with ILRT compared to EBRT alone [11-13]. A meta-analysis of prospective studies on brachytherapy conducted by Fuccio et al. stated that brachytherapy is a highly effective and relatively safe treatment option currently underused [14]. In this study, we attempt to report our experience with ILRT boost following concurrent chemotherapy with EBRT in locally advanced unresectable carcinoma esophagus. While only a few studies have reported the use of ILRT boost following concurrent chemoradiation. Zhang et al. reported that patients receiving a radiation dose of 54 Gy or more, along with concurrent chemotherapy, exhibited significantly better locoregional control, disease-free survival, and overall survival [15]. Similarly, Khurana *et al.* found that median survival improved from 9 months with EBRT alone and 10 months with concurrent chemotherapy plus EBRT to 14.5 months when an ILRT boost was added [16]. A study by Calais et al. showed a local control rate of 74% at one year and a three-year survival rate of 27%, with 75% of patients retaining their swallowing function. [17] In our study, with a median follow-up period of eight months, the progression-free survival (PFS) was six months. Dysphagia is one of the most common and distressing symptoms, affecting over 90% of cases. It is important to alleviate dysphagia; there are various means, including laser therapy, external beam radiotherapy, chemotherapy, and endoluminal stent placement. Multiple trials have established the clinical superiority of intraluminal brachytherapy in relieving dysphagia compared to stent placement, yielding better outcomes. A randomized trial by Homs et al. of patients treated with ILRT experienced more days with mild or no dysphagia compared to patients with stent placements [18]. Moreover, many patients treated with EBRT plus ILRT reported long-term relief from dysphagia [19]. Dysphagia was alleviated in up to 90% of patients in the study by Voung *et al.* [20]. We evaluated for swallowing clinically by the ability to take a normal diet. In our study, 81.3% of patients maintained their swallowing function, with no stent placement required during the follow-up period. In our study, no stent placement was needed till the time of our follow-up. As in the report of the RTOG 8501 trial, patients receiving chemoradiation have a higher incidence of grade 3+ toxicity (66%) compared to radiation alone.[5]. However, in our study, treatment was well tolerated, and no grade 3 or grade 4 acute toxicities were reported. The incidence of acute mucositis in our study was 28.3%, and late complications were 5.6%. In the RTOG 92-07 study, an additional benefit of ILRT followed by concurrent chemoradiation was established. However, the study had an increased incidence of fistulae formation, which led to dose modification from 15 Gy in 3 fractions to 10 Gy in 2 fractions [21]. Sharma *et al.* [22] reported a 12% incidence of fistula, whereas Montravadi *et al.* reported no fistula post-treatment [23]. In our study, only 1 patient developed a fistula post-treatment, which may be due to initial disease status, which was not related to the treatment. In our study, only 2 patients developed strictures.

It is quite evident that complications following ILRT are attributable to higher doses per fraction, concurrent use

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of chemotherapy, and doses delivered to the esophageal mucosa. The procedure can be made safer by reducing the dose per fraction, with no concurrent chemotherapy with brachytherapy. In our study, we emphasized lowering the dose per fraction with no concurrent chemotherapy along with brachytherapy. Using 4 Gy per fraction in 2 fractions resulted in no higher grade of toxicity, and treatment was well tolerated by all patients. In our study, the treatment outcome was better than other studies.

CONCLUSIONS

In patients with locally advanced unresectable disease, a combination of chemoradiation with the addition of a brachytherapy boost is a relatively safe and feasible treatment protocol. It is well tolerated with manageable toxicities and with improvement in swallowing in most of the patients. Further studies are required to include a greater number of patients and long follow-ups to identify its role in the definitive treatment of locally advanced unresectable esophageal cancers. Further studies with larger cohorts and extended follow-up are needed to confirm its long-term efficacy.

LIMITATION

Our study constitutes a small number of patients and a shorter duration of follow-up.

CONTRIBUTION OF AUTHORS

Research concept- Ekta Kotwal, Pinky Sarahiya
Research design- Laxmi Singotia, Lalit Mohan Patel, Garima Uikey
Supervision-Shyamji Rawat
Materials- Ekta Kotwal, Pinky Sarahiya
Data collection- Ekta Kotwal, Pinky Sarahiya
Data Analysis and Interpretation-Laxmi Singotia, Lalit Mohan Patel
Literature search- Pinky Sarahiya, Garima Uikey
Writing article- Ekta Kotwal, Pinky Sarahiya, Lalit Mohan Patel, Garima Uikey
Critical review-Shyamji Rawat
Article editing- Ekta Kotwal, Pinky Sarahiya, Lalit Mohan Patel
Final approval-Shyamji Rawat

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