Original paper

Comparative study of concomitant chemoradiation versus concomitant chemoradiation followed by high-dose-rate intraluminal brachytherapy in locally advanced esophageal carcinoma: a single institutional study

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Abstract

Purpose: The aim of this study is to compare efficacy and toxicity between concurrent chemoradiotherapy (CCRT) followed by high-dose-rate intraluminal brachytherapy (ILBT) and CCRT in inoperable, locally advanced esophageal carcinoma.

Material and methods: Thirty-four patients with inoperable, locally advanced esophageal carcinoma were randomized into two arms. In the CCRT + ILBT arm (arm A), eighteen patients received 50.4 Gy at 1.8 Gy per fraction over 5.6 weeks, along with concurrent cisplatin (75 mg/m^2) intravenously on day 1, and 5-fluorouracil (1000 mg/m^2) continuous intravenous infusion on days 1-5, starting on the first day of irradiation and repeated after 28 days. This was followed by ILBT boost with a dose of 10 Gy in 2 fractions, one week apart. In the CCRT arm (arm B), sixteen patients received two cycles of chemotherapy, using the same schedule, along with external beam radiotherapy fractionated in a similar manner without brachytherapy boost. The endpoints were tumor response, acute and late toxicities, disease and progression-free survival.

Results: With a median follow-up of 13 months, the complete response rate was 88.89% in arm A and 87.50% in arm B (p = 0.71). Acute esophageal toxicity was higher in CCRT followed by ILBT arm (p = 0.60). There was no significant difference between the Kaplan Meier survival plots of disease-free survival (p = 0.68) and progression-free survival (p = 0.55).

Conclusions: In our study, addition of brachytherapy as a boost following concurrent chemoradiation failed to improve treatment outcomes without additional toxicity in locally advanced esophageal cancer.

J Contemp Brachytherapy 2018; 10, 3: 225–231
DOI: https://doi.org/10.5114/jcb.2018.76843

Key words: concurrent chemoradiotherapy, disease-free survival, esophageal cancer, intraluminal brachytherapy.

Purpose

Esophageal carcinoma is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide [1]. Poor outcomes in patients are related to diagnosis at advanced and metastatic stages, and the propensity to metastasize, even in small tumors [2]. Multimodal therapy is now a well-established strategy for treatment of esophageal carcinoma. A Radiation Therapy Oncology Group study (RTOG 8501) demonstrated a survival benefit with the addition of platinum-based chemotherapy to radiation compared with radiation alone for patients with locally advanced esophageal cancer [3]. The management of locally advanced esophageal or gastroesophageal junction cancer has shifted from surgery or radiation as a single modality approaches to bi- or trimodality therapy, with the addition of chemotherapy. Definitive chemoradiotherapy treatment is usually reserved for patients with extensive locoregional esophageal carcinoma that is not resectable, or for patients who are not suitable candidates for surgery because of medical risk [4]. Brachytherapy, as compared to external beam radiation therapy (EBRT), offers rapid tumor reduction of intraluminal portion of the tumor, thus rapidly restoring the swallowing function and at the same time, delivers relatively low-dose to the surrounding normal tissues particularly lung, spinal cord, and adjacent normal esophageal mucosa [5].

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Received: 07.01.2018
Accepted: 13.05.2018
Published: 30.06.2018

The aim of this study is to compare the response pattern, survival, and toxicity in non-metastatic locally advanced esophageal cancer treated by concurrent chemoradiotherapy (CCRT) with or without intraluminal brachytherapy.

Material and methods

Previously untreated patients with histologically confirmed primary squamous cell carcinoma/adenocarcinoma of esophagus were recruited from an oncology outpatient department of a tertiary care hospital. The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all study participants. The eligibility criteria included age 18-70 years, Eastern Cooperative Oncology Group (ECOG) status ≤ 2, histologically proven squamous/adenocarcinoma of esophagus, locally advanced stage (clinically defined as a T3N0 or T3N1 tumor, and stage T2N0 or T2N1 inoperable due to age or medical contraindications), hematological and biochemical parameters suitable for radiotherapy or chemotherapy, no tracheo-esophageal fistula, no prior chest radiotherapy or chemotherapy or definitive surgery, no other primary cancer, and any severe co-morbid disease. Presence of distant metastasis and carcinomas of cervical esophagus were excluded from the study.

The pretreatment assessment included clinical history in detail (including grading of dysphagia), thorough clinical examination, symptom assessment, nutritional assessment, and psychosocial assessment. Acceptable baseline hematological and biochemical parameters included hemoglobin level > 10 g/dl, leukocyte count > 4.0 x 10^9/ml, platelet count > 150 x 10^9/ml, urea < 40 mg/dl, creatinine < 1.5 mg/dl, total bilirubin < 1 mg/dl, and alanine aminotransferase and aspartate aminotransferase levels < 40 IU/ml. Upper gastrointestinal (GI) endoscopy, chest X-ray, barium swallow, and contrast enhanced computerized tomography (CECT) scans of thorax and abdomen were done in all patients before the treatment.

Subjects fulfilling the above criteria were randomly assigned into two arms. One arm (arm A) was given concomitant CCRT consisting of concomitant EBRT (50.4 Gy in 28 fractions over 5.6 weeks, given five fractions per week) and two five-day cycles of chemotherapy with cisplatin (CDDP) (75 mg/m^2) intravenously on day 1 and 5-fluorouracil (5-FU) (1000 mg/m^2) intravenously on day 1-5 day at the first and fifth weeks. This was followed by a boost of intraluminal high-dose-rate brachytherapy (ILBT), with a dose of 10 Gy in 2 fractions one week apart, starting two weeks after completion of EBRT.

The other arm (arm B) received concomitant chemoradiotherapy consisting of concomitant EBRT (50.4 Gy in 28 fractions over 5.6 weeks, given five fractions per week) and two 5-day cycles of chemotherapy with CDDP (75 mg/m^2) and 5-FU (1000 mg/m^2) at the first and fifth weeks, in a similar manner as in arm A.

Radiotherapy was administered as EBRT by a megavoltage beam utilizing cobalt-60 tele-therapy machine. Conventional fractionated radiotherapy was performed throughout the entire treatment process in both arms, and a total dose of 50.4 Gy was delivered in twenty-eight fractions at the rate of 1.8 Gy per fraction (single fraction per day and five fractions per week). Immobilization was done by thermoplastic mold. CT scan was taken in the treatment position with arms placed overhead with 3 mm thick slices from the level of cricoid cartilage to upper abdomen. Oral and intravenous contrasts were administered to better define the esophagus and the tumor. The two-dimensional conventional radiation technique was used, and radiotherapy was consisted of initial anterior and posterior opposed fields at 1.8 Gy per day to a total dose of 39.6 Gy. This was then followed by a three-field technique using two posterior oblique fields ('off-cord') and an anterior field at 1.8 Gy per day to a total dose of 50.4 Gy. The initial fields encompassed the gross disease (as seen in the CT and barium swallow examination), at a minimal proximal and distal 5 cm margins, and radial margin of 1 cm. The treatment field was reduced to include the tumor plus a 2 cm margin at 39.6 Gy. The dose delivered to the spinal cord was kept below 46 Gy.

Two weeks after completion of EBRT, patients in arm A were planned for two settings of high-dose-rate (HDR) ILBT, delivered 1 week apart. Barium swallow was done 2 days prior to initiation of ILBT for treatment planning. The location of the tumor was identified using the initial endoscopic and computed tomography (CT) findings. Superior and inferior borders of the length to be treated by ILBT were marked on the patient's chest with metal clips to facilitate the ILBT planning. After local analgesia with lidocaine spray and sedation using midazolam, a flexible guide wire was introduced into the esophagus. The applicator (Mallinckrodt Medical, Petten, The Netherlands) with a 1 cm external diameter applicator was then inserted into the esophageal lumen over the guide wire and fixed using a mouth-guard or tape. Applicator positioning was controlled by orthogonal chest X-rays after insertion of radiopaque dummy source into the applicator. The treatment was delivered on a MicroSelectron HDR remote after-loading device (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). GTV borders for brachytherapy were defined by endoscopic measure of the distance from teeth to the beginning and end of the tumor at diagnosis. A 2 cm cranial and caudal margin was added to the superior and inferior borders of the gross tumor volume (GTV), providing that total treated length not to exceed 10 cm, as per American Brachytherapy Society guideline. The total prescribed dose was 10 Gy in 2 fractions one week apart. The reference point for dose prescription was 1 cm away from the central axis. Once the planning process had been completed, the patient was transferred to the treatment room. Finally, the afterloading machine was connected by means of transfer tubes and the brachytherapy treatment was performed.

The primary end-points were to assess the treatment response using RECIST (Response Evaluation Criteria in Solid Tumor) criteria after six weeks of completion of treatment in both arms as well as assess one-year disease-free survival (for complete responders) and one-year progres-

sion-free survival (for partial responders and stable disease) in both arms. During radiotherapy, weekly toxicity assessment was done using Radiation Therapy Oncology Group (RTOG) radiation morbidity scheme. Acute toxicity assessment continued for an additional eight weeks from the last date of radiation. During follow-up period, patients were assessed for the appearance of any late toxicity. Common toxicities were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (CTCAE 4.0). Patients were assessed at six weeks after completion of treatment by clinical, hematological, and biochemical tests, endoscopic examination and CECT scan of thorax and abdomen. Follow-up was continued thereafter till the end of study, with clinical, hematological, and biochemical tests, endoscopic examination at three monthly interval, and CECT scan of thorax and abdomen were done every six months. Recurrence was proven by biopsy. The median follow-up period of the study was 13 months.

Statistical analysis was done using SPSS version 16. The *t*-test/χ^2/Fisher-exact test was used for comparing baseline profiles, the response rates, and toxicities among patients of two treatment arms, with p value < 0.05 as significant. Disease-free survival (DFS) was measured from the date of declaration of complete response to the date of first relapse (locoregional or distant metastasis) or death. Progression-free survival (PFS) was measured from date of declaration of partial response or stable disease to date of first progression. The disease-free survival and progression-free survival were determined using the Kaplan Meier survival analysis with log-rank test for comparing the DFS and PFS.

Results

Thirty-seven treatment naive locally advanced esophageal cancer patients were assessed for eligibility for inclusion in the study. Three patients were ineligible for study after failing to meet the eligibility criteria (n = 2) or declined to participate (n = 1). The remaining thirty-four patients were randomly assigned into two arms: arm A and arm B by using block randomization technique. Seven patients were lost to follow-up due to socioeconomic conditions (n = 6) or died within the study period due to non-oncological causes (n = 1). At the end of study, thirty-four patients were analyzed as per intention to treat protocol (ITT) (18 patients in arm A and 16 patients in arm B). Figure 1 depicts the flow of patients in the two study arms. Table 1 presents the baseline demographic and clinical features of patients. All baseline parameters were comparable between the two study groups.

Overall response rate (CR + PR) was 88.89% in arm A and 87.50% in arm B (p = 0.71). As seen from Table 2, the complete response rate was 55.56% in the arm A and 56.25% in the arm B; partial response was achieved in 33.33% and 31.25%, respectively in the two arms. One patient in arm B had stable disease. Two patients in arm A and one patient in arm B were found to have progressive disease.

Patients were evaluated for dysphagia before the treatment was started, during the treatment period, and in subsequent follow-up. Any lower grade following treatment was considered as the improvement of dysphagia over the pretreatment grade. In our study, 88.89% patients in the CCRT + ILBT arm and 87.5% patients in the CCRT arm had improvement in dysphagia.

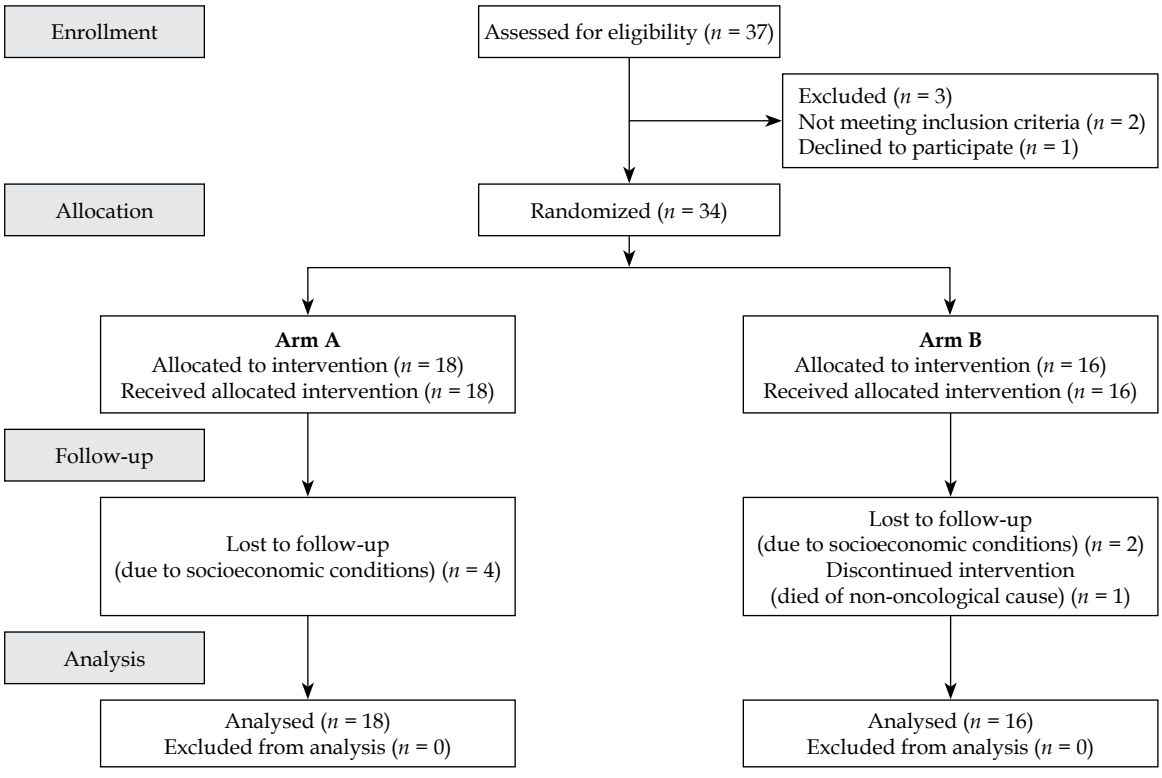

Fig. 1. Consort diagram depicting flow of patients in the study

Table 1. Comparison of baseline demographic and clinical characteristics of the study arms

Baseline characteristic	CCRT + ILBT (arm A)* (n = 18)	CCRT (arm B)† (n = 16)	p value
Age (years)			
Range	31-68	40-68	0.74
Median	58	58.5	
Sex			
Male	16 (88.88%)	14 (87.5%)	0.65
Female	2 (11.12%)	2 (12.5%)	
Performance status			
ECOG I	3 (16.66%)	2 (12.5%)	0.55
ECOG II	15 (83.34%)	14 (87.5%)	
Site of primary			
Middle	11 (61.11%)	11 (68.75%)	0.5
Lower	7 (38.89%)	5 (31.25%)	
Stage			
I	3 (16.66%)	3 (18.75%)	0.42
II	5 (27.78%)	5 (31.25%)	
III#	10 (55.56%)	8 (50.0%)	
Duration of dysphagia (months)			
Range	0.5-6.0	0.5-6.0	0.999
Median	4	4	
Severity of dysphagia			
Grade I	3 (16.66%)	3 (18.75%)	0.18
Grade II	6 (33.33%)	5 (31.25%)	
Grade III	8 (44.44%)	7 (43.75%)	
Grade IV	1 (5.55%)$	1 (6.25%)	
Hemoglobin (g/dl)			
Range	9.3-12.9	9.6-13.4	0.39§
Mean ± SD	10.2 ± 0.4	10.38 ± 0.42	
Creatinine clearance (ml/min)			
Range	52-78	50-77	0.79§
Mean ± SD	65.22 ± 1.66	65.43 ± 1.76	

**Concurrent chemoradiotherapy and intraluminal brachytherapy*
†Concurrent chemoradiotherapy
#T3N1 stage (AJCC 7th edition) only
$requiring percutaneous gastrostomy placement
§P value from Student's independent samples t test for numerical variables and Fisher's exact probability test
χ^2 test or χ^2 test for trend (as applicable) for categorical variables

The acute toxicity profile is presented in Table 3. The acute grade 1 and grade 2 skin toxicity assessed by RTOG Acute Morbidity Scoring were comparable in both arms (p = 0.48). Combined grade 1 and grade 2 pharyngeal mucositis were 88.89% and 87.5% in arm A and arm B, respectively (p = 0.86). RTOG acute esophageal toxicity grade 2 and grade 3 (77.78% in arm A and 68.75% in arm B) were higher in arm A than arm B (p = 0.60). Other acute toxicities were comparable between the two arms.

Late esophageal toxicity was comparable in both arm A and arm B (p = 0.83) (Table 4). Only one patient in arm A had severe fibrosis requiring esophageal dilation. With a median follow-up of 13 months, recurrence occurred in four out of ten patients who achieved complete response in the CCRT + ILBT arm, and three out of nine who achieved complete response in the CCRT arm (p = 1.000). The disease-free survival (p = 0.678) (Figure 2) and progression-free survival (p = 0.548) (Figure 3) were comparable in both arms.

Discussion

Esophageal carcinoma accounts for approximately 6% of all gastrointestinal malignancies with a male: female ratio of 3.7 : 1 [6]. Most cases occur in elderly males, and those below 55 years are rarely affected. Dysphagia is the most common presenting symptom, occurring in more than 90% of patients [6]. These features were also encountered in our study population. During the past two decades, a number of studies investigating concurrent radiotherapy and chemotherapy to treat esophageal cancer have been reported. In a Canadian practice guideline, Wong *et al*. [7] stated that chemoradiation is superior to radiotherapy alone when a nonsurgical approach is selected. It should be noted that most patients enrolled in these phases II or III trials had early clinical stage disease [8]. Despite this fact, local control was poor, with 44% patients relapsing within irradiated fields [9]. A meta-analysis on the pathological complete response (pCR) rates following definitive chemoradiotherapy suggested higher rates of pCR with higher doses of radiotherapy. However, only three of the twenty-six studies in this 'published data' meta-analysis used doses higher than 50 Gy [10]. Zhang *et al*. reported that patients who received a dose of 54 Gy or higher with concurrent chemotherapy had a significantly better locoregional control, disease-free survival,

Table 2. Tumor response evaluation by Response Evaluation Criteria in Solid Tumors (RECIST)

Response	Arm		p value
	A (n = 18)	B (n = 16)	
CR	10 (55.56%)	9 (56.25%)	0.71
PR	6 (33.33%)	5 (31.25%)	
SD	0 (0.00%)	1 (6.25%)	
PD	2 (11.11%)	1 (6.25%)	

CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease

and overall survival [11]. Similarly, Suh *et al*. [12] showed in a retrospective study that high-dose radiotherapy of 60 Gy or higher with concurrent chemotherapy improved locoregional control and progression-free survival without a significant increase of treatment related toxicity in patients with stages II-III esophageal cancer.

The necessity to improve local control is clear, especially in patients with locally advanced disease. Addition of brachytherapy boost and, when feasible, surgery could improve local control and perhaps survival. There were only a few published results of external beam radiation, brachytherapy boost, and concurrent chemotherapy for meaningful numbers of patients [13,14,15].

This study is an attempt to report our experience with ILBT boost following concurrent chemoradiotherapy in esophageal cancers. There are several trials that have reported on the use of ILBT following concurrent chemoradiotherapy. RTOG 92-07 report was designed to study if there was an additional benefit of adding brachytherapy to the concurrent chemoradiotherapy regimen. After the initial dose of 15 Gy in three fractions of HDR brachytherapy led to significant increase in the incidence of fistula, the protocol was modified to deliver a dose of 10 Gy in two settings. Persistence of disease was observed in 19% of the patients. However, the 1-year survival rate was reported as 49%. The incidence of fistula post-treatment continued to be high at 12%, and the authors urged caution in the use of brachytherapy boost to concurrent chemoradiotherapy [15]. The investigators concluded that survival was no different with the addition of brachytherapy and should be cautioned given their fistula rate. Similar results were found in our study, where statistically no significant difference was found in two arms regarding DFS (log-rank test p value 0.678) and PFS (log-rank test p value 0.548). However, there were no cases of fistula in brachytherapy arm. The difference of this observation from RTOG 92-07 was due to high brachytherapy dose that was delivered during chemotherapy.

Since the RTOG 92-07 study, there have been several reports on improved outcomes with concurrent chemoradiotherapy followed by ILBT in esophageal carcinoma [16,17,18]. Calais *et al*. [18] reported a local control rate of 74% at one-year and a three-year survival rate of 27%, following treatment with concurrent chemoradiotherapy followed by brachytherapy, with a good retained swallowing score for 75% of patients. Khurana *et al*. [17] reported in their study that patients receiving chemoradiotherapy followed by ILBT had the highest median survival of 14.5 months, compared to EBRT alone (9 months), EBRT with ILBT (10 months), and concurrent chemoradiotherapy (11 months). The authors, however cautioned that the results could have been confounded by bias, as fitter pa-

Table 3. Frequency of acute treatment related toxicities in the two study arms

Toxicities	CCRT + ILRT* (n = 18)	CCRT† (n = 16)	p value
Skin			
G1	10 (55.56%)	9 (56.25%)	0.48
G2	8 (44.44%)	7 (43.75%)	
Pharynx			
G0	2 (11.11%)	2 (12.5%)	0.86
G1	10 (55.56%)	10 (62.5%)	
G2	6 (33.33%)	4 (25.0%)	
Esophagus			
G1	4 (22.22%)	5 (31.25%)	0.60
G2	8 (44.45%)	8 (50.0%)	
G3	6 (33.33%)	3 (18.75%)	
Lungs			
G0	3 (16.67%)	3 (18.75%)	0.96
G1	11 (61.11%)	10 (62.5%)	
G2	4 (22.22%)	3 (18.75%)	
Heart			
G0	16 (88.89%)	13 (81.25%)	0.53.
G1	2 (11.11%)	3 (18.75%)	
Hematological			
G1	4 (22.22%)	3 (18.75%)	0.78
G2	8 (44.45%)	9 (56.25%)	
G3	6 (33.33%)	4 (25.0%)	
Upper G.I.			
G1	6 (33.33%)	4 (25.0%)	0.86
G2	9 (50.0%)	9 (56.25%)	
G3	3 (16.67%)	3 (18.75%)	
Lower G.I.[$]			
G0	7 (38.89%)	7 (43.75%)	0.95
G1	6 (33.33%)	5 (31.25%)	
G2	5 (27.78%)	4 (25.0%)	

[$]Toxicity grading using CTCAEv4; G – grade; All other toxicities were graded using RTOG Acute Radiation Morbidity Scoring Criteria
**Concurrent chemoradiotherapy and intraluminal brachytherapy*
†Concurrent chemoradiotherapy

Table 4. Frequency of late treatment related toxicities in the two study arms

Toxicity type	Toxicity grade 2 and 3		Toxicity grade 0 and 1		p value
	CCRT + ILRT* (n = 18)	CCRT† (n = 16)	CCRT + ILRT*(n = 18)	CCRT† (n = 16)	
RTOG late skin toxicity	5 (27.77%)	3 (18.75%)	12 (66.67%)	10 (62.5%)	0.90
RTOG late esophageal toxicity	4 (22.22%)	3 (18.75%)	13 (72.22%)	10 (62.5%)	0.83

**Concurrent chemoradiotherapy and intraluminal brachytherapy*
†Concurrent chemoradiotherapy

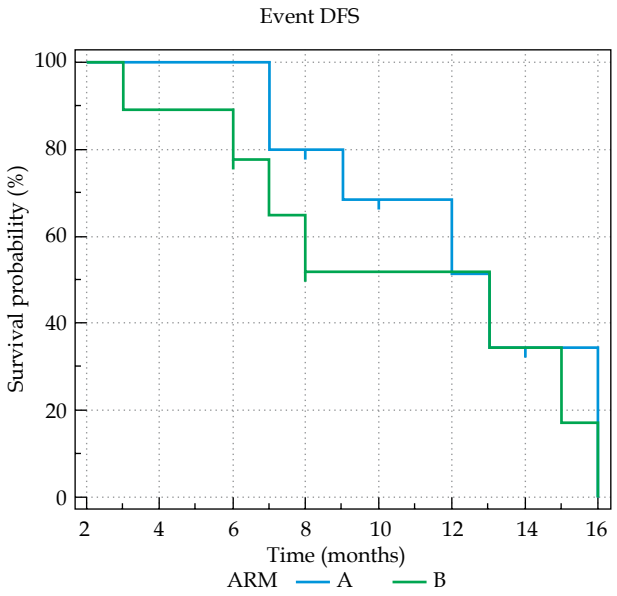

Fig. 2. Kaplan-Meier plot depicting disease-free survival in the two study groups

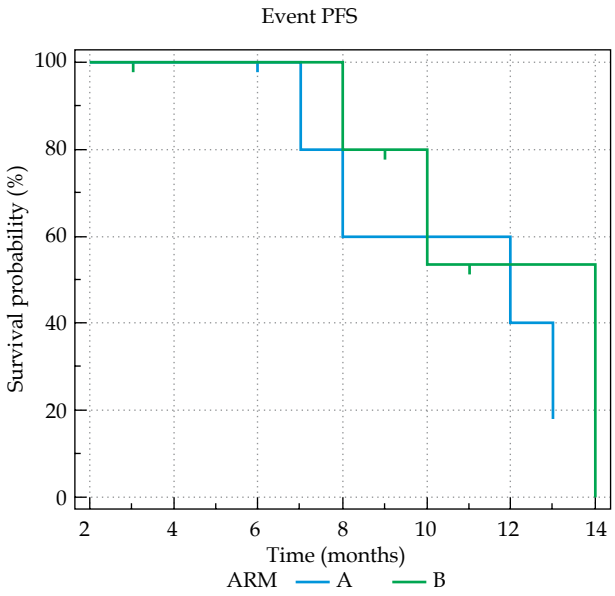

Fig. 3. Kaplan-Meier plot depicting progression-free survival in the two study groups

tients were more likely to receive aggressive regimens. Similarly, in our study, overall median survival was thirteen months in chemoradiotherapy followed by ILBT arm. A few other reports suggest a benefit of incremental radiotherapy dose on outcomes [19,20,21,22]. Chauhan *et al*. [23] conducted a retrospective study on patients with carcinoma esophagus who were treated with external radiation therapy followed by intraluminal brachytherapy. Twenty-one patients with unresectable carcinoma esophagus without any history of previous anticancer treatment were given external radiotherapy, 40 Gy in 20 fractions over 4 weeks. After gap of two to three weeks, all patients were given intraluminal high-dose-rate brachytherapy (5 Gy/3 fraction/one week apart) who were enrolled in this retrospective study. After completion of treatment, complete response was noted in 19 (90.4%), and persistent disease was seen in 2 (9.52%) patients.

In our study, CR was seen in 10/18 (55.56%) patients, PR in 6/18 (33.33%) patients, and persistent disease in 2/18 (11.11%) cases in CTRT followed by ILBT arm. This difference in observation from Chauhan *et al*. study exist, possibly because of greater number of ILBT fractions applied, which resulted in better local control. Our results showed that the response rate of esophageal cancer patients to CCRT with ILBT boost was relatively high and reached 88.89%, indicating that can effectively kill tumor cells and rapidly reduce tumor size. This is consistent with clinical observation that CCRT with ILBT can relieve dysphagia in these patients. The response profile was similar in both arms ($p = 0.71$).

In our study, 4 out of 10 (40%) patients who achieved complete response recurred in the arm A, and 3 out of 9 (33.33%) patients who achieved complete response recurred in the arm B. Although this difference was not statistically significant, in view of the small numbers, it would not be correct to draw any definite conclusions regarding local recurrence rate from the present study.

The treatment was well tolerated. Complications following the use of ILBT with chemoradiotherapy have been variably reported by different investigators. While Montravadi *et al*. [14] reported no patient developing fistula post-treatment, Sharma *et al*. [24] on the other hand reported a 12% incidence of fistula formation and 29% incidence of post-treatment esophageal ulcers. Notably, the patients in this study were administered chemotherapy just prior to ILBT. Significantly fewer incidences of strictures was seen when ILBT dose was reduced from 20 to 15 Gy (24% vs. 8%). As mentioned earlier, we did not find any fistula in our study; only one patient developed stricture requiring dilation. Other acute and late toxicities assessed by RTOG acute and late morbidity scoring criteria were found comparable in both arms and were statistically non-significant.

This study has its limitations. Our sample size was small, so any statistical data have to be interpreted with caution. It was a single institutional study, and two-dimensional planning was used both for EBRT and ILBT; hence, the results derived cannot be extrapolated on entire population. However, in developing countries like India where majority of centers are equipped with ^{60}Co machines and uses two-dimensional planning, our presented data could be helpful. No patient underwent an endoscopic ultrasonography, so accurate T-staging was not possible in most patients. Usually these cancers recur within twenty-four months, more so in first twelve months post-treatment. Entire study duration was almost 1.5 years including patient accrual, intervention, and assessment, so the toxicity profile or DFS/PFS may have been changed with longer follow-up.

Conclusions

In our study, addition of brachytherapy as a boost following concurrent chemoradiation failed to improve

treatment outcomes without added toxicity in locally advanced esophageal cancer. Further studies with larger sample size, more conformal radiotherapy technique, and longer follow-up period are required for establishing this observation.

Disclosure

The authors report no conflict of interest.

References

1. Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108.
2. Pennathur A, Farkas A, Krasinskas AM et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. *Ann Thorac Surg* 2009; 87: 1048-1055.
3. Cooper JS, Guo MD, Herskovic A et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999; 281: 1623-1627.
4. DeVita VT Jr, Lawrence TS, Rosenberg SA (eds.). Cancer: Principles & Practice of Oncology. Wolters Kluwer, Philadelphia 2015; 582.
5. Safaei AM, Ghalehtaki R, Khanjani N et al. High-dose-rate intraluminal brachytherapy prior to external radiochemotherapy in locally advanced esophageal cancer: preliminary results. *J Contemp Brachytherapy* 2017; 9: 30-35.
6. Jemal A, Siegel R, Xu J et al. Cancer statistics, 2010. *CA Cancer J Clin* 2010; 60: 277-300.
7. Wong R, Malthaner R, Zuraw L et al.; Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group. Combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. *Int J Radiat Oncol Biol Phys* 2003; 55: 930-942.
8. Smith T, Ryan L, Douglass H et al. Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1998; 42: 269-276.
9. Hennequin C, Gayet B, Sauvanet A et al. Impact on survival of surgery after concomitant chemoradiotherapy for locally advanced cancers of the esophagus. *Int J Radiat Oncol Biol Phys* 2001; 49: 657-664.
10. Geh JI, Bond SJ, Bentzen SM et al. Systematic overview of preoperative (neoadjuvant) chemoradiotherapy trials in oesophageal cancer: Evidence of a radiation and chemotherapy dose response. *Radiother Oncol* 2006; 78: 236-244.
11. Zhang Z, Liao Z, Jin J et al. Dose-response relationship in locoregional control for patients with stage II-III esophageal cancer treated with concurrent chemotherapy and radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; 61: 656-664.
12. Suh YG, Lee IJ, Koom WS et al. High-dose Versus Standard-dose Radiotherapy with Concurrent Chemotherapy in Stages II–III Esophageal Cancer. *Jap J Clin Oncol* 2014; 44: 534-540.
13. Staar S, Mueller RP, Achterrath W. Intensified treatment for inoperable esophagus cancer: simultaneous radiochemotherapy combined with HDR intraluminal brachytherapy-results of a phase II trial [abstract]. Proc ASCO 1993; 12: 223.
14. Montravadi RVP, Gates JO, Bajpai D et al. Combined chemotherapy and external radiation therapy plus intraluminal boost with high dose rate brachytherapy for carcinoma of the esophagus. *Endocuriether Hyperthermia Oncol* 1995; 11: 223-233.
15. Gaspar LE, Qian C, Kocha WI et al. A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): preliminary toxicity report. *Int J Radiat Oncol Biol Phys* 1997; 37: 593-539.
16. Vuong T, Szego P, David M et al. The safety and usefulness of high-dose-rate endoluminal brachytherapy as a boost in the treatment of patients with esophageal cancer with external beam radiation with or without chemotherapy. *Int J Radiat Oncol Biol Phys* 2005; 63: 758-764.
17. Khurana R, Dimri K, Lal P et al. Factors influencing the development of ulcers and strictures in carcinoma of the esophagus treated with radiotherapy with or without concurrent chemotherapy. *J Cancer Res Ther* 2007; 3: 2-7.
18. Calais G, Dorval E, Louisot P et al. Radiotherapy with high dose rate brachytherapy boost and concomitant chemotherapy for Stages IIB and III esophageal carcinoma: Results of a pilot study. *Int J Radiat Oncol Biol Phys* 1997; 38: 769-775.
19. Chatani M, Matayoshi Y, Masaki N. Radiation therapy for the esophageal carcinoma: External irradiation versus high dose rate intraluminal irradiation. *Strahlenter Onkol* 1992; 168: 328-332.
20. Fietkau R, Grabenbauer GG, Sauer R. Radiotherapy of esophageal cancer. Results following radiotherapy alone and simultaneous radiochemotherapy and intracavitary irradiation. *Strahlenther Onkol* 1994; 170: 69-78 [Article in German].
21. Yorozu A, Dokiya T, Oki Y et al. Curative radiotherapy with high-dose-rate brachytherapy boost for localized esophageal carcinoma: Dose-effect relationship of brachytherapy with the balloon type applicator system. *Radiother Oncol* 1999; 51: 133-139.
22. Nishimura Y, Okuno Y, Ono K et al. External beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for patients with superficial esophageal carcinoma. *Cancer* 1999; 86: 220-228.
23. Chauhan A, Kaur P, Annex E. Radical External Beam Radiotherapy with Intraluminal High Rate Dose Brachytherapy in Patients with Carcinoma Esophagus. *Internet J Gastroenterol* 2008; 8.
24. Sharma V, Agarwal J, Dinshaw K et al. Late esophageal toxicity using a combination of external beam radiation, intraluminal brachytherapy and 5-fluorouracil infusion in carcinoma of the esophagus. *Dis Esophagus* 2000; 13: 219-225.