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Research Article

A PROSPECTIVE AND COMPARATIVE STUDY ON CONCURRENT RADIOTHERAPY WITH GEFITINIB VERSUS RADIOTHERAPY ALONE IN THE TREATMENT OF ELDERLY PATIENTS WITH CARCINOMA OESOPHAGUS

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ABSTRACT

Objective: Concurrent chemoradiotherapy (CTRT) is the primary treatment for inoperable carcinoma esophagus. However, elderly patients are often not capable of tolerating CTRT, leaving radiotherapy as only option available for them. Many studies showed efficacy of anti-EGFR agent Gefitinib with acceptable toxicity profile in carcinoma esophagus patients. Hence, in this study, we compared radiation along with Gefitinib against radiation alone for the treatment of inoperable esophageal carcinoma in elderly patients in terms of locoregional control and toxicity profile.

Methods: Patients of 50–70 years age group with inoperable squamous cell carcinoma esophagus were randomized in two groups – the control group received external beam radiotherapy 50.4 Gy in two phases over 5 weeks and the study group received radiotherapy with same dose along with Tab Gefitinib-250 mg daily during the radiotherapy. Response assessment was done after completion of treatment and all patients were followed up weekly during the course of treatment and then at every month for at least 6 months.

Results: Overall response rate (complete+partial response) was better in study arm (80% vs. 70%), but not statistically significant (p=0.221). Just after treatment completion dysphagia of grade2 and above was more in control arm but after 3 months there was rise in incidences of dysphagia in study arm (66.6% vs. 60% p=0.632). Although statistically not significant, gefitinib containing study arm showed more incidences of higher grade of diarrhoea (20% vs. 15%, p=0.843) and moderate to severe grade of anaemia (90% vs. 66%, p=0.921).

Conclusion: We can say that concomitant treatment with Gefitinib and radiotherapy was well tolerated and effective in elderly patients of inoperable carcinoma esophagus.

Keywords: Carcinoma esophagus, Gefitinib, Radiotherapy, Elderly patients.

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INTRODUCTION

According to GLOBOCAN 2020, in India, esophageal carcinoma is the fifth most common cancer estimating more than 60,000 cases yearly. It contributes 6.9% of all cancer related deaths in India [1]. Surgery is the primary modality of treatment for middle and lower esophageal disease. Radical surgery in carcinoma esophagus has several complications and has some quality-of-life related issues [2]. Concurrent chemoradiotherapy has been established as one of the standard therapies for patients with locally advanced, unresectable esophageal carcinoma based on the results of the radiation therapy oncology group (RTOG) 85–01 and 95–04 trials, which demonstrated a significant survival advantage of concurrent chemoradiation over radiation alone [3,4]. 5 FU and cisplatin combination is the most common regime used as concurrent chemotherapy for the treatment of carcinoma esophagus [5].

However, as most of the patients of esophageal carcinoma are elderly and several comorbidities coexist in such patients, such as — cardiac, respiratory, and nephrologic; many of them are not suitable for undergoing radical surgery or receiving concurrent chemotherapy along with radiation. Hence, treatment with radiotherapy alone is the only option left for such patients.

Gefitinib, an EGFR, TKI, and other tyrosine kinase inhibitors, has shown their efficacy in the treatment of esophageal carcinoma with relatively less toxicity in many previous Phase I and Phase II studies [6,7]. Hence, we combined Gefitinib with radiation therapy in this study for the treatment of elderly patients with inoperable disease those who are unfit for cisplatin and 5-FU-based chemoradiation and treated with only radiotherapy.

In this study, we compared definitive radiation therapy against radiation with concurrent Gefitinib in elderly carcinoma esophagus patients in terms of locoregional control and treatment related toxicity.

METHODS

It was a double arm, single institutional prospective, and comparative study in patients with Histologically confirmed, inoperable, and Stage I-IVA squamous cell carcinoma of esophagus aged between 50 and 70 years having adequate hepatic, renal, hematological parameters, and an ECOG score of 0–2. Patients with recurrent carcinoma, previous history of any other malignancy, or chemotherapy or radiotherapy were excluded from the study. The study was conducted between January 2019 and January 2020.

Study technique

Patients were selected using above mentioned inclusion and exclusion criteria and randomized into two groups.

Control arm (radiation only)

Participants in this arm received external beam radiotherapy (EBRT) with a dose of 36 Gy/18 fractions once daily, 5 days a week for 3.5 weeks (first phase) followed by boost radiation of 14.4 Gy/8 fractions/1.5 weeks sparing the spinal cord (second phase).

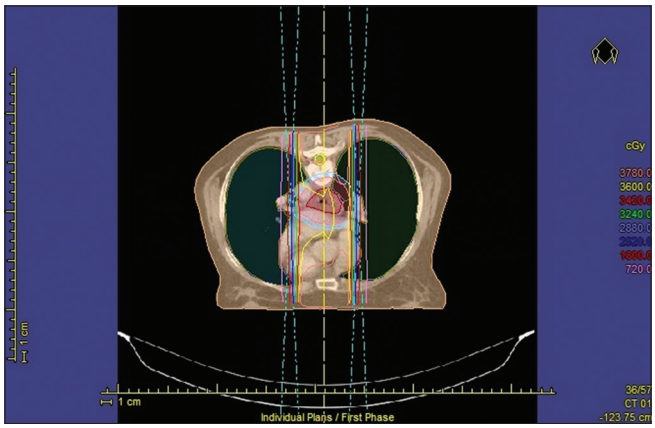
Study arm (radiation with gefitinib)
Patients in this group received radiation with a dose of 36 Gy/18 fractions once daily, 5 days a week for 3.5 weeks (first phase), along with Tab Gefitinib 250 mg orally daily during radiotherapy. This phase will be followed by boost RT 14.4 Gy/8 fractions/1.5 weeks (second phase), sparing the spinal cord along with Tab Gefitinib 250 mg orally daily.

Radiotherapy technique
First Phase: 36 Gy in 18 fractions, 2Gy/fraction, and 5 days in a week from Monday to Friday for 3.5 weeks through AP and PA fields.

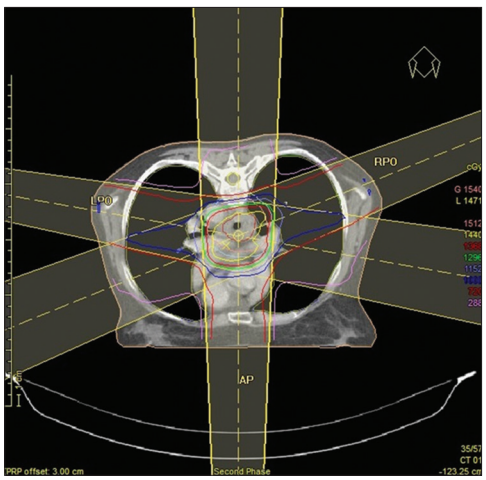
Seond Phase: 14.4 Gy in 8 fraction, 1.8 Gy/fraction, and 5 days in a week from Monday to Friday for 1.5 weeks through three fields technique one anterior and two posterior oblique fields sparing the spinal cord.

In prone, head first position of the patient, after proper immobilization, proper isocenter markings, and placing of radio opaque balls (ROB) over the patient's body surface, planning CT with contrast was done with 5 mm slice cut and was exported to the treatment planning system (TPS).

GTV included the gross tumor and all visible lymph nodes.
CTV=GTV+2 cm margin laterally and 5 cm margin along the esophagus craniocaudally.
PTV=CTV+1 cm margin.
OARs such as heart, lung, and spinal cord were contoured accordingly.
Necessary optimization was done with a view to deliver maximum dose to the tumor and minimum dose to surrounding OARs.



AP and PA field in the first phase of treatment



Three field technique in the second phase of treatment; AP=Anteroposterior beam, RPO=Right posterior oblique, and LPO=Left posterior oblique.

Follow-up
Response assessment was done using RECIST 1.1 after completion of treatment. All patients were followed up weekly for the treatment-related acute toxicity during the entire course of treatment and then at every month for 6 months for each patient after completion of treatment. Follow-up included proper history of complaints, clinical examination, CBC, LFT, KFT parameters, and other necessary investigations as indicated including imaging. Treatment-related toxicities were assessed as per toxicity assessment tools-CTCAE (common terminology criteria for adverse events scale version 5.0) and with RTOG scoring. Patients developing Grade III or above toxicity were given treatment interruption and were managed as required. Patients with progressive disease were managed with chemotherapy as per requirement.

Approval for study was taken from the Institutional Ethics Committee.

There is no source of financial grant or other funding.

Statistical analysis
Data were analyzed and compared according to appropriate statistical tests using SPSS version 20 software and Microsoft Word-Excel. Data were summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. Any $p<0.05$ will be considered statistically significant.

RESULTS

Both the arms were comparable in terms of age of presentation, gender distribution, and performance status at the time of presentation (Table 1).

Response assessment
Overall response rate (complete response+partial response) was 80% in study arm compared to 70% of control arm. Incidence of progressive disease was also lower in the study arm (3.3% vs. 10%). However, these differences were not statistically significant (p=0.221) (Table 2).

Toxicity assessment
At the end of the treatment, higher grade of dysphagia (Grade 2 or more) was seen in 20% of the study arm compared to 40% of the control arm. However, the difference was not statistically significant (p=0.080). During follow-up, 3 months after completion of treatment, higher grade (Grade 2 or more) dysphagia increased in the study arm reaching up to 66.6% whereas 60% of control arm patients experienced the same; differences were not significant (p=0.632) (Figs. 1 and 2).

Mucosal toxicity was comparable between the two arms. Grade 3 toxicity was only numerically higher in the study arm, but not statistically significant (10% vs. 6.67%, p=0.056) (Table 3).

Higher grade (Grade 2 or above) of diarrhea was numerically higher in Gefitinib containing study arm than the radiation only control arm (20% vs. 15%, p=0.843) (Table 4).

Both moderate (73.3% vs. 63.33%) and severe grade (16.6% vs. 3.33%) of anemia were higher in Gefitinib containing study arm, though the difference was not statistically significant (p=0.921) (Table 5).

Grade 2 leukopenia was more in Gefitinib containing arm than the radiation only arm, although the difference was not statistically significant (20% vs. 10%, p=0.472).

About 13.33% of control arm patient suffered moderate weight loss (5%–10% of total body weight) in comparison to 6.67% of the study arm. However, the difference was not statistically significant (p-value-0.671).

Table 1: Distribution of baseline characteristics

Characteristics	Arm of the study		Total	p value
	Control arm (n=30)	Study arm (n=30)		
Age of patient (in years)				
50–60	14 (46.6%)	11 (36.6%)	60	0.382
61–70	07 (23.3%)	12 (40%)		
71–80	09 (30%)	07 (23.3%)		
Total	30 (100%)	30 (100%)		
Gender of patient				
Male	25 (83.3%)	21 (70%)	60	0.222
Female	05 (16.6%)	09 (30%)		
Total	30 (100%)	30 (100%)		
Performance status (ECOG score)				
1	14 (46.6%)	19 (63.3%)	60	0.194
2	16 (53.3%)	11 (36.6%)		
Total	30 (100%)	30 (100%)		

Table 2: Comparison of treatment response between the two arms

Arm of study	Treatment response				Total	p value
	Complete response	Partial response	Stable disease	Progressive disease		
Study	13 (43.33%)	11 (36.67%)	05 (16.67%)	01 (3.33%)	30 (100%)	0.221
Control	07 (23.33%)	14 (46.66%)	06 (20%)	03 (10%)	30 (100%)	
Total	20	25	11	04	60	

Table 3: Comparison of mucosal toxicity between the two arms

Arm of study	Acute mucosal toxicity				Total	p-value
	Grade 0	Grade 1	Grade 2	Grade 3		
Study	06	13	08	03	30	0.056
Control	00	18	10	02	30	
Total (n)	06	31	18	05	60	

Table 4: Comparison of diarrhea between the two arms

Arm of study	Diarrhoea				Total	p value
	Grade 0	Grade 1	Grade 2	Grade 3		
Study	20	04	05	01	30	0.843
Control	23	02	04	01	30	
Total (N)	43	06	09	02	60	

Table 5: Comparison of anemia between the two arms

Arm of study	Anemia during treatment			Total	p value
	Mild	Moderate	Severe		
Study	03	22	05	30	0.921
Control	10	19	01	30	
Total (n)	13	41	06	60	

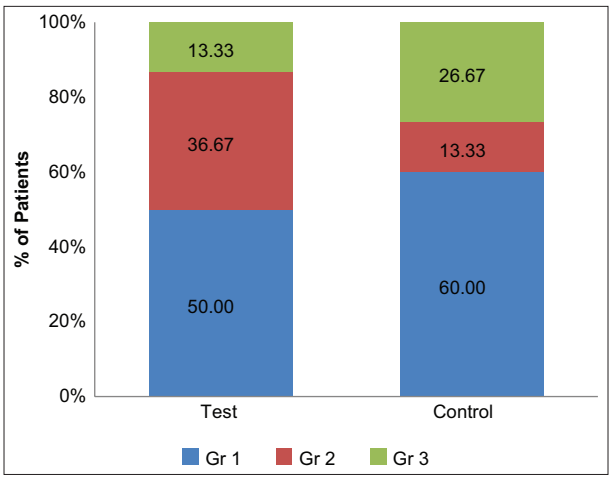


Fig. 1: Dysphagia after the treatment completion

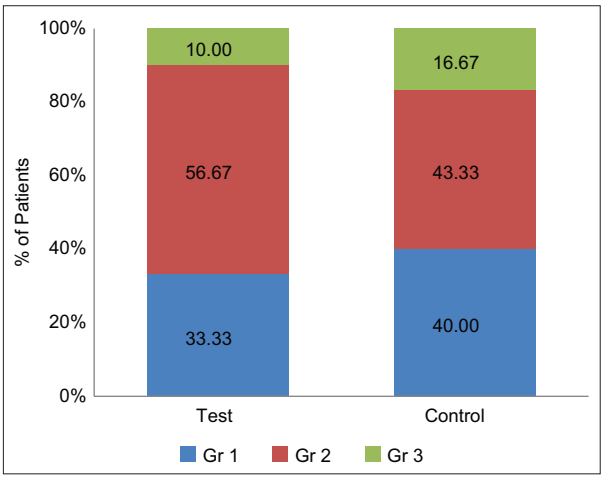


Fig. 2: Dysphagia during follow-up (3 months after the treatment)

DISCUSSION

Patients of carcinoma esophagus are generally nutritionally deprived leading to poor performance status to endure any kind of intense cytotoxic therapies used generally. Geriatric patients are more prone toward treatment-related toxicities precluding concurrent chemotherapy as a treatment option [8]. Thus, there is a strong need for new, effective, and well-tolerable treatment approaches. Epidermal growth factor receptors (EGFR) which are abundantly expressed by cells of carcinoma esophagus promote a multitude of important signaling pathways associated with cancer development

and progression [9]. Hence, if anti-EGFR agents like Gefitinib can be used along with radiation for elderly patients due to its tolerability and efficacy [6,7].

For this study, elderly people over 50 years having esophageal squamous cell carcinoma (histopathologically proved) were selected in whom operative treatment is not possible either due to location of the tumor, that is, cervical esophagus or the patient is not fit to undergo the operative procedure and also not fit to take chemotherapy with 5 FU and platinum-based regime as well. Hence, the only suitable option left for those patients was treatment with definitive radiotherapy and here we compared radiation alone against radiation with Gefitinib in terms of treatment response and treatment-related toxicities.

In this study, participants of both the arms were comparable in terms of baseline characteristics such as – age at presentation, gender distribution, and performance status at the initiation of the study (Table 1).

Six months after the treatment completion, the response to treatment in both the arms was assessed by comparing the pre- and post-treatment computed tomography scan of thorax and Upper G I Endoscopy. It was found that 43.33% of Gefitinib containing study arm patients showed complete response in comparison with 23.33% of radiation only control arm. On the other hand, 46.66% patients showed partial response in control arm against 36.66% of the study arm. However, these differences were not statistically significant (p=0.221) (Table 2).

In a similar study done by Yaping Xu *et al.* with 20 patients of esophageal carcinoma showed that 5 (25%) experienced complete response (CR), 13 (65%) experienced partial response (PR), and 2(10) had stable disease [10]. The overall response rate (CR+PR) was 90%, the median overall survival (OS) was 14.0 months (95% confidence interval [CI]: 10.0–17.9 months), and the median progression-free survival was 7.0 months (95% CI: 0–17.2 months). Treatment-related grade 3/4 toxicity occurred in five patients. No case of grade 3/4 impaired liver function or hematological toxicity was observed. Concurrent radiotherapy with Gefitinib is effective and tolerable in elderly patients.

At the end of the treatment, higher grade of dysphagia (Grade 2 or more) was seen in 20% of the study arm compared to 40% of the control arm. However, the difference was not statistically significant (p=0.080). During follow-up, 3 months after completion of treatment, higher grade (Grade 2 or more) dysphagia increased in the study arm reaching up to 66.6%; differences were not significant (p=0.632) (Figs. 1 and 2).

Acute mucosal toxicity was comparable between the two arms with Grade 2 and above toxicity was slightly less in Gefitinib containing study arm but not statistically significant (36% vs. 40%, p=0.056) (Table 3).

Higher grade (Grade 2 or above) of diarrhea was numerically higher in Gefitinib containing study arm but not statistically significant (20% vs. 15%, p=0.843) (Table 4). Gefitinib-induced damage to intestinal epithelium is the main cause of increased incidences of higher-grade diarrhea in the study arm.

Gefitinib containing arm showed moderate-to-severe grade of anemia in 90% of cases whereas only 66% patients of control arm patients experienced the same. However, the difference was not significant (p=0.921) (Table 5). Although Grade 2 leukopenia was also more in Gefitinib containing arm than the radiation only arm, it was not statistically significant (20% vs. 10%, p=0.472). Higher incidences of myellotoxicity in the study arm were due to the toxicity of Gefitinib itself as hematological toxicity is one of the prominent toxicities of EGFR inhibitors.

However, there are certain limitations in this study. Primarily, the sample size was small. Second, it was a single institutional study; hence, results derived cannot be extrapolated on entire population. Entire study duration was almost 12 months including patient accrual, intervention and assessment. Hence, the late toxicity profile, disease free survival/ progression free survival, overall survival, and quality of life after the treatment cannot be assessed appropriately. Moreover, although daily oral 250 mg Gefitinib was administered for 2 months concurrently to the radiotherapy, the optimal duration was not determined, and further studies are needed to identify the optimal targeting treatment duration for esophageal cancer.

CONCLUSION

It can be said although statistically not significant, the overall response rate (complete and partial response) was better in patients who received radiotherapy with concomitant oral Gefitinib than radiation alone. Toxicity profile in terms of dysphagia (just after treatment completion and during follow-up), mucosal toxicity, and myelosupprerssion was also comparable in both the arms. However, to come to a conclusion regarding the use of Gefitinib with radiation as an alternative to radiation alone in elderly patients with carcinoma esophagus, a larger study with a greater number of patients and longer follow-up is required.

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AUTHORS' CONTRIBUTION

Dr. Subhadip Bandyopadhyay and Dr. Linkon Biswas designed and conducted the research and finalize the manuscript; Dr. Sumitava De and Dr. Biswarup Banerjee did the literature review, statistical analysis, interpretation of data, and reviewing and editing of the manuscript. Dr. (Professor) Srikrishna Mandal did the final editing of manuscript, interpretation of data, and gave intellectual contribution.

CONFLICTS OF INTEREST

None of the authors had any conflict of interest to declare.

AUTHORS' FUNDING

None.

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