Standard-dose versus high-dose radiotherapy with concurrent chemotherapy in esophageal cancer: A prospective randomized study

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Abstract

Objective: The objective of this study is comparision of local and distant control rates with high-dose versus standard-dose radiotherapy along with concurrent chemotherapy in esophageal cancer – a prospective randomized study. **Materials and Methods:** Histologically proven Stage I–III patients with carcinoma esophagus were randomized into two groups. One group has been treated with standard-dose radiotherapy, i.e., a total dose of 50.4 Gy (1.8 Gy/day, 28#, 5 days/week). The other group (study arm) has received high-dose radiotherapy, i.e. a total dose of 64.8 Gy (1.8 Gy/day, 36#, 5 days/week). Both groups have received 2 cycles of 3 weekly concurrent chemotherapy (cisplatin 75 mg/m^2 on day 1 and 5-fluorouracil 750 mg/m^2 continuous intravenous infusion over 24 h on day 1–4). Follow-up response evaluation was done by both endoscopy and computed tomography scan after 6–8 weeks and after 2 months thereafter. **Results:** Out of a total of 28 patients, 68% showed a complete response, 14% showed partial response, and 18% patients developed progressive disease at first and subsequent follow up (median follow-up of 21 months). Among the complete response patients, rates were higher in high-dose group compared to standard-dose radiotherapy group (71% vs. 64%, P = 0.38). Treatment-related toxicities were acceptable in both groups. **Conclusion:** High-dose radiotherapy with concurrent chemotherapy seems to be more effective with acceptable toxicity in our study. However, further follow-up and large sample size may be required to validate the current study conclusion.

Key words: Concurrent chemotherapy, esophageal cancer, high dose, radiotherapy, standard dose

Introduction

Esophageal cancer is one of the most lethal malignancies. It accounts for approximately 6% of all gastrointestinal malignancies. It is the eighth most common cancer worldwide, with an estimated 456,000 new cases in 2012 (3.2% of the total) and the sixth most common cause of death from cancer with an estimated 400,000 deaths (4.9% of the total).[1] Around 80% of the cases worldwide occur in less developed regions. In 2012, the total number of cancer cases registered at Dr B. Borooah Cancer Institute, Guwahati were 7090, out of which esophageal cancer cases were 967 (13.6%).[2] Esophageal cancer has a poor prognosis due to high rates of local recurrence and distant metastasis.[3,4] About one-half of patients present with locally advanced stage at the time of diagnosis[5] and have a 5-year survival rate of <30% after surgical resection or multimodality therapy. In the past decade, many single institutions and cooperative groups have investigated the use of concurrent chemoradiotherapy (CCRT) as a definitive treatment or as a preoperative treatment for patients with localized esophageal cancer. Definitive CCRT or preoperative CCRT with surgery results in better survival than single modality treatments such as surgery or radiotherapy.[6-11]

A 2003 Cochrane review found that combined chemoradiotherapy led to an absolute increase in mortality difference of 7% at 2 years compared with radiation alone. Consequently, the National Comprehensive Cancer Network (NCCN) esophageal cancer guidelines recommend preoperative CCRT or definitive CCRT for patients with Stage II or III esophageal cancer. However, in the setting of definitive CCRT, the dose of radiotherapy requires further investigation. In the Radiation Therapy Oncology Group (RTOG) trial 94-05 study, which compared 50.4 Gy radiotherapy with 64.8 Gy radiotherapy in a CCRT setting, there was no significant difference in overall survival (OS) and locoregional control (LRC) between the high and standard dose treatment arms.[12] However, Zhang *et al*.[13] reported that radiation dose >51 Gy improved locoregional control, disease-free survival, and survival in patients treated with 5-fluorouracil (5-FU)-based chemotherapy. Yang-Gun Suh *et al*.[14] also reported that high dose radiotherapy of 60 Gy or higher with concurrent chemotherapy improves locoregional control and progression-free survival and may also improve the survival of Stages II–III esophageal cancer patients. Furthermore, in multivariate analysis, high-dose radiotherapy was a significant prognostic factor for improved LRC, PFS, and OS. Although 50.4 Gy is the standard dose as per evidence, many trials now support the use of high-dose radiotherapy >60 Gy which may have a better outcomes but needs to be validated in large groups with adequate support and evaluation.

In this study, we are further investigating the clinical response rates (local and distant control) in the standard-dose versus high-dose radiotherapy with concurrent chemotherapy in esophageal cancer at our institute, i.e., Dr. B. Borooah Cancer Institute, Guwahati, India.

Materials and Methods

Patients

A prospective, randomized study was conducted with patients of histologically proven esophageal cancer of Stage I–III. An informed consent was taken from those who fulfilled the inclusion criteria [Table 1]. Patients were randomized into two arms. One arm received standard-dose radiotherapy with concurrent chemotherapy, and the study arm received high-dose radiotherapy with concurrent chemotherapy.

Radiotherapy

Radiotherapy was delivered with linear acclerator using 6 MV photons. A conventional fractionation schedule

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(5 days/week, 1.8 Gy/fraction daily), and cone-down technique was used in all patients. Initially, in Phase I, two-field technique using AP-PA portals were used to encompass the primary tumor with a craniocaudal margin of at least 5 cm and circumferential margin of 2 cm to the tumor. A dose of 39.6 Gy (22 fractions) was used in Phase I before cone down. In phase II, to restrict the spinal cord dose to below 45 Gy, appropriate technique (use of 3DCRT permitted in phase II) and fields encompassing the primary tumor with a 2–3 cm craniocaudal margin was used to a total dose of 50.4 Gy (28#) in standard-dose group and to a total dose of 64.8 Gy (36#) in high-dose group. The field borders were modified as per clinical requirement.

Chemotherapy

All patients received two cycles of cisplatin and fluorouracil regimen as a concurrent chemotherapy. Cisplatin 75 mg/m^2 intravenous (IV) on day 1 and 5-FU 750 mg/m^2 IV continuous infusion over 24 h daily on day 1–4. The cycle was repeated after 21 days.

Follow-up

During the course of treatment, all patients were examined weekly to monitor treatment-related toxicities and general condition. After completion of treatment, follow-up was done at 2 months interval at 2, 4, and 6 months and thereafter in the outpatient department. Follow-up included complete clinical examination and endoscopic examination. Computed tomography scan of the chest and upper abdomen was performed to determine the local control of the disease. Acute toxicity was assessed as per CTCAE criteria (v4.03),[15] and treatment response was evaluated according to response evaluation criteria in solid tumors (RECIST; version 1.1).[16]

Patients suspected of having metastatic disease on follow-up were subjected to an appropriate investigation and were managed accordingly.

Statistical analysis

Statistical analysis of data was done on GraphPad prism software version 7.01 (https://www.graphpad.com/scientific-software/prism) for windows and *P* calculated using Fisher's exact test. $P < 0.05$ was considered as statistically significant.

Results

Out of the 28 patients included in this study, 14 patients received standard dose radiation to a dose of 50.4 Gy (standard-dose group) and 14 patients received high-dose radiation, i.e., 64.8 Gy (high-dose group). Pretreatment patient and tumor characteristics of the two groups are listed in Table 2.

Patients were equally distributed in two groups with respect to age, histologic subtype, tumor location, primary tumor size, or stage of the disease (*P* value not significant). For surviving patients, the median follow-up time was 21.5 months (range, 18–25.5) and 21 months (range, 19–26) in the standard-dose group and the high-dose group, respectively. Six patients died after 1st checkup due to disease progression. Three patients died due to lung metastasis (distant failure) in the high-dose group while two patients died due to local failure and one patient died due to hepatic metastasis (distant failure) in the standard-dose group.

At first checkup, the complete response, partial response, and progressive disease rates in the standard-dose group were 64%, 22%, and 14% respectively, while these rates were 71%, 7%, and 22%, respectively, in the high-dose group. The complete response rate was greater in the high-dose group than the standard-dose group; however, this result was not statistically significant ($P = 0.38$). Treatment-related toxicities were assessed. None of the patients developed > Grade 2 toxicity. Patients who developed Grade 2 anemia required blood transfusion [Tables 3, 4, and Figure 1].

Further, follow-up data (median follow-up of 21 months), shows that OS is same i.e. 78.6% in both the group ($P = 0.975$) [Figure 2] and disease-free survival is 64.3% in standard-dose and 57.1% in high-dose group ($P = 0.835$) [Figure 3].

Table 1: Inclusion - Exclusion criteria

Inclusion criteria	Exclusion criteria
Histologically proven esophageal cancer - squamous cell carcinoma or adenocarcinoma	Patient's refusal
AJCC 2010 Stage I–III	AJCC 2010 Stage IV
Age <70	Carcinoma involving GE junction
KPS >70% or ECOG <2	KPS <70% or ECOG >2
CBC – normal	Prior or concurrent other malignancy
KFT – normal	Prior history of irradiation or chemotherapy
	Presence of tracheoesophageal fistula

ECOG=Eastern Cooperative Oncology Group, KPS=Karnofsky performance score, CBC=Complete blood count, KFT=Kidney function test, GE=Gastroesophageal, AJCC=American Joint Committee on Cancer

Table 2: Patient characteristics

Characteristics	Standard dose (*n*=14), *n* (%)	High dose (*n*=14), *n* (%)	*P*
Age (years)			
<45	2 (14)	3 (21)	1.00
>45	12 (86)	11 (79)	
Sex			
Male	6 (43)	12 (86)	0.04
Female	8 (57)	2 (14)	
Pathology			
MDSCC	12 (86)	9 (64)	0.26
WDSCC	2 (14)	3 (22)	
PDSCC	0	2 (14)	
Tumor location			
Mid-thoracic	12 (86)	12 (86)	1.00
Upper-thoracic	2 (14)	2 (14)	
Primary tumor size			
≤5 cm	6 (43)	2 (14)	0.20
>5 cm	8 (57)	12 (86)	
Stage			
IIB	6 (43)	6 (43)	0.86
IIIA	5 (36)	6 (43)	
IIIB	3 (21)	2 (14)	

MDSCC=Moderately differentiated squamous cell carcinoma, WDSCC=Well-differentiated squamous cell carcinoma, PDSCC=Poorly differentiated squamous cell carcinoma

Discussion

In the present study, we compared clinical responses between standard-dose radiotherapy (50.4 Gy) and high-dose radiotherapy (64.8 Gy) in the setting of concurrent chemoradiation for Stage I–III esophageal cancer. We demonstrated that high-dose radiotherapy has better clinical response than standard-dose radiotherapy without a significant

Table 3: Toxicities developed during or after the course of therapy

Toxicities	Standard-dose group (*n*=14), *n* (%)	High-dose group (*n*=14), *n* (%)	*P*
Skin reaction			
Grade-1	14 (100)	14 (100)	
Anemia			
Grade-1	3 (21)	2 (14)	1.0
Grade-2	4 (29)	4 (29)	
Neutropenia			
Grade-1	6 (43)	8 (57)	0.46
Grade-2	1 (7)	0	
Diarrhea			
Grade-1	0	0	1.0
Grade-2	0	1 (7)	
Vomiting			
Grade-1	8 (57)	2 (14)	0.27
Grade-2	0	1 (7)	
Odynophagia			
Grade-1	9 (64)	7 (50)	1.0
Grade-2	0	0	

Table 4: Clinical responses at first checkup

Responses	Standard-dose group (*n*=14), *n* (%)	High-dose group (*n*=14), *n* (%)	*P*
Complete response	9 (64)	10 (71)	0.38
Partial response	3 (22)	1 (7)	
Progressive disease			
Local failure	1 (7)	0	
Distant failure	1 (7)	3 (22)	

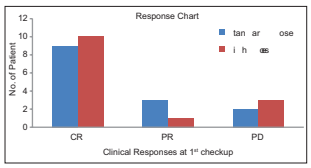

Figure 1: Clinical response at first checkup

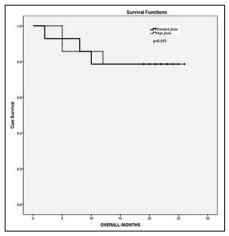

Figure 2: Kaplan–Meier plot of overall survival

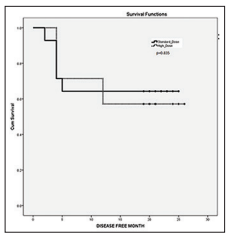

Figure 3: Kaplan–Meier plot of disease-free survival

increase in treatment-related mortalities or toxicities. However, the data is not statistically significant.

Although, NCCN esophageal cancer guidelines[17] recommend radiation dose of 50 or 50.4 Gy for definitive concurrent chemoradiation, radiation dose escalation for treating esophageal cancer should be studied further. The NCCN esophageal cancer radiation dose recommendations are based on the results of the RTOG 94-05 trial. RTOG 94-05 trial compared treatment response to concurrent chemoradiation using 64.8 Gy versus 50.4 Gy radiotherapy in patients with Stages I–III squamous cell carcinoma or adenocarcinoma.[12] This trial failed to show that high-dose radiotherapy with concurrent chemotherapy had any advantage over standard-dose radiotherapy with concurrent chemotherapy. Treatment-related deaths were more frequent in the high-dose group than the standard-dose group, and patients in the high-dose group tended to have a worse prognosis. However, 7 of the 11 deaths in the high-dose arm occurred in patients who received 50.4 Gy or less; therefore, high-dose radiation was not responsible for the increased mortality in this group. The potential benefits of high-dose radiotherapy for esophageal cancer should, therefore, not be ignored based only on this study. In our study, we have found higher rate of complete response in high-dose group compared to standard-dose group with almost similar toxicity in both the treatment groups without much effect (no treatment interruptions) on the treatment protocols.

A recent randomized clinical trial comparing surgery alone with chemoradiation followed by surgery in patients with T1N1 or T2-3N0-1 esophageal cancer showed that preoperative chemoradiotherapy improved survival among patients with potentially curable esophageal or esophagogastric junction tumor.[9] In this study, chemoradiation followed by surgery showed excellent outcomes with median OS of 49.4 months. However, two randomized clinical trials and a recent meta-analysis, which compared chemoradiation alone with chemoradiation followed by surgery failed to show benefit of surgery on OS, while the addition of surgery to chemoradiation improved local control.[18-20] However, this improvement in local control rate may not be entirely due to radiotherapy. However, surgery after RT improved local control rates in these patients. Local progression-free survival was better in the surgery group (2-year progression-free survival, 64.3%; 95% confidence interval [CI], 52.1% to 76.5%) than in the chemoradiotherapy group (2-year progression-free survival, 40.7%; 95% CI, 28.9% to 52.5%).[18] and 2-year-local control rate was 66.4% in patients with chemoradiation followed by surgery compared with 57% in patients with chemoradiation alone, and stents were also less required in the surgery arm (5% vs. 32%).[19]

Although the survival rate has been slowly improving likely because of multimodality strategies and improved supportive care, the survival rate remains modest at 20% at 5 years. Considering the high local failure rates after 50 Gy[13] for patients that are not going to be candidates for surgery after peroperative or radical RT, or surgery can not be possible due to comorbitities or patient's wish, we think that high-dose radiotherpy (plus concurrent chemotherapy) should be the optimal treatment in these groups of patients. Surgery might be preserved as a salvage option if there is a residual disease after high dose RT in selected patients. Therefore, many institutions now have adopted high-dose (60 Gy or higher) radiotherapy with concurrent chemotherapy for the treatment of esophageal cancer. In our institution, we also practice high-dose (63 Gy)

radiotherapy with concurrent chemotherapy for the patients in whom surgery is not considered as an option. Our study also strengthed the use of high-dose radiotherpay with concurrent chemotherapy in our patients with acceptable toxicity compared to the standard dose RT. However, due to lack of definite level 1 data in favor of high-dose, it is difficult to conclude that high-dose radiotherapy is really beneficial in terms of local control rate or OS without causing much toxicity. The present study was taken to answer this unresolved issue. In this study, we found that high-dose radiotherapy is more effective without producing significant toxicities. Although the result was not statistically significant, it showed trends toward improved control rate. The main limitation in our study was the small sample size and short follow-up period.

Conclusion

The high-dose radiotherapy with concurrent chemotherapy is an effective treatment for Stages I–III esophageal cancer with acceptable toxicity. However, large sample size and further follow-up will be required to get stronger evidence.

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Conflicts of interest

There are no conflicts of interest.

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