

Efficacy of chemo-radiotherapy versus radiotherapy alone in the treatment of esophageal carcinoma

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Background: The treatment of esophageal carcinoma may demand multiple approaches including combination of radiotherapy and chemotherapy, particularly cases which are considered unresectable, such as upper third esophageal cancers, locally advanced middle and lower third cancers. **Methods:** This was a prospective, randomized, open-label, single-center study conducted between December 2014 and July 2016. Patients of either sex aged more than 18 years with the confirmed diagnosis of previously untreated advanced esophageal carcinoma were included in the study. Eligible patients were randomized to receive one of the treatments (chemo-radiotherapy [cisplatin] or radiotherapy alone). Response criteria included dysphasia free survival (DySF), disease free survival (DFS), and overall survival (OS). Tolerability was also assessed. **Results:** A total of 31 patients (chemo-radiotherapy, n=13; radiotherapy alone, n=18) were enrolled in this study. At one year, the probability of remaining dysphagia free was 40% and 20%, respectively for chemo-radiotherapy and radiotherapy alone groups; and the probability of OS was 64% versus 21%, respectively. The median DFS was 12 months and 5 months for chemo-radiotherapy and radiotherapy alone group, respectively. There were no significant differences in both the groups in EBRT, total treatment duration and duration of EBRT. No patient reported thrombocytopenia or nephrotoxicity. **Conclusions:** Concurrent chemo-radiotherapy with cisplatin can improve dysphasia and OS in patients with esophageal carcinoma.

Keywords: Chemotherapy, cisplatin, Esophageal neoplasm, Radiotherapy, Esophageal carcinoma

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Introduction

Carcinoma of the esophagus is the seventh most common cancer worldwide, the sixth most common cause of cancer-related deaths worldwide [1], and fourth most common cause of cancer-related deaths in India [2]. In India, every year more than 47,000 new cases are reported of which around 90% of patients die [2].

The two major sub-types of esophageal carcinoma are esophageal squamous cell carcinoma (SCC) and adenocarcinoma. The history and incidence of these two types differ considerably. The predominant factors responsible for esophageal carcinoma are age, gender, race, environmental toxins, nutritional deficiency, alcohol consumption etc [3-6]. SCC affects the stratified squamous epithelial lining of the organ whereas adenocarcinoma affects columnar glandular cells that replace the squamous epithelium. Esophageal carcinoma is the most frequently occurring type having features like late presentation, late diagnosis, rapid progression, and low survival rates. An overall survival at 5 years ranged between 0% to 12% for patients treated with radiotherapy and 1% to 7% for patients treated with surgery [7-9].

Esophageal cancer is staged using the TNM system that implies the extent and presence of primary tumor, spread to lymph nodes and organs beyond lymph nodes. Common imaging modalities used in staging include computed tomography (CT), endoscopic ultrasound and positron emission tomography scans [10]. Studies suggest esophageal tumor length and diameter as important prognostic factors for nonsurgical T staging in SCC patients undergoing definitive chemo-radiotherapy [11]. The treatment of esophageal carcinoma may demand multiple approaches including combination of radiotherapy and chemotherapy, particularly cases which are considered unresectable, such as upper third esophageal cancers, locally advanced middle and lower third cancers [2].

Diagnosis reveals majority of patients with advanced stage of SCC, hence surgery is not feasible. So, a non-surgical treatment modality like radiotherapy combined with chemotherapy is preferred but has poor response and survival rates [12, 13]. Few recent meta-analyses have demonstrated that the use of chemo-radiotherapy has significant survival benefits in patients with esophageal carcinoma.

In a meta-analysis by Zhu et al, nine studies which included 1,135 cases (612 received concurrent chemoradiotherapy and 523 received radiotherapy alone) showed that patients who received concurrent chemoradiotherapy, demonstrated significantly higher overall response rate and reduced the risk of persistence and recurrence of disease [14-18].

Few Indian studies are reported in literature revealing the treatment outcomes of chemo-radiotherapy. There is a need to assess an efficient and safe combination treatment modality to treat esophageal cancer.

The present paper reports results of a prospective study that evaluated the efficacy of chemo-radiotherapy versus radiotherapy alone for the treatment of patients with advanced esophageal SCC.

Methods

Study population- Patients of either sex aged more than 18 years with the confirmed diagnosis of previously untreated advanced esophageal carcinoma were included in the study.

Study design- This was a prospective, randomized, open-label, single-center study conducted between December 2014 and July 2016 at S.N. Medical College and Hospital, Agra, Uttar Pradesh, India. Eligible patients were randomized to receive one of the treatments (chemo-radiotherapy or radiotherapy alone).

Study group received external beam radiation therapy (EBRT) in two phases (phase 1-40 Gy/20#/5#/Week with two AP/PA fields; phase 2-20 Gy/10#/5#/Week with two posterior oblique fields) along with concurrent chemotherapy (cisplatin 35 mg/m² weekly for 5-6 cycles).

Control group received EBRT alone in two phases (phase 1 - 40 Gy/20#/5#/Week with two AP/PA fields; phase 2-20 Gy/10#/5#/Week with two posterior oblique fields).

Patients from study group received granisetron before and mannitol (20%) after chemotherapy. On the day of chemotherapy, radiotherapy was given within 30 minutes of cisplatin infusion.

Inclusion criteria- The study included patients with histopathologically proven squamous cell carcinoma, Karnofsky performance status (KPS) ≥ 50 , hemoglobin ≥ 10 gm%, total leucocyte count

$\geq 4000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, serum creatinine $\leq 1.6 \text{ mg/dL}$, and serum bilirubin $\leq 1 \text{ mg/dL}$.

Exclusion criteria: Patients with adenocarcinoma, second primary neoplasm, and with recurrent disease were excluded from the study.

Ethical considerations: The institutional review board reviewed and approved the study protocol.

The study was conducted in accordance with the approved protocol, International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, and the ethical principles laid down in the Declaration of Helsinki 2013.

Each study participant provided written informed consent before participation in the study.

Response assessment and follow-up: Response criteria included dysphasia free survival (DySF), disease free survival (DFS), and overall survival (OS).

A patient was considered locally disease free only if the barium swallow at one month after completion of radiotherapy or at subsequent follow-up was smooth.

A local recurrence was scored if there was a positive pathological diagnosis (on endoscopic biopsy), evidence to suggest recurrence on a barium swallow, or signs and symptoms of mediastinal disease.

Dysphasia scores were recorded pre-and post-treatment and at every follow-up. Patients was considered dysphasia free only if solids or soft solids could be consumed without appreciable difficulty during or after treatment.

The dysphasia free status was terminated when patient reported any sustained inability to swallow solids or soft solids in spite of repeated attempts at dilatation when feasible.

Adverse events were recorded throughout the study duration using WHO criteria for acute and sub-acute toxicities. During follow-up period, ulcers, strictures and trachea-esophageal fistula were recorded along with recurrences, distant metastasis and second primaries.

Statistical analysis: There was no formal sample size calculation employed for this study. Statistical significance was computed using Chi square test, t test and log rank test.

Patients alive or controlled at the time of reporting were considered censored observations. Patients lost to follow-up were handled according to the worst-case scenario and all endpoints were terminated when last seen.

All p values were set at 0.05 and confidence intervals were calculated at the 95% level.

The DyFS, DFS and OS were measured from day one of treatment and analyzed from intent-to-treat (ITT) population, which included all randomized patients who received at least one dose of study medication.

Results

A total of 31 patients (chemo-radiotherapy, $n=13$; radiotherapy alone, $n=18$) with advanced SCC of the esophagus were enrolled in this study. Overall, study groups were comparable, except for mean duration of dysphasia, which was longer in chemo-radiation group (7.7 months vs. 3.3 months).

Among patients who received chemo-radiotherapy and radiotherapy alone the mean age was 57.3 years and 58.3 years, respectively. Overall, males were more in both the groups. Number of patients with stage III disease were higher in radiotherapy alone group; however, the number of patients with complete circumference involvement were higher in chemo-radiotherapy group.

A total of 93% of patients from chemo-radiotherapy group and 83% from radiotherapy along group had improvement or at least remained unchanged in their dysphasia after completion of treatment.

At one year, the probability of remaining dysphagia free was 40% and 20%; and the median DyFS was 12% versus 5% (chemo-radiotherapy and radiotherapy alone groups, respectively; $p=0.05$). The duration of follow-up ranged from 2 to 17 months (median, 7.5 months) and a total of 11 patients died till the time of analysis.

At one year, the probability of OS was 64% versus 21% and the median was 13 months versus 6 months, for chemo-radiotherapy and radiotherapy alone groups, respectively. Among patients who received chemo-radiotherapy, 6 had local recurrence, 2 had distant metastasis, and 7 were living with the disease; however, among patients who received radiotherapy alone, 10 had local recurrence, 4 had distant metastasis, and 4 were living with the disease.

A univariate analysis that assessed factors influencing DyFS, DFS, and OS is summarized in Table 2, which showed generally comparable results between the groups.

There were no significant differences in both the groups in EBRT, total treatment duration and duration of EBRT (Table 3). Seven patients received 6-7 cycles of chemotherapy, of which, two patients discontinued the treatment, one died due to disease progression and four patients reported grade 2-3 neutropenia. No patient reported thrombocytopenia or nephrotoxicity.

Among patients from chemo-radiotherapy group, seven patients reported anemia (grade 1, n=3; grade 2, n=2 and grade 3, n=1); six patients reported leucopenia (grade 1, n=4; grade 2, n=2); and 12 patients reported emesis (grade 1, n=4; grade 2, n=3; grade 3, n=5).

Table-1: Demographics and baseline characteristics.

Parameters	Chemo-radiotherapy N=13	Radiotherapy alone N=18
Age (years), mean (SD)	57.3 (12.8)	58.3 (10.5)
Age group		
≤55 years	5 (38.5)	11 (61.1)
>55 years	8 (61.5)	7 (38.9)
Sex, n (%)		
Male	8 (61.5)	10 (55.6)
Female	5 (38.5)	8 (44.4)
KPS		

50	1 (7.7)	1 (5.6)
60	1 (7.7)	2 (11.1)
70	3 (23.1)	5 (27.8)
80	4 (30.8)	6 (33.3)
90	4 (30.8)	4 (22.2)
Weight loss (%), Mean (SD)	13.3 (10.5)	11.4 (7.9)
Hemoglobin (gm%)	12.1 (1.6)	12.6 (1.8)
Dysphasia duration (months), mean (SD)	7.7 (6.7)	3.3 (2.4)
Dysphasia grade		
To solids	3 (23.1)	6 (33.3)
To soft solids	6 (46.2)	7 (38.9)
To liquids	3 (23.1)	5 (27.8)
Absolute	1 (7.7)	0
Site		
Upper	3 (23.1)	6 (33.3)
Middle	7 (53.8)	8 (44.4)
Lower	3 (23.1)	4 (22.2)
Length (cm), mean (SD)	7.7 (1.9)	8.5 (3.4)
Circumference		
<Complete	7 (53.8)	5 (27.8)
Complete	6 (46.2)	13 (72.2)
Features		
Proliferative	8 (61.5)	10 (55.6)
Ulceroinfiltrative	5 (38.5)	7 (38.9)
Stricture	0	1 (5.6)
Stage		
I	0	1 (5.6)
II	10 (76.9)	11 (61.1)
III	3 (23.1)	6 (33.3)
IV	0	0
Data shown as n (%), unless otherwise specified. KPS, Karnofsky performance status; SD, standard deviation.		

Table-2: Summary of univariate analysis - factors influencing DyFS, DFS, and OS

Variables (N=31)	Median DyFS (months)	P value	Median DFS (months)	P value	Median OS (months)	P value
Age group		0.8		0.24		0.89
≤55 years (n=16)	7		0		7.5	
>55 years (n=15)	9.5		8.0		9.5	
Sex, n (%)		0.58		0.44		0.36
Male (n=18)	9.5		8.0		9.5	
Female (n=13)	5.0		3.5		5.0	
KPS		0.2		0.4		0.09
50-60 (n=5)	5		5		5	
70-80 (n=18)	4		4		6	
90-100 (n=8)	11		10		15	
Weight loss (%)		0.12		0.44		0.07
≤10% (n=18)	9.5		8		9.5	
>10% (n=13)	5		3.5		6.0	
Hemoglobin (gm%)		0.4		0.8		0.8
≤10 (n=5)	5		3.5		6	
>10 (n=26)	7.5		8		7.5	

Dysphasia duration (months)		0.82		0.96		0.6
≤3 months (n=18)	6.5		7.5		7.5	
>3 months (n=13)	10		10		7	
Dysphasia grade		0.32		0.3		0.3
To solids (n=9)	10		10		10	
To soft solids (n=13)	13		13		13	
To liquids (n=8)	6		0		7	
Absolute (n=1)	0		0		2	
Length (cm)		0.8		0.9		0.9
≤7 cm (n=18)	9.5		8.0		9.5	
>7 cm (n=13)	7.5		3.5		7.5	
Circumference		-		-		0.02
	NR		NR		17	
Complete (n=19)	6.5		3.5		7	
Features		0.3		0.09		0.02
Proliferative (n=18)	9.5		8		9.5	
Ulcer infiltrative (n=12)	10		10		10	
Strictive (n=1)	0		0		3	
Stage		-		-		-
I + II (n=22)	NR		NR		NR	
III (n=9)	9.5		8		9.5	
IV (n=0)	0		0		3.5	
Radiotherapy duration		0.77		0.90		0.43
≤54 days (n=21)	7.5		7.5		7.5	
>54 days (n=10)	5		8		7.5	
Protocol		0.4		0.6		0.8
Radiotherapy alone (n=18)	5		3.5		6	
Chemo-radiotherapy (n=13)	7.5		8		7.5	

DFS, disease free survival; DyFS, dysphasia free survival; KPS, Karnofsky performance status; NR, not reached; OS, overall survival.

Table-3: Summary of study treatment and duration

Parameters	Chemo-radiotherapy N=13	Radiotherapy alone N=18	P value
EBRT			0.5
≤60 GY	10	16	
>60 GY	3	2	
Total treatment duration (days), Mean (SD)	57.9 (9.2)	58.3 (9.7)	0.5
EBRT duration (days), Mean (SD)	56.8 (6.8)	55.3 (11.2)	0.5
Chemotherapy cycles			-
4-5	6 (46)	-	
6-7	7 (54)	-	

Data shown as n (%), unless otherwise specified. EBRT, external beam radiation therapy; SD, standard deviation.

Table-4: Summary of survival outcomes for patients who completed the treatment.

Survival probability	DyFS		DFS		OS	
	CTRT N=13	RT N=18	CTRT N=13	RT N=18	CTRT N=13	RT N=18
	3 months	88%	78%	75%	56%	87%
6 months	79%	59%	75%	49%	87%	63%
9 months	79%	40%	75%	35%	74%	42%
12 months	47%	20%	62%	24%	74%	21%
Mean (months)	10.9	7.8	10.3	6.7	11.8	8.8
95% CI	8.4-13.5	5-10.5	7.2-13.4	3.4-10	9.4-14.3	6.2-11.3
Median (months)	12	7	13	3.5	13	7
95% CI	9.7-14	4-10	0	0-11.5	6.4-19.6	5.2-8.8
Events	6/13	12/18	6/13	12/18	5/13	11/18
P value	0.07		0.07		0.06	
CI, confidence interval; CTRT, chemo-radiotherapy; DFS, disease free survival; DyFS, dysphasia free survival; OS, overall survival; RT, radiotherapy.						

Overall, the morbidity during follow-up period was comparable (p>0.05) between the groups

(Ulcerations [n=6 vs. n=4]; strictures [n=6 vs. n=10]; fistulae [n=2 vs. n=1]; and retrosternal pain/epigastric discomfort [n=5 vs. n=2]; dilatation/stenting procedure [n=3 vs. n=2]; respectively for chemo-radiotherapy and radiotherapy alone group).

Table 4 summarizes survival outcomes for patients who completed the treatment, which demonstrates no significant difference between the groups. However, the outcomes were slightly higher in chemo-radiotherapy group than radiotherapy alone group.

Discussion

Esophageal carcinoma can be managed by endoscopic mucosal resection, surgery, chemotherapy, radiotherapy, palliative therapy or a combination of these modalities depending on the stage and extent of the disease. Concurrent chemo-radiotherapy or radiotherapy alone are generally recommended in patients with upper or middle third carcinomas, inoperable cases, and in locally advanced cases. A meta-analysis by Ma et al, stated that concurrent chemo-radiotherapy significantly improves progression-free survival and OS in patients with esophageal cancer compared to surgery [19].

Another meta-analysis by Sun et al, investigated the safety and efficacy of treatment modalities used in concurrent radiotherapy. It revealed that concurrent therapy increased adverse reactions rather than patient survival [20]. In this prospective randomized study, we aimed to compare the efficacy of chemo-radiotherapy with radiotherapy alone in the treatment of locally advanced esophageal squamous cell carcinoma.

The present study was conducted in a teaching hospital in India, where patients are treated using concurrent chemo-radiotherapy or radiotherapy alone based on physicians' preference and disease condition. This study was a part of postgraduate thesis at a single center and hence was limited by the study period that could have resulted in smaller sample size.

Both the groups showed male preponderance and comparable mean age. Smith et al, conducted a study to determine the efficacy of chemo-radiation in comparison to radiation alone that showed male predominance and a longer median survival with chemoradiation (14.8 months) compared to patients with radiation therapy alone (9.2 months) [21].

Lyu et al, reported a similar study having male predominance, age between 18-75 years, majority of patients with upper thoracic tumor location and having stage 4 SCC. It was observed that concurrent chemotherapy was better and had manageable adverse events [22].

The EBRT included in this study were 40 Gy/20#/5#/week with two AP/PA fields for phase 1 and 20 Gy/10#/5#/week with two posterior oblique fields for phase 2. A previous study, which compared two radiotherapy protocols (50 Gy in 25 fractions over 5 weeks and 35 Gy in 15 fractions over 3 weeks) in inoperable SCC of the esophagus showed dysphagia relief in 75% and 49% of patients; and the probability of survival at 1, 2 and 5 years was 35.8% versus 34.8%, 13.9% versus 14.5% and 10% versus 0%, respectively [23].

Several studies have demonstrated the efficacy of chemo-radiotherapy in the treatment of esophageal carcinoma. Basis behind the addition of chemotherapy to radiotherapy is to potentiate the effects of radiotherapy to local disease and to decrease the incidence of distant metastasis. Hence, survival outcomes are expected to vary both as a function of selection of patients and the intensity of chemoradiation. In this study, one patient from chemo-radiotherapy and two patients from radiotherapy alone group developed distant metastasis.

A recent meta-analysis that included nine studies, demonstrated that concurrent use of chemo-radiotherapy significantly improved OS, reduced the risk of persistence and recurrence, but increased the occurrence of acute toxic effects, compared with radiotherapy alone [14]. A previous study from India that included 125 patients with unresectable SCC of the esophagus, showed 57.6%, 38.9% and 24.8% versus 32.3%, 22.8% and 13.7% OS at 1, 2, and 5 year, for chemo-radiotherapy and radiotherapy alone groups, respectively [24].

Uthors concluded that the addition of concurrent cisplatin to radiotherapy can improve survival with manageable acute and late morbidity [23]. Another study by Ruler et al, showed median OS of 13.1 months (95% CI 4.7-21.5 months) and a 2-year OS of 30% (95% CI 18%-42%)[24]. In this study the 1-year OS was slightly higher (74%) in chemo-radiotherapy group and was slightly lower (21%) for radiotherapy alone group.

Patients with esophageal carcinoma mainly present with dysphagia;

However, to our knowledge limited data is available regarding its relief. In a previous study, patients receiving fluorouracil and cisplatin showed improvement from baseline to week 15 (37.6 versus 29.9, $p=0.047$) [25].

Another retrospective study that included patients (N=66) with esophageal carcinoma and treated with chemoradiotherapy (carboplatin and paclitaxel) demonstrated that around 70% of patients had relief of dysphagia [26]. In the present study, dysphasia relief was achieved in 64% and 48% of patients from chemo-radiotherapy and radiotherapy alone group, respectively. The median DFS was 12 months and 5 months for chemo-radiotherapy and radiotherapy alone group, respectively.

Chemotherapy compliance was observed in 76% of patients. Overall, both treatments were generally tolerable with no new safety signals. Chemotherapy associated acute toxicities were also consistent with the previous study [24]. There were no reports of thrombocytopenia or nephrotoxicity. None of the patients from chemo-radiotherapy group reported grade 4 toxicity. The worst chemotherapy toxicities observed were grade 3 neutropenia and grade 3 emesis.

Previous studies suggest that preoperative chemo-radiotherapy for esophageal SCC significantly increased patients' risk of cardiopulmonary complication [27]. As per European Society for Medical Oncology (ESMO) recommendations, the patients unable or unwilling to undergo surgery, a combined chemo-radiotherapy is superior to radiation therapy alone and four courses of cisplatin/5-Fluorouracil combined with radiation doses of 50.4 Gy in fractions of 1.8 Gy are regarded as standard for definitive chemo-radiotherapy [28].

Intensity modified radiotherapy (IMRT) with concurrent chemotherapy has demonstrated reduction in radiation-induced toxicities, enhanced local control and improved long-term survival combining [29]. Literature has documented studies that have confirmed patient outcomes favoring chemoradiation compared to radiation alone [30].

This study with a small sample size showed concurrent chemo-radiotherapy with cisplatin can improve dysphasia and OS in patients with esophageal carcinoma; however, the difference was not statistically significant. Future research may be needed to corroborate these outcomes.

Conclusion

This prospective study implies better outcomes with concurrent chemo-radiotherapy in patients with esophageal cancer. The overall survival of patients is improved with tolerable side effects.

What the study adds to the existing knowledge?

Dose escalation with concurrent chemoradiation feasible with good compliance and response rates. This study with a small sample size showed concurrent chemoradiation with cisplatin can improve dysphasia and overall survival in patients.

Author's contribution

Dr. Pradeep Kumar K N and **Dr. Ashwini L.** contributed to the concept of the study, study design, data collection, interpretation, review of the literature, writing and review of the manuscript.

Dr. Pradeep Kumar K N. additionally contributed to the statistical analysis. All authors met ICMJE authorship criteria.

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