

Effect of Definitive Concurrent Chemo Radiotherapy in Patients with Inoperable Esophageal Squamous Cell Carcinoma - A Prospective Study

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ABSTRACT

Introduction: Cancer of the esophagus is a highly lethal malignancy, particularly in the developing world. Despite advances in both surgery and radiotherapy, the treatment of esophageal cancer remains a challenge for both surgeons and oncologists. The biggest problem affecting patient outcome is late presentation, as most symptomatic patients present with advanced disease. Definitive concurrent Chemoradiotherapy (dCRT) remains as an alternative for those patients unsuitable for surgery due to medical co-morbidities or extensive loco-regional disease.

Objectives: Aim of this study was to assess the outcome of patients treated with dCRT in our center and compare it with treatment outcome in major clinical trials in order to audit our treatment protocol.

Material and Methods: The study was done in Department of Radiotherapy and oncology, Government Medical College, Thrissur, Kerala. It was a single arm prospective study. Forty consecutive patients with inoperable esophageal squamous cell carcinoma who met the inclusion criteria were taken for dCRT with Cisplatin + 5 FluroUracil (5-FU) and 50.4Gy in 28 fractions.

Results: Median follow-up was for 15.8 months. Two patients lost to follow-up. The overall survival rate was 84.2% and mean survival period was 17.8 months. Progression free survival was 68.4% with mean progression-free survival duration of 16.4 months. Overall survival and progression-free survival were comparable to those of RTOG 85-01 trial and INT0123 trial.

Conclusion: Definitive Concurrent chemo-radiation with cisplatin and 5-FU was well tolerated, promising a reasonable therapeutic option for patients with inoperable locally advanced squamous cell carcinoma of the esophagus.

Keywords: Chemo-radiation; Carcinoma Esophagus; Overall Survival

indicative of the advanced stage of disease (local-regional or metastatic) at diagnosis in most patients.² Management of loco-regional esophageal cancer has undergone a major evolution over the past 25 years. Low cure rates after sole loco-regional therapy prompted inclusion of systemic chemotherapy in multimodality treatment approaches, to control distant micro-metastatic disease and enhance local radiation effects. The seminal Radiation Therapy Oncology Group (RTOG 85-01) trial demonstrated a survival benefit for the addition of cisplatin-based chemotherapy to radiation therapy (RT) in non-surgically treated patients.^{4,5} Less than one-third of all patients were cured by multimodality therapy, and distant failure accounted for three-fourths of all recurrences.⁶

Despite many advances in both surgery and radiotherapy, the treatment of esophageal cancer remains a challenge for both surgeons and oncologists. The biggest problem affecting patient outcome is late presentation, since most symptomatic patients present with advanced disease; further there is lack of an effective screening program.⁴ Only a minority of patients are suitable for curative treatment. Five-year survival for all patients remains poor at just 13%; surgical series report survival of 20%.⁵

This overview examines the role of definitive concurrent chemo-radiotherapy (dCRT) in localized esophageal cancer. For patients with early localized and resectable disease, surgery, with or without neo-adjuvant chemotherapy or CRT, remains widely regarded as the gold standard treatment option, leaving dCRT as the alternative for those patients unsuitable for surgery due to medical co-morbidities and

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INTRODUCTION

Cancer of the esophagus is a highly lethal malignancy, ranked as the 6th most common cause of cancer deaths worldwide. It is more common in men than women.¹ It is endemic in many parts of the world, particularly in the developing countries, where it is the 4th most common cause of cancer-related deaths.¹ High-prevalence areas include Asia, southern and eastern Africa, and northern France.² According to data from the US Surveillance Epidemiology and End Results (SEER) Program, five-year survival of esophageal cancer improved only modestly over the years; from 5% during 1975 to 1977, to 19% during 2001 to 2007.³ These sobering figures were

the extent of loco-regional disease.^{5,7} With the emergence of improved radiotherapy techniques with lower rates of morbidity, together with the development of more effective and targeted systemic treatments, there is the trend towards treating more patients with organ-preserving dCRT or the same as a part of tri-modality treatment. Out of the 3780 new cancer registrations of 2015-2016 in the department of Radiotherapy & Oncology, Government Medical College Hospital, Thrissur, 220 (6%) were esophageal cancers and about 70% of our patients present in the locally advanced stage (Stage II-III, American Joint Committee on Cancer 7th Edition).⁸ In the current study we aimed to assess the overall survival and progression-free survival rate in esophageal cancer patients treated with dCRT.

MATERIAL AND METHODS

242 Consecutive cases of locally advanced carcinoma esophagus, registered in the department of Radiotherapy and Oncology, Government Medical College, Thrissur, Kerala from December 2014 to May 2016, undergoing dCRT were selected for the study. Ethical committee approval and Informed consent was obtained. The study was planned as a single arm prospective study. The inclusion and exclusion criteria are detailed in Table 1.

Initial assessment: Apart from routine hematological and biochemical lab tests, staging of the disease was done using contrast enhanced computerized tomography (CECT) scan of thorax/abdomen and upper gastro-intestinal endoscopy and biopsy with histological confirmation.

Radiotherapy: All patients were irradiated by external beam radiation with megavoltage beams on tele-cobalt machine to a total dose of 50.4 Gy given in 28 fractions of 1.8 Gy per fraction, 5 fractions per week. The Gross Tumor Volume (GTV) was defined by the primary tumor and any enlarged regional lymph node and was drawn on each relevant CT slice. The GTV was determined using all available information (physical examination, endoscopy, CECT-thorax/abdomen). Planning Target Volume (PTV) had a proximal and distal margin of 5 cm. A 2cm radial margin around the GTV was provided to include the area of subclinical involvement around the GTV and to compensate for tumor motion and set-up variations.

Chemotherapy: During each chemotherapy cycle, 5-Fluorouracil (5-FU) 1000 mg/m² was given for 4 days (day one to day four) and Cisplatin 75mg/m² were given by intravenous infusion on day one. Chemotherapy cycles were repeated on week 1, 5, 8 and 11. Radiation was started from day one of first cycle chemotherapy. All patients receiving Cisplatin were hydrated before, during, and after the drug administration. Usual approach was to give at least one liter of 0.9% sodium chloride before and one liter after the drug treatment. Mannitol diuresis was used after hydration. Half an hour before the start of the Cisplatin infusion, 3 mg of Granisetron, 16 mg of dexamethasone and 50mg of Ranitidine were given as premedication intravenously. Anti-emetic prophylaxis with granisetron orally was continued for

three days after each cycle of chemotherapy.

Evaluation of patients during treatment: The regimen was administered on an outpatient basis. During irradiation, all patients were scored weekly during the course of CRT for neutropenia using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) acute radiation morbidity scoring scheme.⁹ Clinical examination, complete blood picture, liver and kidney function tests were done before each cycle.

Follow up: The first follow-up was 6-weeks from completion of therapy to assess response, toxicity and disease status. Subsequent follow-up visits were at every three months. At follow-up, patients underwent thorough clinical examination for detection of loco-regional disease. Patients who have not completed the treatment course or lost to follow-up were excluded. Disease progression was considered as clinico-radiological loco-regional disease after complete clinical response to treatment or persistence/increase in disease volume during treatment course.

STATISTICAL ANALYSIS

Patient characteristics, responses and toxicities were shown by descriptive methods. Chi-square test was used to compare qualitative variables. The Overall Survival [OS] was defined as the interval between the date of diagnosis and the date of the last follow-up point or death. The OS and Progression Free Survival (PFS) were calculated according to the Kaplan–Meier method. The impact of clinico-pathologic factors (age, sex, site of tumor and stage involvement at presentation) on OS and PFS were examined. The evaluation of differences were performed with the log-rank test.

RESULTS

Out of the registered 242 cases of carcinoma esophagus during the study period, 40 patients satisfied the inclusion criteria and were taken up for the study after informed consent. Two patients lost to follow-up. The median age of the study population was 58.2(45-70) years, majority being between 51 to 60 years. The study group involved 8(20%) females and 32(80%) males. Four (10%) patients were addicted to smoking, 26(65%) to both alcohol and smoking and 7(17.5%) to smoking only.

Five (12.5%) patients had upper third of the esophagus as the primary site of the disease, 13(32.5%) had lower third and the majority, 22(55%), had middle third as the primary site. Seven (17.5%) patients had T2 tumor, 25(62.5%) had T3 tumor and 8(20%) had T4 tumor. Nineteen (47.5%) patients had N1, 18(45%) had N2 and 3(7.5%) had N3 nodal involvement. Stage wise, 40% of the patients were stage 3A, 10% were stage 2B; stage 3B and stage 3C constituted 25% each of the total number of the patients. Forty percent had normal neutrophil count and among the remaining patients, grade 1 neutropenia was found in twelve (30%), grade 2 in six (15%), grade 3 in five (12.5%) and grade 4 in one (2.5%) patient. Transient stomatitis was observed in four (10%) patients.

Inclusion Criteria	Exclusion Criteria
Histologically confirmed, potentially unresectable squamous–cell carcinoma of the esophagus Tumors of clinical stage T4N0 or T4 N1-3 Inoperable or loco-regionally advanced disease Age group 18 to 70 years WBC count > 4000 cells/mL Platelet count of >100,000 platelets/ mL Serum Creatinine<1.5 mg/dL Creatinine clearance>80 mL/min	Histology other than squamous cell carcinoma Operable carcinoma esophagus Presence of Tracheo-Esophageal Fistula Age > 70 years WBC count < 4000 cells/mL Platelet count <100,000 platelets/ mL Creatinine clearance < 80 mL/min

Table-1: Inclusion and Exclusion criteria

Characteristics	Category	Survived	Death	P value
Age group	<50	7	0	0.224
	51-60	16	2	
	>60	9	4	
Gender	Female	7	0	0.569
	Male	25	6	
Site	Upper one third	5	0	0.841
	Middle one third	17	4	
	Lower one third	10	2	
CT Stage	2B	4	0	0.500
	3A	14	2	
	3B	8	1	
	3C	6	3	

Table-2: Association of overall survival with age, sex, site and CT stage

Trials	Year	No. of Patients	OS 1 year	DFS 1 year	Median Survival
RTOG 85-01	1997	121	80.30%	52.10%	15.4 months
INT0123	2002	236	69.70%	46.50%	18.1 months
D Tougeron et al	2008	109	62.50%	-	15.2 months
Present study	2016	38	84.20%	68.40%	17.8 months

Table-3: Comparison of study results

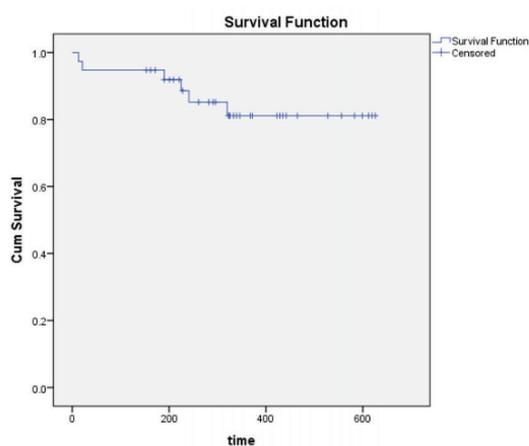


Figure-1: Overall survival

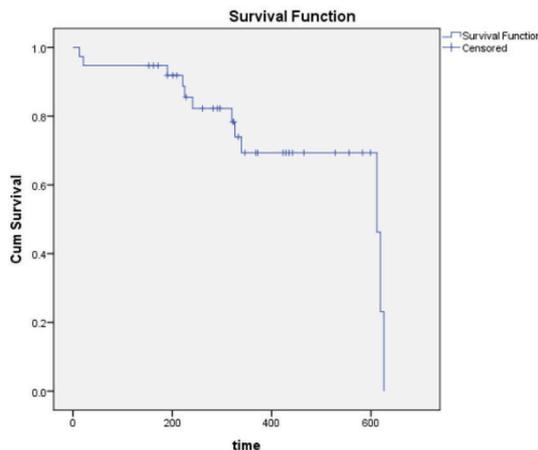


Figure-2: Progression free survival

Disease progression and death during treatment or follow-up was seen in 14(35%) patients whereas the disease not progressed in the rest 26(65%).Thirty-eight patients completed follow-up and the median follow up duration was 15.8 months. The overall survival rate was 84.2% and the mean survival period was 542.7 days (17.8 months). (Figure.1)The progression free survival was 68.4% with the mean progression free survival duration of 16.4

months(mean 20.1 months).(Figure.2)The OS and PFS were not significantly related to age and sex of patient or site and clinical stage of the disease.(Table.2)

DISCUSSION

Treatment of carcinoma esophagus is a nightmare since, at the time of disease presentation, more than a half have metastatic disease, a third have the locally advanced disease

and only the rest less than 20% have curable localized disease.¹⁰ The treatment of inoperable esophageal carcinoma is challenging, and optimal sequencing of treatment modalities remains controversial. While combined modality therapy offers a small but real chance of PFS and potentially prolonged OS, improvement in the quality of life and sustained relief of dysphagia can be achieved in the majority of patients.¹¹ On this background, we from a Government tertiary care teaching hospital in South India aimed to audit our treatment protocol. So we examined our patients with inoperable esophageal squamous cell carcinoma undergoing definitive concurrent chemo-radiotherapy (dCRT) for the survival and toxicity profile.

Our study group included 40 patients with a median age of 58.2 years; 80% of them being males. Addiction to smoking, alcohol or pan chewing was extremely common (92.5%) in our cohort. The majority had good performance status at the study entry. Middle and lower third of the esophagus were the common sites of affection compared to the upper third and the majority presented at 3A, 3B and 3C stage of the disease with only 10% patients in stage 2B.

Neutropenia was the major toxicity observed, and it was present in 60% of patients. Out of them, severe neutropenia (Grades 3 and 4) was present in only a quarter. This was comparable to the 17.5% neutropenia observed in a recent study.¹²

Two patients died during the treatment whereas the rest completed the treatment without a break. Two patients lost to follow-up. The overall survival (OS) rate was 84.2% with a mean survival period of 17.8 months. Progression of the disease was noted in 35% of patients, and four patients died during the follow-up period. The progression-free survival (PFS) was 68.4% with a mean progression-free survival time of 16.6 months. None of the patient related or tumor-related factors were found to be significantly related to OS and PFS. This may be due to small sample size and short median follow up duration of the study. Results of the present study are comparable to two seminal studies, RTOG 85-01 trial^{4,5} and INT0123 trial.¹³ (Table.3) However the toxicities were minimum, compared to as that of RTOG 85-01 trial.

CONCLUSION

Definitive Concurrent chemo-radiation with cisplatin and 5-FU was well tolerated, promising a reasonable therapeutic option for patients with inoperable locally advanced esophageal squamous cell carcinoma. One year Overall Survival and Progression Free Survival were comparable with other major trials, showing median survival duration of 17.8 months. Though the present audit of our institutional protocol was reassuring, further studies with larger sample sizes are required to confirm the predictive factors for progression-free and overall survival. The need for adjuvant treatment in reducing the progression of locally advanced disease should be evaluated. Carefully designed randomized clinical trials with more number of patients would be the answer to these issues.

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