



EFFECTIVENESS OF CHEMORADIATION VS RADIOTHERAPY IN DYSPHAGIA RELIEF IN PATIENTS HAVING LOCALLY ADVANCED ESOPHAGEAL CARCINOMA

Oncology

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ABSTRACT

The aim of the study was to evaluate the effect of chemotherapy with radiotherapy in dysphagia relief in patients with locally advanced carcinoma of esophagus. This is a prospective study comprised of 60 patients of various age group and were randomly divided into two equal groups. One group was treated with induction chemotherapy followed by chemoradiation while the other group was treated with radiotherapy alone. Post therapy both the groups were followed up for evaluation of dysphagia relief. During the study period the response to chemoradiation was 70 % whereas in radiotherapy alone group the response was 63.3%. However, statistically no significant difference ($p > 0.05$) was observed between the groups in respect of dysphagia relief. The combination of chemotherapy with radiotherapy significantly improves dysphagia relief in patients with carcinoma of esophagus.

KEYWORDS

Esophagus, dysphagia, chemotherapy, radiotherapy

INTRODUCTION

Esophageal cancer consist of esophageal adenocarcinoma and esophageal squamous cell carcinoma, is one of the most lethal malignant tumours in the world, especially in south Iran and China.¹ It is a very fatal disease and about 480,000 new patients are recorded every year. It has been reported that its incidence is 5th in men and 8th in women.² There is a wide variation in incidence, between the different regions of the world, as it ranging from 0.8 per 100,000 in western Africa in men and 0.2 per 100,000 in Micronesia/Polynesia to 7.8 per 100,000 in eastern Africa in women.³

Cancer esophagus, though less common in western countries like United States with a lifetime risk of being diagnosed with the disease is less than 1%.⁴ However, its incidence is high in India and particularly in the state of Assam. Age adjusted incidence rate in Dibrugarh district of Assam according to three year report of the population based cancer registry (2006–2008) are 16.9% in males and 12.8% in females.

Tobacco and alcohol use are considered the major contributing factors in the development of esophageal cancer worldwide. It is estimated that up to 90% of the risk of squamous cell carcinoma of the esophagus in Western Europe and North America can be attributed to tobacco and alcohol use.⁵ There appears to be a dose-response effect related to the duration and intensity of smoking and, importantly, there is an impressive (up to 50%) reduction in risk of developing squamous cell carcinoma of the esophagus for those who quit smoking and an inverse relationship between risk and the length of time since cessation of tobacco use.⁶ The prognosis of esophageal cancer especially squamous cell carcinoma (ESCC) is very poor because it is typically diagnosed after the presence of symptoms. The survival rate of ESCC patients is 19%; the fourth in all the types of cancers in the USA.⁷

Progressive dysphagia is the most common symptom among the patients of esophageal cancer. The common treatments of esophageal carcinoma are surgery, radiotherapy and chemotherapy of which surgery is the effective treatment option. Although with advancement in surgical techniques and treatment the prognosis of esophageal cancer slowly improved during the past three decades but the five year survival rate (14%) remains very poor. Of course, treatment decisions are often depend upon the individual patient and stage of cancer. Patients with advanced tumour may not be cured by surgical intervention alone and hence preoperative chemoradiation expected to yield better results. But most of the patients with locally advanced disease are found to be inoperable at the time of the diagnosis. In patients having inoperable locally advanced disease, the more effective treatment is chemo-radiotherapy.⁸ Though many

combinations of chemotherapy drugs have been used,^{9,10} but multi-institutional cooperative trials have employed concurrent cisplatin and 5-fluorouracil (5-FU) as a standard chemotherapy regimen in locally advanced esophageal cancer. Therefore, a study was conducted to compare the effectiveness of chemoradiation vs radiation alone in dysphagia resolution.

MATERIALS AND METHOD

Selection Of Patients

The study was conducted in the Department of Radiotherapy, Assam Medical College, Dibrugarh. Sixty patients were randomly selected and divided into two groups. One group was treated with induction chemotherapy followed by chemoradiation while the other group was treated by radical radiotherapy alone.

Patient eligibility

All the patients had histologically confirmed carcinoma of the oesophagus. Patients having locally advanced carcinoma of esophagus T3 N+ and T4 N0/N+ were taken for the study. Participants had Karnofsky performance status of 70% or greater and normal haematological, renal, and hepatic function. They had no prior anti-cancer therapy. The patients with metastatic disease or tracheo-esophageal fistula were not included. Moreover, patients with a prior history of any malignancy were excluded. Patients with gastric involvement by carcinoma of the lower esophagus were also not included.

Pretreatment Evaluation

Pretreatment evaluation included a detailed medical history and physical examination, complete blood count, biochemical tests including liver function assessment and electrolytes and ECG. Radiologic evaluation included a CT scan of the chest and abdomen. Patients were required to undergo endoscopy with biopsy of the primary tumour. Bronchoscopy was performed in patients with tumours of the cervical or proximal third of thoracic oesophagus.

The 2010 AJCC staging system was used in this study.

The patients who fulfilled the above mentioned inclusion criteria and had none of the exclusion criteria were explained about the study, and written informed consent were obtained.

Details Of Treatment

- (A) Details of chemotherapy - In the chemoradiation treatment group, chemotherapy was administered on every 28 days for five cycles. 3 Three cycles of chemotherapy was administered before radiotherapy and 2 cycles along with radiotherapy. Radiation dose

delivered was 60 Gy to each patient. Inj. Cisplatin 75 mg/m² I.V on day 1 and Inj. 5-FU 1000mg/m² I.V on days 1-4. Prior to each cycle of chemotherapy Routine blood examination, Platelet count, Random Blood Sugar, Renal Function Test, Liver Function Test, Serum Sodium, Serum Potassium were regularly carried out. If there was any disparity in the parameters, chemotherapy was momentarily discontinued till the patient recovered.

During the chemotherapy, at the start of each cycle, the following data were collected - Weight gain or loss, subjective response, that is, the degree of relief of dysphagia as stated by the patient and Karnofsky status.

(B) Details of radiotherapy – both the groups were treated by Cobalt teletherapy (Theratron 780C). Radiotherapy was delivered by source to axis technique. Source to axis distance was kept at 80cm. Both the groups received total dose of 60 Gy. 2 Gy per fraction 5 days a week for 6 weeks (Total 30 fractions).Radiation treatment planning was done in CMS-XIO computer treatment planning system. In phase 1 of treatment, two field technique was used i'e AP and PA portals, later in phase 2, fields were modified to spare the spinal cord. 4000 cGy was delivered in phase 1 and 2000 cGy was delivered in phase 2 of treatment. Maximal allowable overall dose to the spinal cord was 4500. Daily dose of 200 cGy was equally divided among the treatment fields. The superior and inferior borders of the radiation field were 5 cm beyond the primary tumor. The lateral, anterior, and posterior borders of the field were 2 cm beyond the borders of the primary tumor. The tumor size was defined by barium swallow. The primary and the regional lymph nodes were included. All fields were treated each day. The dose was prescribed to the isocentre, which covered the volume at risk. Lung inhomogeneity corrections were not used.

The patients were carefully followed up on weekly basis during the radiation course to look for any deterioration of general health and to monitor the radiation reactions.

Follow-Up Evaluation

Patients were called for first follow-up after 2 months of completion of therapy. They were asked about their dysphagia relief and any other new symptoms. Dysphagia was recorded prior to therapy, after completion of induction chemotherapy, after completion of chemoradiation and after completion of radiotherapy using a previously published dysphagia scale.¹¹ An upper gastrointestinal endoscopy and a CT scan were repeated to assess response. Clinical complete response was defined as no tumour detectable on upper gastrointestinal endoscopy and no appearance of lymph nodes or distant metastasis on CT scan.^{12,13} When patients achieved a complete clinical response, follow-up was carried out at every 2 months interval till 1 year. All toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0.

RESULTS

The patients were followed-up every two months for a period of one year after completion of treatment. The median follow-up time was four months. Total sixty patients were randomly selected for the study of which 35 patients (58.3%) belong to 51-70 years, 17 patients (28.3%) belong to 31-50 years, 7 patients (11.7%) belong to >70 years and 1 (1.7%) below 30 years age group. It is interesting to note that the youngest patient was of 23 years whereas the eldest was of 73 years. Of the 60 patients 35 (58.3%) were male and 25 (41.7%) were female and the ratio of male to female being 1.4:1. It was observed that diabetes mellitus was the most commonly associated co-morbidity occurring in 11 (18.3%) patients followed by hypertension in 8 (13.3%) cases. Of the total sixty patients, 56(93.3%) had history of either single or multiple addictions, whereas, 4 patients (6.7%) did not have any addiction or habituation. The most common form of addiction was chewing of betelnut and vine 43(71.7%) patients followed by smoking in 24 (40%) patients and consumption of alcohol in 19 (31.7%) patients for a duration of 10-30 years. Thirty four patients (56.7%) were from lower income group whereas 20 patients (30.3%) belong to middle income group and six patients (10%) from the higher income group. There was no history of any malignancy in other members of the family. The various symptoms observed in **Table 1**.

| Sl. No. | Symptoms | No. of cases | Percentage |
|---------|-----------|--------------|------------|
| 1 | Dysphagia | 60 | 100 |
| | -partial | 46 | 76.7 |
| | -total | 14 | 23.3 |

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|----|-------------------------------|----|------|
| 2 | Retrosternal pain | 24 | 40 |
| 3 | Cough | 19 | 31.7 |
| 4 | Vomiting | 8 | 13.3 |
| 5 | Regurgitation | 7 | 11.7 |
| 6 | Hoarseness of voice | 1 | 1.7 |
| 7 | Interscapular pain | 5 | 8.3 |
| 8 | Epigastric pain | 4 | 6.7 |
| 9 | Haematemesis | 3 | 5 |
| 10 | Fever | 9 | 15 |
| 11 | Swelling and pain in the neck | 5 | 8.3 |
| 12 | Haemoptysis | 3 | 5 |
| 13 | Weight loss | 16 | 26.7 |
| 14 | Belching & hiccough | 6 | 10 |

Dysphagia was the most common symptom that was seen in all the patients. The average duration of dysphagia was for 4-6 months which was progressive in nature. Fourty six patients (76.7%) had dysphagia for solid food whereas 14 patients (23.3%) has dysphagia for semisolid food. Other commonly observed symptoms were retrosternal pain (40%), cough (31.7%), and weight loss (26.7%). Thirty-three patients (55%) weighed between 30-50 kg. The lower weight recorded in patients could be attributed to poor food intake due to difficulty in swallowing. Palpable supraclavicular nodes were found in six patients (10%). However, no abdominal organomegaly was found in any patient. In hematological investigations, it was observed that majority of patients had hemoglobin level of <9g%. Fourteen patients (23.3%) had hemoglobin level <8g% for which they received blood transfusion. Rest of the hematological investigations were found to be within the normal range prior to start of the treatment. On barium swallow examination, all the patients showed irregular filling defect of esophagus. None of the patients had any evidence of diverticulum or fistula. In upper gastrointestinal endoscopy, 40 patients (66.7%) had shown growth in the middle third of esophagus whereas 16 patients (27.7%) had growth in upper third and four patients (6.7%) had growth in lower third of esophagus. Fiftythree patients (88.3%) had shown ulceroproliferative growth whereas in 7 patients (11.7%) had shown stenotic lesions. CT scan was done to establish the extent of disease and to document mediastinal and hilar lymphadenopathy. Squamous cell carcinoma was the most predominant histology seen in 58 patients (96.75), whereas, adenocarcinoma was seen in only two patients (3.3%).

RESPONSE TO TREATMENT- Patients response to treatment was recorded under two categories i'e Subjective Response (patient's own assessment) and Objective Response (response assessed by investigator) as shown in **Table 2** and **Table 3** respectively. Local recurrences occurred in three patients (10%) in chemoradiation treated group while six patients (20%) in radiotherapy alone treated group. All the recurrences in radiotherapy treated group occurred within 6 months of completing radiotherapy.

TABLE 2 SUBJECTIVE RESPONSE

| Subjective response | No. of patients in CT-RT group | Percentage | No. of patients in RT group | Percentage |
|---------------------|--------------------------------|------------|-----------------------------|------------|
| No response at all | 6 | 20 | 6 | 20 |
| 1-25 % relief | 4 | 13.3 | 3 | 10 |
| 26-50 % relief | 3 | 10 | 6 | 20 |
| 51-75 % relief | 7 | 23.3 | 8 | 26.7 |
| 76-100 %relief | 10 | 33.3 | 7 | 23.3 |

TABLE 3 OBJECTIVE RESPONSE

| Type of response | No. of patients in CT-RT group | Percentage | No. of patients in RT group | Percentage |
|---------------------------|--------------------------------|------------|-----------------------------|------------|
| NR (No response) | 8 | 26.7 | 9 | 30 |
| PR (partial response) | 11 | 36.7 | 11 | 36.7 |
| CR (complete response) | 10 | 33.3 | 8 | 26.7 |
| PD (progressive disease) | 1 | 3.3 | 2 | 6.7 |

DISCUSSION

Several studies have shown that chemotherapy when combined with radiotherapy improves local response rate in patients with esophageal cancer.^{14, 15} The present study compared in a randomized fashion the

use of radiotherapy alone vs chemoradiation with cisplatin and 5-FU in patients with carcinoma of esophagus. During one year study period the response to combination of radiotherapy with chemotherapy was 70% while in radiotherapy alone group the response was 63.3%. The non responders constitute 36.7% in radiotherapy alone treated patients, whereas, it was 30% in chemoradiation group. Statistically, no significant difference ($p>0.05$) was observed between the groups in respect of dysphagia relief. Ilson et al, reported significant improvement in dysphagia relief using chemoradiation in patients with carcinoma of esophagus.¹⁶ In contrast, Michel et al 2006 did not find any significant improvement in dysphagia relief using chemoradiation in esophageal cancer patient.¹⁷ Araujo et al, while comparing radiotherapy vs the combined use of chemoradiation in 59 patients observed response rate of 58 % for radiotherapy and 75% for chemoradiation group ($p=0.77$), the response rate of chemoradiation group was in good agreement with many studies.^{18,19,16} However, the result of the present study must be interpreted with caution because of less number of patients recruited for the study to detect a clinically significant improvement in dysphagia relief.

CONCLUSION

The combination of chemotherapy with radiotherapy significantly improves dysphagia relief in patients with carcinoma of esophagus. Further studies are required to evaluate the effect of combination therapy of chemotherapy with radiotherapy in locally advanced squamous cell carcinoma of esophagus.

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Ethical approval: The study was approved by the Institutional Ethics Committee

References :

- Zali H, Ahmadi G, Bakhshandeh R, Rezaei-Tavirani M. Proteomic analysis of gene expression during human esophagus cancer. *J Paramed Sci.* 2011;2:37-44.
- Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. *CA Cancer J Clin* 60(5):277-300, 2010.
- Globocan , 2012 ; Estimated cancer incidence , mortality and prevalence world wide in 2012. Available at <http://globocan.inac.fr>.
- Ries L, Melbert D, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2004. National Cancer Institute. Bethesda, MD. <http://seer.cancer.gov/css/1975-2004/>, based on November 2006 SEER data submission, posted to SEER website, 2007.
- Schottenfeld D. Epidemiology of cancer of the esophagus. *Semin Oncol* 1984;11(2):92
- Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control* 1993;4(2):123.
- Jemal, A., Siegel, R., Xu, J. and Ward, E. (2010), *Cancer Statistics, 2010*. CA: A Cancer Journal for Clinicians, 60: 277-300.
- Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-52.
- Enzinger PC, Ilson DH, Kelsen DP. Chemotherapy in esophageal cancer. *Semin Oncol.* 1999;26 Suppl 15:12-20.
- Geh JJ. The use of chemoradiotherapy in oesophageal cancer. *Eur J Cancer.* 2002;38:300-313.
- Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of esophagogastric neoplasms at fiberoptic endoscopy. *Gut.* 1982;23:1060-1067.
- Kelsen D., Hilaris B., Coonley C., Chapman R., Lesser M., Dukeman N., Heelan R., Bains M., D Cisplatin, Vindesine and Bleomycin chemotherapy of local regional and advanced esophageal carcinoma. *Am. J. Med.* 75(4): 645-52, 1983.
- Jones DR, Parker LA Jr, Detterbeck FC, et al. Inadequacy of computed tomography in assessing patients with esophageal carcinoma after induction chemoradiotherapy. *Cancer* 1999; 85: 1026-1032.
- Wobbes T, Baron B, Paillot B, et al: Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus. *European Journal of Cancer* 37:470-477, 2001
- Zupanc D, Roth A, Kolaric K, et al: A randomized clinical study of chemoradiotherapy versus radiotherapy in locoregional advanced unresectable esophageal cancer. *J Clin Oncol* 25(suppl 18):2007 (abstr 4565).
- Ilson DH, Saltz L, Enzinger P, et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. *J Clin Oncol.* 1999;17:3270-3275.
- Michel P, Adenis A, Di Fiore F, et al. Induction cisplatin-irinotecan followed by concurrent cisplatin-irinotecan and radiotherapy without surgery in oesophageal cancer: multi-center phase II FFC trial. *Br J Cancer.* 2006;95:705-709.
- Araujo CM, Souhami L, Gil RA, et al: A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. *Cancer* 67:2258-2261, 1991
- al-Sarraf M, Martz K, Hershkovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: An intergroup study. *J Clin Oncol* 1997;15:277-284.