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Long Term Survival and Late Toxicities in Inoperable Carcinoma Esophagus Treated wth Concurrent Chemotherapy and Radiotherapy

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Abstract

Introduction: Results of treatment in carcinoma esophagus have not been very encouraging as it usually presents in an advanced stage. We treated these inoperable carcinoma esophagus patients with concurrent chemotherapy and radiotherapy and got early symptomatic relief and good long term survival. *Material & Methods:* 46 patients included in this study were treated with induction chemotherapy with methotrexate on day 1 and cisplatin on days 2 to 5 followed by radiotherapy from day 6 and further cisplatin was given on days 21, 28 and 35 concurrently with radiotherapy. *Results:* Symptomatic relief was seen during the second week and 69.56% patients had local control at 1 year. The 3-year and 5-year overall survival (OS) was 47.83% and 15.22% respectively, with a median survival period of 32 months. *Conclusion:* This regime of sequential chemotherapy followed by radiotherapy and concurrent chemotherapy has given better overall survival with acceptable toxicities.

Keywords: Survival; Esophagus; Chemo-radiotherapy; Long Term.

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Introduction

Cancer is considered a major health problem across the globe and is the 2nd most common cause of death after cardiac diseases. A significant number of cancers with various histology occurs in Gastrointestinal tract (GIT), of which, colorectal, stomach, esophagus, liver, gall bladder and pancreas are the 6 most common Gastrointestinal (GI) malignancies [1]. In the United States, esophagus accounts for approximately 1% of the overall malignancies & 6% of all the GI malignancies. With 456,000 newly diagnosed cases in 2012, it has become the 8th most common cancer in the world, though the incidence is variable with respect to geography, ethnicity and gender. In 2012, out of the estimated 1.01 million newly diagnosed cancer cases in India, 227000 were located in the GIT. GI malignancies were accountable for nearly 182000 deaths out of an approximate 682000 cancer-related deaths [2].

Esophagus is a hollow tubular structure with a length of 25 cm with most of it present in the thoracic cavity. For clinical purpose, it is divided into 3 major parts: upper 1/3rd (cervical: 15-18 cm distance from the incisors and upper thoracic: 18-24 cm), middle 1/3rd (24-32 cm) and lower 1/3rd (32-40 cm) esophagus. It is lined by stratified keratinized squamous epithelium except lower 1/3rd, which may contain glandular elements, as well. Histologically, squamous cell carcinoma is most predominant arising from squamous epithelium [3] followed by adenocarcinoma (from columnar lined distal esophagus) [4,5]. Sarcomas

and small cell carcinoma account to <1-2% of all esophageal cancers [6,7]. Moreover, esophageal melanomas, leiomyosarcomas, carcinoids & lymphomas are rare.

Carcinoma esophagus presents with the symptoms of dysphagia in 90% of the patients, odynophagia (50%), weight loss (40-70%) [8]. The incidence of adenocarcinoma is steadily on the rise in the United States. Risk factors for esophageal carcinoma are cigarette & hookah smoking, red meat, alcohol, tobacco chewing, hot tea consumption, nitrosamines in food, poor oral health, low intake of fresh fruits & vegetables, HPV, obesity, genetic alteration and low socioeconomic status [9,10,13]. Endoscopic ultrasound and CT Scan are used for proper staging & workup [11]. Despite various advances in the different modalities of treatment of carcinoma esophagus such as surgery, external beam radiotherapy (EBRT) ± chemotherapy & intraluminal brachytherapy, it still carries poor results [12]. A large number of patients succumb to the disease as a result of failure of primary lesion treatment as most of the patients present in a locally advanced stage and infiltration of disease in adjacent organs and lymph nodes. Patients who require surgery as the sole treatment have improved prognosis (owing to the evolution of surgical techniques & better postoperative care). Trials have demonstrated comparable results for concurrent chemo-radiation versus surgery in locally advanced carcinoma esophagus [22]. Here, the patients of carcinoma esophagus middle 1/3rd treated with concurrent chemo-radiation were evaluated for their clinical response, overall survival and associated late toxicities.

Materials and Methods

A retrospective observational study was carried out on 54 patients of locally advanced inoperable carcinoma esophagus who underwent definitive chemo-radiotherapy between September 2010 to 2014 and were followed up till June 2017. All the patients had histologically proven Stage III or more (locally advanced) cancer of the middle 1/3rd of esophagus with KPS ≥ 80%. After pretreatment and metastatic evaluation, all the patients were started on chemotherapy with Methotrexate (MTX) 50 mg (fixed dose) in 8 hours on day 1 and Cisplatin 20 mg/m2 on days 2 to 5 followed by radiotherapy from Day 6 combined with concurrent chemotherapy with Cisplatin 30 mg/m^2 given on days 21, 28, 35 day. CT simulation with proper immobilization in supine with arm above head position was done on SOMATOM CT Scanner. The images were then registered on Eclipse treatment planning system (TPS) version 8.9 and contouring of treatment planning volumes and organs at risk (OARs) was done as per RTOG guidelines. A repeat CT scan for replanning was done as and when required. A total of 66 Gy in 33 fractions was given to the GTV with 3DCRT or IMRT keeping the doses to OARs within tolerance limits. Overall survival (OS) was measured from start of the treatment till last follow up/death assessed till June 2017. Follow up was noted at monthly interval for initial 6 months, at 3 months for the next 12 months and 6 monthly, thereafter. Imaging and UGI Endoscopy were done on every follow up to evaluate the local control and metastatic work up. Evaluation of tumor response was done by RECIST criteria version 1.1 and of chronic toxicity was done using CTCAE version 4.0. Clinical evaluation was based on assessment of dysphagia as per RTOG/EORTC radiation morbidity grading. Pattern of failure was determined in terms of local recurrence as reappearance of primary lesion on endoscopy after treatment completion and distant metastases when there was presence of lung and liver metastases on follow up. These patients were subjected to salvage chemotherapy.

Observations and Results

In our study, the male to female ratio was approximately 2: 1. Out of 54 patients, 35 patients (64.81%) were males and 19 (35.19%) were females with median age of 55 years. Most male patients were in the age group of 51-60 years and female patients were between 61-70 years of age (Table 1). Histologically, 50 (92.59%) had squamous cell carcinoma, 3 (5.57%) had adenocarcinoma and 1 (1.85%) had small cell carcinoma esophagus. Out of 54 patients only 46 patients completed the treatment. 7 patients defaulted and did not receive complete treatment and 1 female patient who died during the treatment were excluded from the study.

Table 1: Age-wise distribution of patients

Age (yrs)	No. of Male	No. of Female	Total (%)
21-30	0 (0%)	2 (10.52%)	2 (3.7%)
31-40	3 (8.57%)	3 (15.79%)	6 (11.11%)
41-50	12 (34.29%)	2 (10.52%)	14 (25.92%)
51-60	14 (40%)	3 (15.79%)	17 (31.48%)
61-70	5 (14.28%)	6 (31.57%)	11 (20.37%)
71-80	1 (2.85%)	3 (15.79%)	4 (7.40%)
Total (%)	35 (64.81%)	19 (35.19%)	54 (100%)

Clinical evaluation was based on assessment of dysphagia as graded according to NCI CTC Toxicity Scale Version 2.0. On initial presentation, 23 (42.59%) patients had Grade 2 dysphagia and 31 (57.4%) patients had Grade 3 dysphagia. After 1 month of post-treatment follow up, 25 (54.35%) had Grade 0 dysphagia, 15 (32.6%) patients had Grade 1 dysphagia, 5 (10.87%) patients had Grade 2 dysphagia and Grade 3 dysphagia was present in 1 (2.17%) patient indicating significant relief in the symptoms of most of the patients. Symptomatic relief was seen very early during the treatment. Most of the patients were able to take oral diet during 2nd week of treatment and then it reduced mildly due to radiation esophagitis. Patients' performance status also improved during the treatment due to improved diet. After 3 years of follow up, 16 (72.72%) out of the 22 alive patients had Grade 0 dysphagia, 3 (13.64%) patients had Grade 1 dysphagia, 3 (13.64%) patients had Grade 2 dysphagia.

Out of the 46 patients, 32 (69.56%) patients had local control of the disease, 2 (4.34%) patients had local failure, 1 (2.17%) patient developed distant metastases and 11 (23.91%) patients died at the end of 1 year of follow up. 24 (52.17%) patients had local control of the disease, 1 (2.17%) patients had local failure, 4 (8.70%) patients developed distant metastases and 17 (36.95%) patients died after 2 years of follow up. After 3 years of follow up, 16 (34.78%) patients had local control of the disease, 3 (6.52%) patients had local failure, 3 (6.52%) patients developed distant metastases and 24 (52.17%) patients died(Figs. 1 & 2).

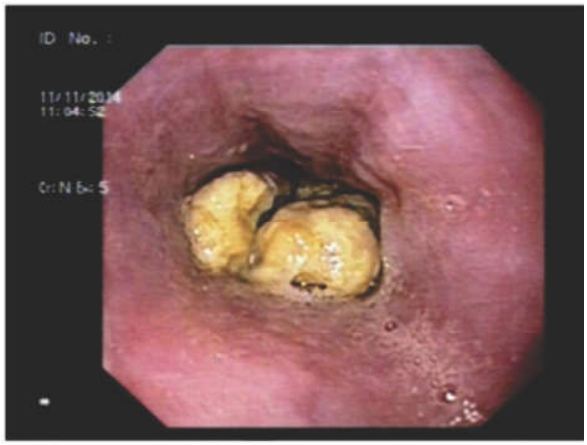

Fig. 1: Ulceroproliferative growth in esophagus

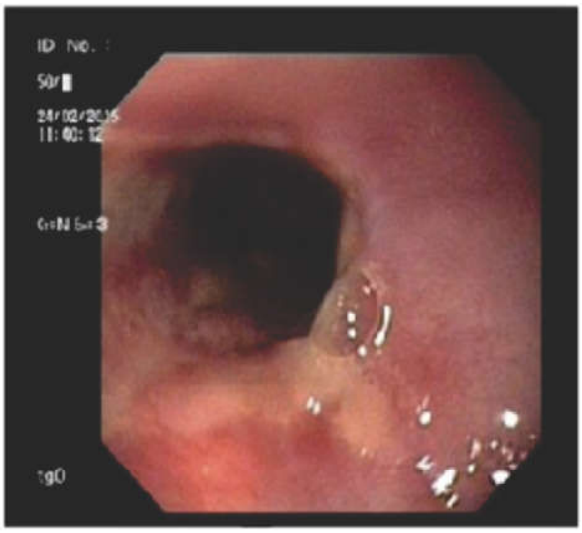

Fig. 2: Complete response after completion of chemo-radiotherapy

During follow up, seven patients developed esophageal stricture (Fig. 3), which were treated with esophageal dilatation and were able to take solid diet. Two patients developed pleural effusion and one patient had pericardial effusion, all were asymptomatic.

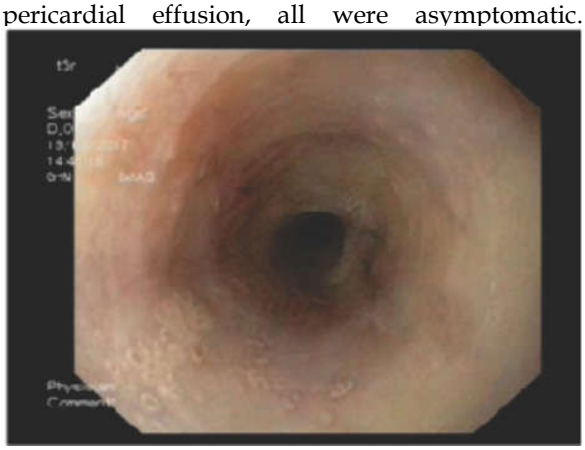

Fig. 3: Stricture post chemo- radiotherapy

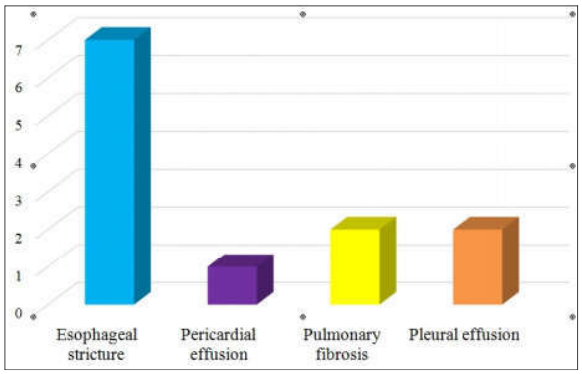

Fig. 4: Late toxicity

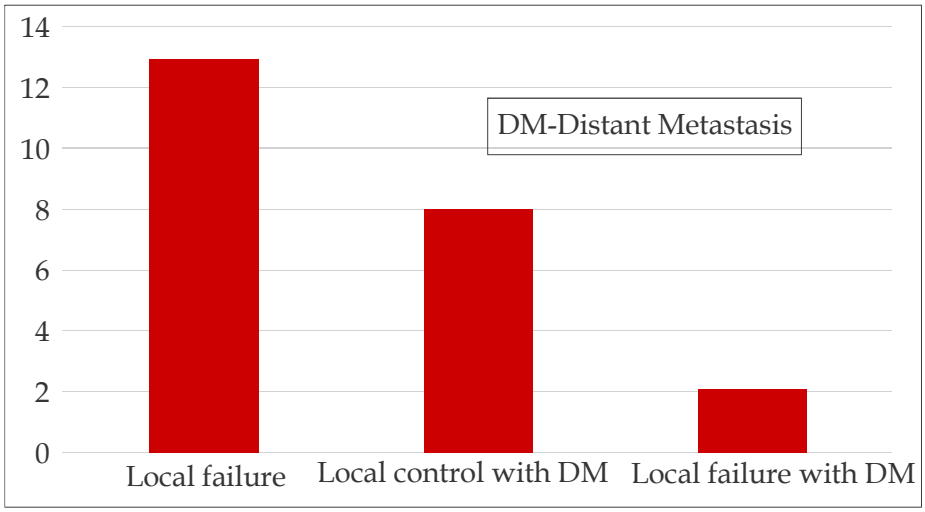

Fig. 5: Pattern of failure

Two patients had pulmonary fibrosis and they were also asymptomatic, and hence were kept on follow up (Fig. 4). None of the patients had trachea-esophageal fistula. Considering the pattern of failure in 46 patients at the time of evaluation (Fig. 5), it was seen that 13 patients (28.26%) showed local failure, 1 patient (2.17%) showed distant failure, 8 patients (17.39%) had distant metastasis and 2 patients (4.35%) had both local failure & distant metastasis.

The 3-year and 5-year overall survival (OS) was 47.83% (22 patients) and 15.22% (7 patients) respectively, with a median survival period of 32 months in this study (Fig. 6). Out of the 33 deaths, 23 were due to the complications related to disease progression (disease specific mortality – 69.7%) and 9 patients died due to other causes with controlled disease (disease non- specific mortality – 27.27%).

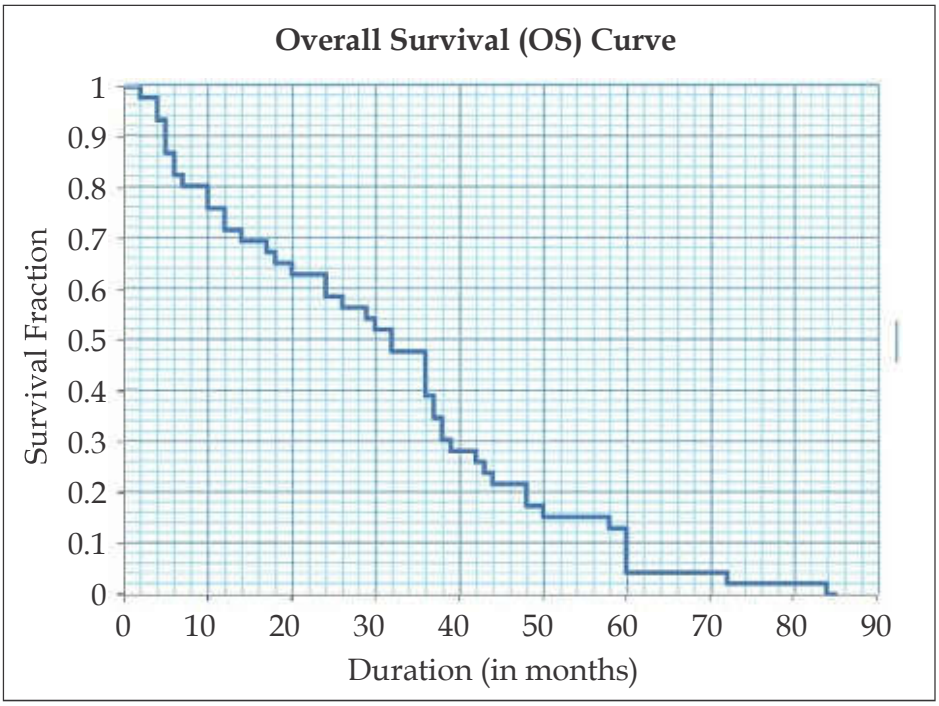

Fig. 6: Overall Survival (OS) Curve

Discussion

Cancer related deaths due to esophageal carcinoma is on increasing trends, it is the 6th leading cause worldwide and 4th in India [14,15]. Historical data suggests only 20% patients present with localized esophageal cancer, indicating that at the time of diagnosis, approximately 80% patients have either locally advanced or distant disease. 90% patients of carcinoma esophagus present with dysphagia as their main complaint leading to nausea, vomiting, cachexia, and ultimately poor quality of life. Majority of patients die due to infiltration of disease into the adjacent organs. The results of the treatment of carcinoma esophagus have been poor in spite of advances in various treatment modalities; hence, the treatment of choice for patients with carcinoma esophagus is controversial. Although surgery continues to be the standard approach for most localized esophageal cancers, cure rates after surgery alone have been poor, with 3- to 5-year survival rates ranging from 6% to 35% [16-18]. Surgery as a sole treatment carries a 2-year survival rate ranging from 35 to 42% & 5-year survival rate of 15 to 24%. As reported historically, EBRT alone carries a 5-year survival rate of 0 to 10%, owing to locoregional persistence or recurrence of the tumour, being as high as 85% [19]. The current trimodality approach, combining chemotherapy, radiation therapy (RT), and surgery, has significantly improved prognosis [20], with several studies showing improved survival rates [21,22]. However, many patients cannot tolerate surgery or decline it; for such individuals, definitive chemo-radiation is the standard approach. Combined modality treatment including radiotherapy and concurrent chemotherapy with Cisplatin and 5-Fluorouracil has lead to a long term survival rate in about 20 to 30% patients compared to surgery alone, but with increased rates of local recurrence of 77% (RT alone) [22]. FFCD 9102 trial [23] (done on 259 locally advanced esophagus cancer patients) suggested similar survival outcomes in 130 patients receiving chemo-radiation alone (2-year survival rate – 34 %) and in 129 patients treated by chemo-radiation followed by surgery (2-year survival rate - 40%) with no benefit for the addition of surgery after chemo- radiation, moreover, compromising the quality of life. Meta-analysis done by Zhu L-L et al. [40] connotes improved overall survival, reduced risk of persistence and recurrence of disease with concurrent chemo-radiotherapy compared to radiotherapy alone. The combination of radiotherapy and chemotherapy has additive effects in terms of local control and overall survival in this select population [18,24-26]. Our study is aimed at determining the 3-year and 5-year survival rates, evaluating the clinical response and observing the late oxicities. In our series, 46 patients with esophageal cancer who received definitive chemo-radiation, showed a median overall survival of 32 months and 63.04%, 47.83%, 15.22% being alive at 2-, 3- and 5-year respectively, and a median disease free survival of 25.5 months and 54.35%, 36.96%, 8.70% as 2-, 3- and 5-year disease free survival rate after diagnosis (Fig. 7).

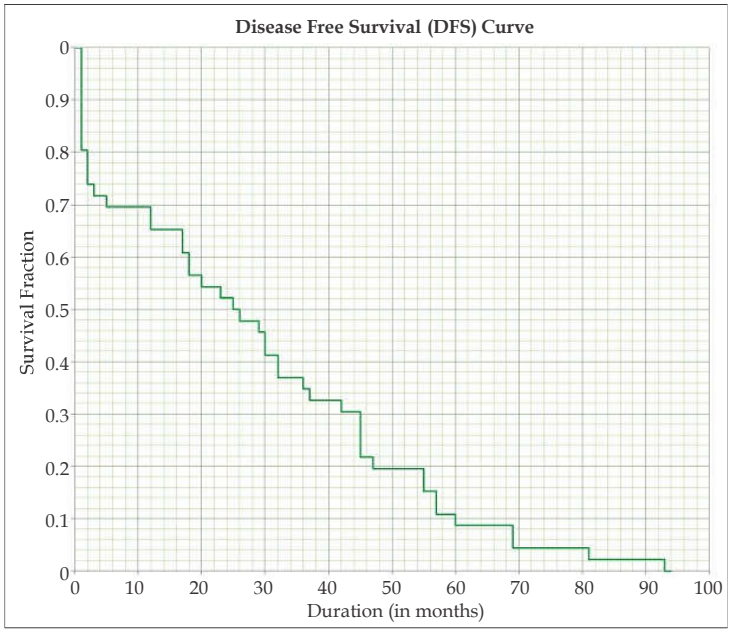

Fig. 7: Disease Free Survival (DFS) Curve

RTOG-85-01 [27] enrolled 129 patients who were treated with concurrent chemo-radiotherapy and only radiotherapy. It was found that the 3-and 5-year survival in the combined arm was 30 and 26% respectively versus in radiation only arm in which the 3-and 5-year survival was 0% each proving combined modality treatment superior to radiation alone. Although combined modality treatment has higher toxicity than radiation only arm. Similarly, ECOG [28] study in which 5FU and Mitomycin-C was used along with radiotherapy, 2 and 5 year survivals were 12% and 7% in radiation alone arm and 27% and 9% in chemo-radiation arm. Patients treated in the chemo- radiation arm had a longer median survival of 14.8 months versus 9.2 months in radiation alone group. Another study by LR Coia et al. [29] in which 90 patients of esophageal cancer were treated with definitive combined chemo-radiation therapy, 3- and 5-year overall survival rate was 29% and 18% respectively. Bhandari[30] treated a total of 31 cases of inoperable cancer esophagus with once weekly Cisplatin 30 mg/ m2 along with radiotherapy (60 Gy in 30 fractions over 6 weeks) on Telecobalt/Linear accelerator and achieved 1 year, 2 year and 3 year overall survival of 80%, 35% and 19%, respectively.

Crosby TD et al. [31] treated 90 patient of esophageal cancer who were inoperable with concurrent chemo-radiation using Cisplatin and 5FU and EBRT (50Gy/25#) and observed a progression free median survival of 18 months. The 2-, 3- and 5-year overall survival rates were 51%, 45% and 26% respectively.

P. Haddad et al. [32] treated 28 patients by two courses of cisplatin and 5-FU chemotherapy with concurrent radiotherapy of 50Gy in 25#. Mean overall survival was 17 months and median survival was not reached. Compared to 283 patients treated by radiotherapy alone with a mean and median survival of 12 and 8 months, chemo radiation was significantly superior. A study done by Smit JK et al. [33] divided 287 patients who surgically unfit or inoperable into two groups. 1st group had 110 patients and they were treated by chemo-radiation the 2nd group had 177 patients and were treated by definitive radiation. They observed that the disease free survival was higher in the group treated with definitive chemo-radiation 16 and 5% at 2 and 5 years.

Bhandari et al. [34] treated 57 patients of carcinoma esophagus, of which 26 patients received sequential chemotherapy (Methotrexate & Cisplatin) followed by radiotherapy and 31 patients underwent concurrent chemoradiotherapy. The study showed a 2-year survival of 38% in sequential therapy setting and 35.5% in concurrent setting, along with a median survival of 19.5 and 18 months, respectively with comparable toxicities.

At least 7 patients in our study developed esophageal stricture out of which 5 patients required dilatation every 6 months, 2 patient developed pleural effusion and underwent pleural tapping, 2 patients developed pulmonary fibrosis, 1 developed pericardial effusion and was asymptomatic as a result of late effect of chemo-radiation. In contrast to a study done by Ito H et al. [35] in Japan after concurrent-chemo-radiation 17 late toxicities of ≥ Grade 3 were observed in 11 patients. Two patients died of late toxicities. Four Grade 3 pericardial effusions and eight Grade 3 pleural effusions and none died of it. In another study done by Ishikura et al. [36], 4 patients suffered benign esophageal strictures and required esophageal dilatation one to three times. 15 patients suffered from benign pleural effusion of grade 2 or more. Pleural effusion after thoracic radiotherapy also has been reported, mainly in Hodgkin's lymphoma [37,38]. The underlying cause of benign pleural effusion after thoracic radiotherapy is thought to be mainly due lymphatic obstruction resulting from mediastinal fibrosis and, in some cases, it may be related to heart disease, such as heart failure and pericardial effusion. There have been many reports of pericardial effusion after thoracic radiotherapy in patients with Hodgkin's lymphoma [39].

Overall 13 (28.89%) out of 45 patients had local failure, 8 (17.78%) had local control with distant metastasis and 2 (4.44%) patients had local failure with distant metastasis post treatment.

In RTOG-85-01 local failure in the form of persistence of disease was 28% in the combined modality arm and 37% in RT only arm [27]. P. Haddad et al. observed 16 (57.14%) out of 28 patients treated with chemo-radiation had recurrences after treatment [32]. TD Crosby et al. noted 21 cases (23%), recurrence after completion of chemo-radiation in 90 patients [31]. This study also shows 29% local failure rate although radiation dose was 66Gy to the primary.

RTOG-85-01 [27] which was a US intergroup trial two cycles of non-concurrent chemotherapy was given after chemo-radiotherapy; only half of the patients were able to tolerate this therapy. In contrast to our study in which Day 1-5 neo-adjuvant chemotherapy was given followed by concurrent chemo-radiotherapy which was tolerated by maximum number of patients. Similar study was done by TDL Crosby et al. [31] in which 4 cycles

of chemotherapy were given put of which 3rd and 4th cycle was given concurrently with radiotherapy and it was well tolerated with maximum number of patients. It is noted that in both studies giving neoadjuvant chemotherapy improved dysphagia to some extent prior to radiation therapy.

Conclusions

Concurrent chemo-radiation is an intensive treatment, in which combined cytotoxic effect of radiation and chemotherapy helps to control the loco-regional disease. In addition to loco-regional disease control, chemotherapy is also effective for distant metastases. There may be some severe acute side effects as seen in the studies quoted which can be managed but decreased late effects are also seen which a positive observation is.

Our study was found to be well tolerated and has given encouraging results in terms of complete and partial response with acceptable toxicities. Role of methotrexate should be further evaluated for better response as achieved in this study.

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Conflicting Interest: NIL

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