Outcomes of treatment of unresectable esophageal carcinoma treated with chemoradiotherapy and oral metronomic chemotherapy: An experience from a rural cancer center

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ABSTRACT

Introduction: Esophageal carcinoma is the eight most common cancer in the world. The management of locally advanced carcinoma esophagus is mainly palliative with chemoradiotherapy. The outcome data of such a modality along with oral metronomic chemotherapy after treatment completion are sparse. Here, we present the outcomes of treatment of locally advanced unresectable esophageal cancer after palliative chemoradiotherapy and oral metronomic therapy from a rural setting in India. **Methods:** Retrospective analysis of all patients of locally advanced unresectable nonmetastatic esophageal carcinoma treated with short course of induction chemotherapy followed by radiotherapy/chemoradiotherapy and oral metronomic chemotherapy was performed. The primary aim was estimation of progression free-survival (PFS) and overall survival (OS). **Results**: A total of 45 patients were analyzed. Mean age was 55 years (30-85 years). A total of 32 patients had tumors in upper and middle esophagus, with the most common histology being squamous cell carcinoma (N-41). The estimated 2 year PFS is 47.2% and the estimated 2 years OS is 57.8%. **Conclusion:** Combined modality therapy with adjuvant oral metronomic therapy shows promising results in the management and should be the basis of further trials.

Key words: *Esophageal cancer, Chamoradiotherapy, Metronomic Chemotherapy*

Esophageal carcinoma is the world's eighth most common cancer. In developing countries, the estimated incidence in 282,000 cases/year, of which 223,000 patients die [1]. The outcome of esophageal cancer is poor, with only 18% of patients surviving at 5 years [2]. The survival depends on the stage. Most of the esophageal cancers are locally advanced at presentation, with stage II and III comprising 80% of cases [3].

In unresectable tumors, the treatment is largely palliative. The commonly used palliative measures are stenting, radiotherapy, chemotherapy, and combined modality chemoradiotherapy. Chemoradiotherapy has shown better survival compared to radiotherapy alone [4,5]. Even with combined modality treatment, the median survival is in the range of 9-12 months in major studies [4]. Severe toxicities occur in 40-50% of cases treated with concurrent chemoradiotherapy. It is the most common cause of stoppage of treatment before completion.

Taxanes have demonstrated significant activity in esophageal cancer. The commonly used taxanes are paclitaxel and docetaxel. Platinum agents such as cisplatin and carboplatin have traditionally being efficacious in esophageal cancers. The combination of paclitaxel with carboplatin is a moderately active and tolerable regimen in advanced esophageal cancer, when used in a 3 weekly regimen [6]. This combination has produced response rates of 60% [7].

In a study by Noronha et al., where metronomic weekly paclitaxel was used, median progression free survival (PFS) was 4.7 months and median overall survival (OS) was 7.5 months [8]. There is no data till now on the outcomes of esophageal cancer from the rural setting. Here, in this study, we analyzed the outcomes of treatment of locally advanced unresectable esophageal cancer from a rural hospital.

MATERIALS AND METHODS

This is a retrospective analysis from the Oncology Department of BKL Walawalkar Hospital, Derwan, Chiplun, Maharashtra, India. Patients with advanced cancer of the esophagus or gastroesophageal junction, both adenocarcinoma and squamous cell carcinoma, who were treated with curative intent, were included in the study. All patients were evaluated at baseline, including history and physical examination, laboratory parameters, upper endoscopy (if indicated), and imaging studies.

The common treatment protocol followed in this hospital is 8 cycles of weekly combination chemotherapy with paclitaxel 80 mg/m^2 intravenous as a 1 h infusion given weekly with standard pre-medications, including antihistamines, antiemetics, H2 antagonists and steroids, along with carboplatin area under curve (AUC) 2 or cisplatin 30 mg/m^2 as a 1 h infusion with standard hydration preceding and following cisplatin. Each dose of chemotherapy was considered one cycle. Similar regimen was used in the chemoradiotherapy setting except that the dose of paclitaxel was reduced to 50 mg/m^2. Complete blood count was checked weekly and patients were evaluated by a physician weekly before chemotherapy. Serum biochemistry (including fasting blood glucose, liver functions, and renal functions) and serum electrolytes were checked once a month. After the completion of radiation, the patients were started on oral metronomic chemotherapy for 18 months that include oral methotrexate at 12.5 mg/m^2 weekly with celecoxib 200 mg twice a day. Follow-up comprised history and physical examination every monthly along with complete blood counts, liver function tests, and chest X-ray. Endoscopy was done when clinically indicated.

Response assessment with contrast-enhanced computerized tomographic scan was performed after 8 weeks. If there was response to chemotherapy in the form of stable disease or partial response (based on response evaluation criteria in solid tumors 1.1), the patients proceeded to concurrent chemo radiation with paclitaxel 50 mg/m^2 and cisplatin 30 mg/m^2 or carboplatin AUC 2. Single agent platinum was used in case of poor tolerance to chemotherapy.

PFS was calculated from the date of receiving the first dose of paclitaxel chemotherapy to the date of radiologic progression, symptomatic deterioration in the absence of progressive disease on scan, start of next line of therapy due to any reason (logistic reasons, financial constraints, or unacceptable toxicity) or death from any cause. OS was calculated from the date of first chemotherapy to the date of death from any cause. Survival analysis was performed by Kaplan–Meier method using SPSS version 20.

RESULTS

Between January 2011 and February 2016, a total of 45 patients for whom survival data were available and were analyzed. The cut-off date for last follow-up was June 2016. Patient details are included in Table 1. All the patients had loco-regionally advanced unresectable esophageal carcinoma with no distant metastasis. Median age was 55 years with a range of 30-85 years. There were 28 females and 17 males. Only 6 patients had hypertension, rest all did not have any comorbidities. The epicenter for the tumor was upper in 13 points, middle in 19 points and lower in 13 points. Adenocarcinoma was present in 4 patients, rest all were squamous cell carcinoma. Node was positive in baseline computed tomography scan in 18.7% of patients. Upfront radiotherapy without neoadjuvant chemotherapy was started in 10 points. Weekly regimen was given in 34 patients; however, rest of the patients received 3 weekly regimen with paclitaxel and platinum. Median radiation therapy (RT) dose delivered was 50 Gy. Median duration of follow-up was 5 months with a range of 1-54 months. The estimated 2 year PFS is 47.2% and the estimated 2 years OS is 57.8%. Results are shown in Tables 1 and 2, and Figures 1a and b.

DISCUSSION

The disappointing rates of survival and local control associated with single-modality therapy and the need for effective nonsurgical management led to the development of definitive chemoradiotherapy paradigms for esophageal cancer. The use of chemoradiotherapy was reported as early as 1968 [9]. In the study by Cooper et al., 5 years of follow-up the OS for combined therapy was 26% (95% confidence interval [CI], 15-37%) compared with 0% following RT. In the succeeding nonrandomized part, combined therapy produced a 5-year OS of 14% (95% CI, 6%-23%). Acute adverse effects were more in combined modality group [10]. In another meta-analysis of chemoradiation, overall response rate (complete remission and partial remission) was 93.4% for concurrent chemoradiotherapy and 83.7% for radiotherapy alone. The relative risk values of 1-, 3-, and 5-year survival rates were 1.14 (95% CI: 1.04-1.24, $p = 0.006$), 1.66 (95% CI: 1.34-2.06, $p < 0.001$), and 2.43 (95%

Table 1: Patient demographics

Total number of patients	45	
Age	Range 30-85 years	Median 55 years
Sex	Male: 17	Female: 28
Comorbidties	Hypertension: 6	
ECOG performance status	1	8
	2	37
Epicenter of tumor	Upper	13
	Middle	19
	Lower	13
Histopathology	SCC	41
	Adenocarcinoma	4
Tumor stage	T2	7
	T3	10
	T4	27
Nodal stage	Node positive	8
Neoadjuvant chemotherapy	Received	35
	Not received	10
Median number of cycles	4	
Median RT dose	50 Gy	

ECOG: Eastern Cooperative Oncologic Group, RT: Radiation therapy

Table 2: Response to NACT

Partial response	29
Stable disease	3
Progressive disease	4
Treatment ongoing	6
Data not available	4

NACT: Neo-adjuvant chemotherapy

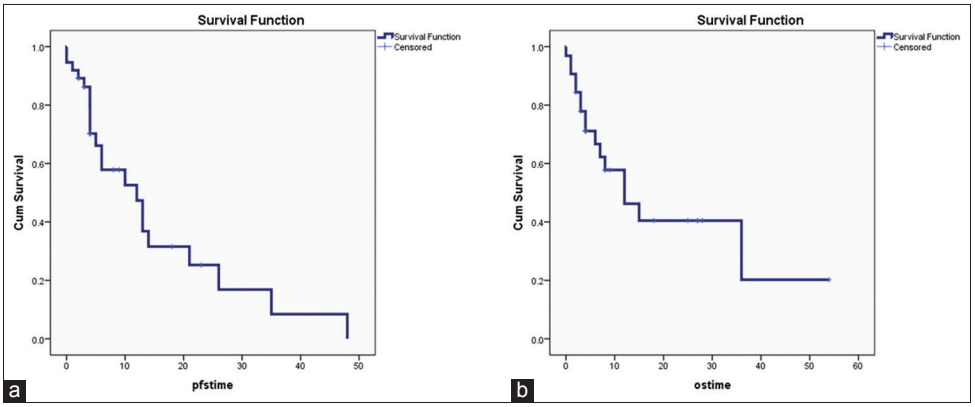

Figure 1: (a and b) Survival graph

CI: 1.63-3.63, p < 0.001), respectively, which proves that combination therapy is better than radiation alone. In our study, the definite treatment was chemoradiotherapy in the majority of patients. A phase II randomized trial was undertaken to clarify the role of chemotherapy before chemoradiation. However, both the arms utilized induction chemotherapy. Both the arms were associated with significant morbidity and did not meet the 1 year survival endpoint of 77.5% [11]. There is a phase III trial currently recruiting patients with locally advanced unresectable tumors, who will be randomized to induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone.

The tumor location in outpatients is consistent with the most common site for esophageal cancers in India, that is, upper and middle third [12]. The most common histology in this region is squamous cell carcinoma. In our study, 90% of patients had squamous cell carcinoma. This is consistent with the feeding habits, smoking prevalence and alcohol usage in the rural areas. A majority of our patients were T3 and T4 disease, which rendered them unresectable at baseline either due to enroachement on surrounding structures or due to their location. Tumors in the upper esophagus are usually not resectable, sometime even in early T-stages. The nodal involvement is less in our patient population. The reasons for this finding are possibly two. First, many of our patients had upper esophageal disease for which they presented to us before nodal involvement, due to the location of the tumor which made them symptomatic earlier. Second, due to financial constraints and logistic issues, we could not do positron emission tomography scan or endoscopic ultrasound for assessment of nodal status, which is the standard diagnostic modality. The usage of the above may nave nodally upstages many of our patients. The majority of our patients were started on induction chemotherapy as a part of the departmental protocol. However, 10 patients were deemed unfit for chemotherapy. Hence, chemo radiation alone was given to them. The survival in our study is comparable to the other publications of similar patients. This underlies the fact that with proper supportive care, standard management is possible in rural cancer centers. There is accumulating data on the use of low dose non-toxic metronomic chemotherapy after primary disease control as an adjuvant. As shown by Patil et al., metronomic chemotherapy has a promising role in oral cancers [13]. There is not much data for esophageal cancer. Our study can for the basis of further research into the role of adjuvant metronomic in these patients. A large proportion of our patients were lost to follow-up, so they could not be used in the survival analysis. A major reason is severe financial and logistic constrains. Most of the patients are elderly, and there is a lack motivation from the family members to continue treatment. The occurrence of toxicity with slow symptom control and the lack of awareness about the disease outcomes are one of the causes.

CONCLUSION

Locally advanced unresectable esophageal cancer remains as one of the most fatal malignancy. Combined modality has proven benefit in palliation of symptoms. This treatment is possible in the rural setting, in a measure to debulk the tertiary cancer centers.

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