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Research Article

Patterns of Treatment and Outcome in Patients with Unresectable or Inoperable Esophageal Cancer: A Real-World Data

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ABSTRACT

Background: Esophageal cancer is the eighth most common cancer in the world with high morality. Our study provides real world data on patterns of treatment and outcome in patients with unresectable or inoperable esophageal cancer.

Materials and Methods: This is a retrospective analysis of all consecutive esophageal cancer patients treated with radical radiotherapy at a tertiary cancer center from January 2016 to December 2017. Data regarding patients' age, histology, location, pre-treatment imaging, disease stage, treatment details, compliance and response to treatment and status at last follow-up were retrieved from their file. Continuous and categorical variables were summarized by descriptive statistics.

Results: A total of 100 patients, mean age of 60.24 years, were included in the study. 60% of the patients were male and upper one-third was the most common site involved. Squamous cell carcinoma was reported in 83% of the patients. About 70% of the patients had a T3/T4 disease, 44% also had nodal metastasis. Radiation dose ranged from 45Gy – 63Gy. 15% and 54% of the patients received neoadjuvant and concurrent chemotherapy respectively. With a median follow-up of 7 months (range 3-58 months), 80% of the patients were alive with 32.22% having no evidence of disease. Univariate analyses showed no significant predictor of loco-regional control. Distant metastases and loco regional failure were seen in 32.22% and 28% of the patients respectively.

Conclusion: Our study showed that esophageal cancer is more common in elderly males. Both distant metastases and loco regional failure continues to be a matter of concern.

Introduction

Esophageal cancer is the eighth most common cancer in the world, with an estimated 604,100 new cases and the sixth leading cause of cancer-related mortality in the world with 544,076 deaths reported as per GLOBOCON 2020 [1]. However, there is a large geographic variation in its epidemiology, with the age-standardized incidence rate of esophageal cancer being 18.2/lakh and 9.4/lakh in Eastern Asia and Southern Africa respectively and only 1.5/lakh in Central America and Western Africa [2]. With an incidence of 63,180 cases in 2020, it is the most common gastro-intestinal cancer in India [3]. The two most common types of esophageal cancer are squamous cell carcinoma and adenocarcinoma, both having different etiologies, biological characteristics and geographic distributions [4]. Overall, esophageal carcinoma is associated with poor survival, and a mortality rate (5.6/100 000) close to the incidence rate (6.3/100 000) [2]. The incidence and mortality of esophageal cancer are higher in developing countries compared to developed countries because of poor lifestyle, lack of adequate infrastructure for early cancer diagnosis, and limited access to standard cancer care for the general population [5, 6]. Patients in these countries usually present with an advanced disease resulting in a 5-year survival rate of only 15% to 25% [7, 8].

Surgery is the treatment of choice for esophageal cancers and radiotherapy is used as an alternative local treatment for cases not amenable to surgery, but the outcome is unsatisfactory due to poor local control and distant metastasis [9, 10]. The addition of chemotherapy to radiotherapy is synergistic as it not only enhances the local effects of

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radiation, but it also eliminates micro metastases and thus decreases distant metastasis [11]. Based on the landmark Radiation Therapy Oncology Group trial 85-01, which showed that the use of Cisplatin, 5-FU and concurrent radiation in esophageal cancer resulted in a 5-year survival rate of 26%, concurrent chemo radiotherapy has been used as the standard treatment for unresectable locally advanced esophageal cancer [12]. To further improve up on the survival rates, different chemotherapy and targeted therapy agents have been tried in combination with radiotherapy in various phase II and III trials [13].

As a result, there are a number of treatment options available for the non-surgical treatment of esophageal cancer. Patients especially those from low socio-economic strata present with long standing dysphagia resulting in weight loss and poor general condition, which preclude them from receiving the standard protocol of chemo radiotherapy. Besides, there are limited data regarding real-world clinical practice in the field of esophageal cancer from our part of the world. So, we conducted this study with an aim to provide real world data on treatment and outcome in patients with esophageal cancer.

Materials and Methods

I Study Population

A total of 128 patients of esophageal cancer who were treated in the department of Radiotherapy, Mahavir Cancer Sansthan, Patna from 1st January 2016 to 31st December 2017 were evaluated for this study. Given the retrospective nature of the study, approval from the Institutional Ethics Committee was not required as a part of our institutional protocol, and the need for obtaining written informed consent was also waived. The inclusion criteria included patients with histologically confirmed unresectable or inoperable esophageal squamous cell carcinoma or adenocarcinoma who underwent radiotherapy or concurrent chemo radiotherapy with a radical intent. Patients were defined as unresectable when they had T4 disease, extensive and bulky nodes or high cervical localization. Inoperable cases were patients who were either medically unfit or refused surgery. Patients were excluded from the study if they had metastatic disease, poor performance status which precluded radical treatment and those with other histology (Figure 1).

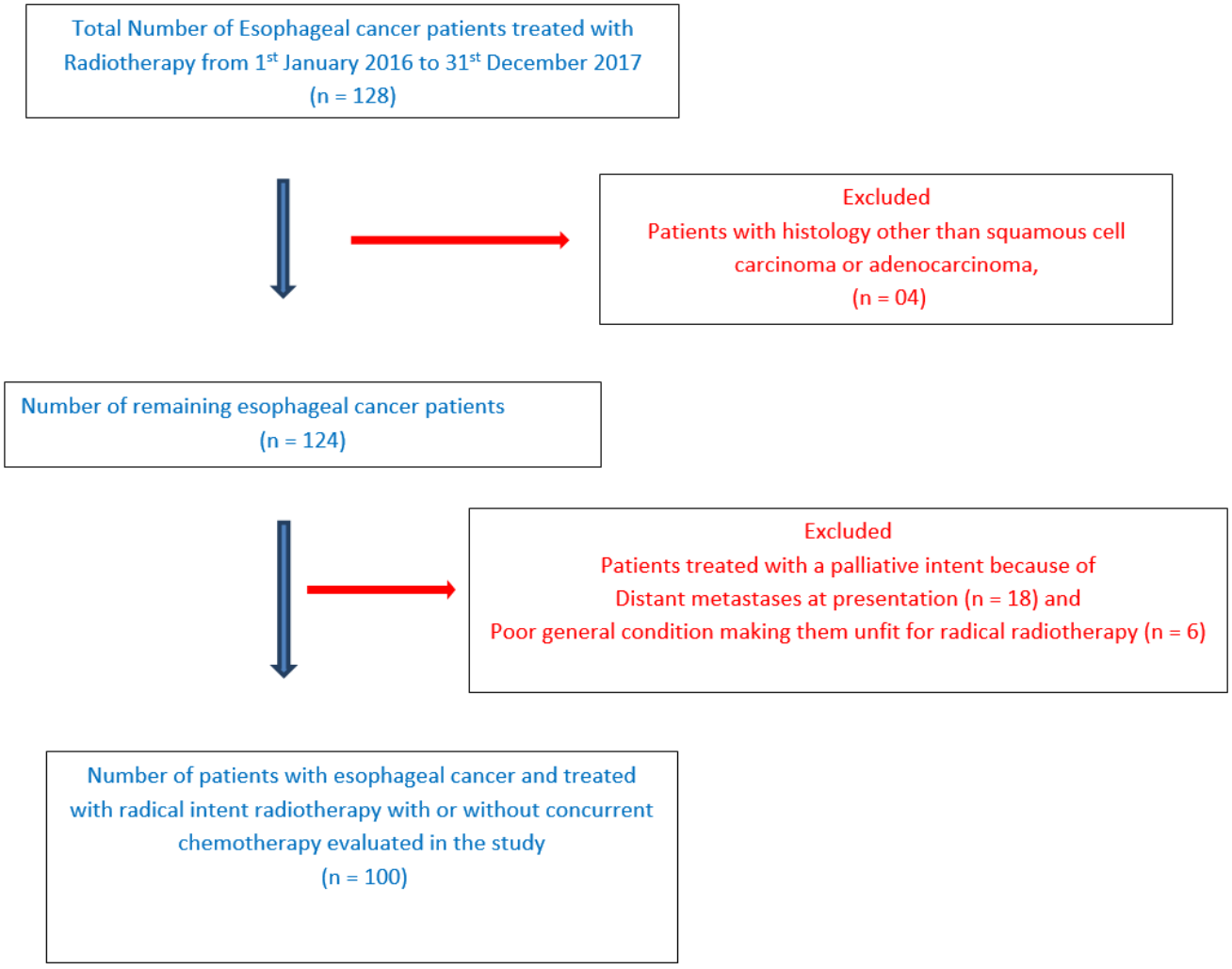

Figure 1: Flowchart.

II Data Collection

Data regarding patients' age, histology, location, pre-treatment imaging, stage, treatment, compliance, response and status at last follow-up were retrieved from their file. The histological subtypes and grades were assigned as per WHO classification. Anatomical location was defined as upper-third (15–25 cm from the incisors), middle-third (>25–30 cm), and lower-third cancer (>30 cm). The cancer stage was defined according to the 7th edition of American Joint Committee on Cancer (AJCC) TNM staging system. The staging was based on findings from barium swallow, endoscopy, chest x-ray, ultrasonography of abdomen, computed tomography, and positron emission tomography, as available. Radiotherapy was delivered on linear accelerators using three-dimensional conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) technique as per RTOG guidelines. Radiotherapy was given to a dose of 50.4Gy/28# to 63 Gy/35# @ 1.8 Gy per fraction for 5.5 to 7 weeks. Concurrent weekly chemotherapy consisted of either single agent Cisplatin (40mg/m^2) or a combination of paclitaxel (50 mg/m2) and carboplatin (AUC 2) for five to seven cycles.

III Follow-up

After treatment completion, patients were evaluated at 6 to 8 weeks for the first follow-up, then at 3-month intervals for 1st year, then every 6 months up to 3rd year. A detailed clinical and physical evaluation was done on every follow-up. CECT scans were advised every 6 months for 3 years and annually thereafter. Other studies, such as endoscopy and PET scan, were done as clinically indicated.

IV Treatment Response

Patients with no clinical evidence of disease and normal imaging at their last follow-up or 3 years after their diagnosis were classified as loco regionally controlled (LRC). Patients who had persistent or worsening of symptoms and showed disease on imaging and/or endoscopy at first follow-up were classified as having residual disease (RES). Patients having an initial complete response to treatment but developing recurrence at the site of the primary tumor and/or at the site or regional lymph nodes was classified as loco regional failure (LRF). Histological confirmation was done whenever feasible and in all cases with suspicious finding on CECT, PET-CT or endoscopic examination. Patients showing metastases to non-regional lymph nodes, distant organs with or without loco regional disease were classified as distant metastases (DM).

V Statistical Analysis

All the relevant data was entered in Microsoft excel sheet. The disease status of the patients was entered until death, local recurrence, or their last follow up. Continuous and categorical variables were summarized by descriptive statistics. Continuous data was analysed in terms of range, mean with standard deviation and median with inter quartile range. Categorical data was expressed in percentage for comparison. Univariate and multivariate analyses were done using Medcalc and Graph Pad Prism 9.0 software. A p-value less than 0.05 were considered significant.

Results

A total of 100 esophageal cancer patients were included in the study. The mean age of the patient was 60.24 ± 11.45 year (range 29 – 85yrs). Sixty percent of the patients were male with a male to female ratio of 1.5:1. Upper one-third of esophagus was the most common site affected followed by lower and middle third in 40%, 36% and 24% of the cases respectively. Squamous cell carcinoma was the predominant histology, reported in 83% of cases with adenocarcinoma in remaining 17%.

Pre-treatment imaging consisted of CECT scan in 59% and PET-CT in 17% of the patients. T and N staging was available for 76% of these patients with 69% showing T3/4 and 7% had T1/2 stage. Further, 44% of the patients had nodal metastasis on imaging (Table 1).

Table 1: Showing baseline characteristics of the patient cohort.

Parameter	Number (%)
Age	
Range	29 – 85 years
Mean ± S.D	60.24 ± 11.45
Median (IQR)	62 (18)
Sex	
Male	60 (60%)
Female	40 (40%)
Ratio	1:5
Site	
Upper	40 (40%)
Middle	24 (24%)
Lower	36 (36%)
Histology	
Squamous cell carcinoma	83 (83%)
Adenocarcinoma	17 (17%)
Grade	
1	26 (26%)
2	54 (54%)
3	11 (11%)
Unknown	9 (9%)
Imaging	
CECT	59 (59%)
PET-CT	17 (17%)
Others	24 (24%)
T status	
T1-2	7 (7%)
T3-4	69 (69%)
Unknown	24 (24%)
N status	
N0	32 (32%)
N+	44 (44%)
Unknown	24 (24%)

CECT: Contrast Enhanced Computed Tomography; PET-CT: Positron Emission Tomography.

Regarding treatment, 15% of the patients received Neoadjuvant chemotherapy before radiotherapy. The most common regimen used was 3 weekly Paclitaxel and Carboplatin (PC) followed by 5-FU with

Cisplatin and 5-FU, Docetaxel and Cisplatin (DCF) in 11, 3 and 1 patient respectively. Fifty four percent of the patients received concurrent chemotherapy with radiation. The most common drug used was weekly Cisplatin in 33%, followed by weekly Paclitaxel and Carboplatin in 21% of the patients. 76% of patients received radiation by 3DCRT technique and remaining 24% by IMRT technique. The radiation dose ranged from 45Gy to 63Gy, with a median dose of 59.4Gy. 90% of the patients completed their planned radiotherapy protocol, while 10% defaulted during radiation because of toxicities, worsening of symptoms or personal reasons (Table 2).

Table 2: Showing treatment pattern and compliance of the patient cohort.

Parameter	Number (%) (N = 100)
Neoadjuvant Chemotherapy	15 (15%)
Paclitaxel + Carboplatin	11 (11%)
Others	04 (4%)
Concurrent Chemotherapy	54 (54%)
Cisplatin	33 (33%)
Paclitaxel + Carboplatin	21 (21%)
Radiation Technique	
3DCRT	76 (76%)
IMRT	24 (24%)
Radiation Dose	
Range	45 – 63Gy
Mean ± S.D	57.84 ±5.72
Median (IQR)	59.4Gy (10.8)
50.4Gy	25 (25%)
> 50.4Gy	75 (75%)
Treatment Compliance	
Completed	90 (90%)
Defaulted	10 (10%)

3DCRT: 3-Dimensional Conformal Radiotherapy Technique; IMRT: Intensity Modulated Radiotherapy Technique.

Among 90 patients who completed their planned radiotherapy, 5 patients had no follow-up. After a mean follow up of 10.98 months (range 3 -58 months, median FU 7 months), a total of 72 patients (80%) were alive with 29 (32.22%) of them having no evidence of disease. A univariate analysis of variables showed no significant predictors of loco-regional control (Table 3). Results of the multiple linear regression showed ($F(1, 83) = 2.33$, $p = .131$, $R2 = 0.03$, $R2adj = 0.02$) indicating that there was a very weak collective non-significant effect of age, gender, site, histology, technique and dose of radiation and loco-regional control in our patients.

Table 3: Univariate analysis for variables associated with loco-regional control.

Parameters	Number	LRC		Univariate Analysis	
	(N= 85)	YES (N=29)	NO (N=56)	Odd's ratio (95% CI)	p-value
Age (years)					
≤ 65	55 (64.70%)	20 (36.36%)	35 (63.63%)	Reference	
> 65	30 (35.29%)	9 (30%)	21 (70%)	0.75 (0.288 to 1.948)	0.554
Sex					
Male	53 (62.35%)	20 (37.73%)	33 (62.26%)	Reference	
Female	32 (37.64%)	9 (28.12%)	23 (71.87%)	0.64 (0.249 to 1.669)	0.366
Technique					
3DCRT	65 (76.47%)	21 (32.30%)	44 (67.69%)	Reference	
IMRT	20 (23.52%)	8 (40%)	12 (60%)	1.39 (0.496 to 3.931)	0.526
Site					
Upper	34 (40%)	14 (41.17%)	20 (58.82%)	Reference	

Middle	19 (22.35%)	7 (36.84%)	12 (63.15%)	0.83 (0.262 to 2.646)	0.757
Lower	32 (37.64%)	8 (25%)	24 (75%)	0.47 (0.166 to 1.363)	0.166
Histology					
Squamous cell carcinoma	68 (80%)	25 (36.76%)	43	Reference	
Adenocarcinoma	17 (20%)	4 (23.52%)	13	0.52 (0.155 to 1.800)	0.308
Imaging					
CECT	43 (50.58%)	15 (34.88%)	28	Reference	
PET	9 (10.58%)	4 (44.44%)	5	1.49 (0.347 to 6.409)	0.589
Others	33 (38.82%)	10 (30.30%)	23	0.81 (0.307 to 2.144)	0.673
T status					
T1-2	4 (4.70%)	3 (75%)	1 (25%)	Reference	
T3-4	51(60%)	18 (35.29%)	33 (64.70%)	0.18 (0.017 to 1.878)	0.152
Unknown	30 (35.29%)	8 (26.66%)	22 (73.33%)	0.12 (0.011 to 1.340)	0.085
N status					
N0	24 (28.23%)	7 (29.16%)	17 (70.83%)	Reference	
N+	29 (34.11%)	11 (37.93%)	18 (62.06%)	1.48 (0.466 to 4.717)	0.503
Unknown	32 (37.64%)	11 (34.37%)	21 (65.65%)	1.27 (0.405 to 3.990)	0.679
Chemotherapy					
NACT	12 (14.11%)	3 (25%)	9 (75%)	Reference	
Con. Cisplatin	33 (38.82%)	11 (33.33%)	22 (66.66%)	1.50 (0.336 to 6.680)	0.594
Con Cisplatin & Taxane	19 (22.35%)	5 (26.31%)	14 (73.68%)	1.07 (0.204 to 5.625)	0.935
Radiation Dose					
50.4Gy	20 (23.52%)	5 (25%)	15 (75%)	Reference	
> 50.4Gy	65 (76.47%)	24 (36.92%)	41 (63.07%)	1.75 (0.567 to 5.439)	0.329

3DCRT: 3-Dimensional Conformal Radiotherapy Technique; IMRT: Intensity Modulated Radiotherapy Technique; NACT: Neoadjuvant Chemotherapy.

Loco-regional failure was seen in 19 (21.11%) patients, while 5 (5.55%) of them had a residual disease. Further, 19 (21.11%) of the patients were alive but with distant metastases. Out of 13 (14.44%) patients who had died, 10 (11.11%) had distant metastases, 2 (2.22%) had complications and 1(1.11%) had a loco regional failure with tracheo-esophageal fistula (Table 4).

Table 4: Showing treatment outcome of the patient cohort.

Parameter	**Number (%) (N = 90)**
No Follow-up	5 (5.55%)
Disease status	
LRC	29 (32.22%)
RES	5 (5.55%)
LRF	19 (21.11%)

DM	19 (21.11%)
Dead	13 (14.44%)
LRF	1 (1.11%)
DM	10 (11.11%)
Complications	2 (2.22%)

LFU: Last Follow-Up; LRC: Loco Regionally Controlled; RES: Residual disease; LRF: Loco Regional Failure; DM: Distant Metastases.

A subset analysis of patients with distant metastases showed liver to be the most common site of metastases followed by lung, bone, brain, and non-regional lymph nodes in 10(11.11%), 8(8.88%), 7 (7.77%), 2(2.22%), 2(2.22%) patients respectively. One patient had bilateral ovarian metastases, and another showed multiple metastatic subcutaneous nodules over upper back. Three patients with lung metastases also had pleural effusion. One patient had both liver and lung metastases, whereas the patient with ovarian metastases had bone metastases (Table 5).

Table 5: Showing sites of distant metastases of the patient cohort.

Site	Number (%) (N = 90)
Liver	10 (11.11%)
Lung	8 (8.88%)
Bone	7 (7.77%)
Brain	2 (2.22%)
Supra clavicular lymph node	2 (2.22%)
Ovary	1 (1.11%)
Sub cutaneous nodules	1 (1.11%)

Discussion

In this study, we retrospectively analysed the clinical characteristics, treatment and outcome in patients with unresectable or inoperable esophageal cancer. The mean age of our patient cohort was 60.24 years with a male to female ratio of 1.5:1. Population based data reveal esophageal cancer to be a disease of the elderly with the peak of incidence in the sixth decade of life [14]. The mean age of patients suffering from esophageal cancer in Asian countries has been reported to be in range of 51–60 years [15]. Further, esophageal carcinoma has a predilection towards males, affecting males 2-4 times more frequently as compared to females worldwide [16]. Chokshi *et al*. in their analysis of esophageal cancer in India reported a mean age of 54.83 years (range 25–89 years) with a male to female ratio of 1.67:1 [17]. Another study from north-west India showed a mean age of 54.1 years and a male to female ratio of 1.15:1 [15]. The reason for higher prevalence in females in India than that reported in studies from Western population needs to be identified. A study from Punjab found poor nourishment and consumption of hot beverages to be linked to SCC carcinogenesis among female patients [18].

Our study showed upper esophagus as the most common site. This finding is in contrast with that of other study from western India where the most common location was mid esophagus [17]. However, a recent study from eastern India reported upper esophagus to be the most common site seen in 47.2% of the patients [19]. Similar to our finding, various Indian studies have reported Squamous cell carcinoma to be present in about 80% of all cases of esophageal cancer [20].

CECT scan was the most common imaging used in our patients. Only 17% underwent PET-CT and none had endoscopic ultrasound (EUS) as a pre-treatment staging modality. EUS helps to delineate the layers of esophagus and is considered superior to CECT scan in regard to loco regional staging of cancer [21]. However, EUS has its own limitations and may not be feasible in obstructive growths [22]. In the Indian setting, because of the advanced nature of disease at presentation and limited availability, the routine use of EUS is debatable [20]. Positron emission tomography provides additional staging information, especially when combined with a CT and is the best modality for detecting distant metastasis [23]. A recent study from TMH, Mumbai, evaluating the role of PET-CT in esophageal cancer patients reported detection of unsuspected metastatic disease in 16% patients [24]. However, the cost, availability, and the high false-positive rate due to infections such as tuberculosis are the practical difficulties in routine use of PET-CT in most cancer centers of our country [25]. Therefore, a CECT scan of the thorax and upper abdomen is widely accepted as the preferred modality of staging for cancer of the esophagus in the Indian setting.

In our study, concurrent chemoradiotherapy was the most common treatment modality used. Definitive concurrent chemoradiotherapy has been recommended as the standard non- surgical treatment for patients with esophageal cancer. Based on the landmark RTOG 85-01 trial, Cisplatin and 5-FU along with radiation has remained the standard protocol for years. The above trial reported a 5-year survival rate of only 26% with a median survival of 14 months and grade 3–4 adverse reactions in 46% of the patients. Besides, this protocol uses continuous infusion of 5-FU for 4 days which requires admission causing logistic issues for the patients [12]. To further improve on the results and decrease the toxicities several chemotherapy combinations have been used concurrently with radiation therapy. These include trials combining radiation with paclitaxel and cisplatin, 5-FU and oxaliplatin, irinotecan and cisplatin, docetaxel cisplatin and 5-fluorouracil, Cisplatin and capecitabine, cetuximab with cisplatin and capecitabine [26-31]. The CROSS trial used a novel regimen of weekly paclitaxel and carboplatin

concurrently with RT as a neo-adjuvant therapy followed by surgery and reported an unprecedented median overall survival of over 4 years [32]. Since then, several oncologists have successfully explored the use of this regimen in the definitive chemo radiation. A study by Noronha *et al.* in Indian patients showed that concurrent chemo radiotherapy with weekly paclitaxel and carboplatin is well tolerated in Indian patients [33].

In our study, about one-third of the patients received radiation with concurrent single agent cisplatin. Use of weekly Cisplatin as radiosensitizer is a well-established drug incorporating concurrent chemotherapy in radical treatment of squamous cell carcinoma of cervix and head and neck cancers [34, 35]. Because of the ease of administration and better treatment compliance, weekly Cisplatin has also been used in definitive chemo radiation for esophageal cancer patients [36]. Ahmed *et al.* reported a median OS of 15.2 months and 2-year OS of 42.6% in esophageal cancer patients treated with concurrent weekly cisplatin and radiation which was similar to that reported in the FFCD 9102 and Cisplatin-5 FU arm of Prodige5/Accord17 [27, 37-38]. The study using single agent cisplatin also had a lower incidence of grade 3 or higher toxicities and all were hematological. Li *et al.* in their multicenter retrospective analysis comparing the therapeutic effects of single-agent and double-agent concurrent chemo radiotherapy in patients with unresectable esophageal squamous cell carcinoma suggested that single therapy is not inferior to dual therapy especially in the elderly patients [39].

Another protocol used to improve on the survival of esophageal cancer patients is neo adjuvant chemotherapy before starting chemoradiation. The underlying rationale is to reduce the bulk of primary tumor and control distant micro metastases. Induction with DCF followed by concurrent chemoradiation using carboplatin has been reported to have a CR rate of 16 % and median OS of 10.8 months in a trial by Chiarion-Sileni *et al* [40]. The phase II COSMOS trial conducted by Yokota *et al.* combining induction chemotherapy using DCF followed by radical CRT, and conversion surgery, when feasible, reported promising results with a 3-year OS of 46.6% at a median follow-up of 39.3 months in locally advanced unresectable esophageal cancer [41]. Based on this result, the JCOG has started a phase III trial (JCOG1510) investigating the efficacy of induction chemotherapy using DCF followed by conversion surgery and/or radical CRT in patients with locally advanced unresectable esophageal cancer [42]. Though efficient, DCF protocol has been associated with considerable toxicities. Further, neoadjuvant treatment with carboplatin and paclitaxel-based chemotherapy produced a 27.9% pathologic complete response rate in patients with resectable esophageal cancer, according to results of the NEOSCOPE trial [43]. Most of the patients in our study received Paclitaxel and Caboplatin in the neo adjuvant setting keeping in view good response to doublet chemotherapy and a higher toxicity and cost associated with the triplet regimen.

However, till date the long-term results of definitive chemo radiation with or without induction chemotherapy show poor survival and multiple new treatment strategies are being tried. As a result, the standard practice of concurrent chemo radiation in carcinoma esophagus varies substantially throughout the world and even in our country. Besides, a considerable number of patients undergo a single modality of treatment as seen in our study because of the fear that multimodality treatment may not be tolerated by the generally frail patients with esophageal cancer and also because of their advanced age at diagnosis with inadequate nutritional support. Similar to our study, a meta-analysis by Zhu *et al.* of concurrent chemo radiotherapy for advanced esophageal cancer showed that 46% of the patients received only radiotherapy. The overall response rate was 93.4% for concurrent chemo radiotherapy and 83.7% for radiotherapy alone (P= 0.05). However, CCRT arm showed a better 3-year and 5-year survival with an increased incidence of acute toxicities [9].

Another important issue in the non-surgical treatment of esophageal cancer is the dose of radiotherapy. On the basis of results from RTOG 94–05, 50.4Gy has been accepted as standard dose in western countries and also recommended by NCCN guideline in both neo-adjuvant and radical setting [44, 45]. Based on the theory of radiation biology, 50.4Gy is inadequate to control a gross tumor lesion and a dose of 60Gy to 100Gy is required to control and cure a gross solid tumor [46]. Further, with the clinical application of more precise radiation techniques such as IMRT, interpretation about the results of RTOG 94–05 should be different. A pooled analysis from Song *et al.* showed that a higher radiation dose could improve clinical outcomes without significantly increasing radiation-related toxicities [47]. On this basis, a radiation dose of 60 to 66Gy is used in many Asian countries including Japan [48]. In our study, 25% of the patients received a radiation dose of 50.4Gy and remaining 75% received radiation dose more than 50.4Gy with a median dose of 59.4Gy. A radiation dose of more than 50.4Gy was well tolerated as 90% of our patients completed the planned radiation protocol. Another reason for the use of high median dose of radiation in our study was the large number of patients with upper esophageal cancer. It is believed that the biological behaviour of upper esophageal cancer differs from those at the mid and lower esophagus, because they are mostly squamous-cell histology with local invasiveness and less prone to distant metastasis, and that they should be treated like head and neck cancer. Wang *et al.* analysed the treatment and outcome of patients with cervical and upper thoracic esophageal cancer and found that radiation dose was the only independent factor associated with improved local control and overall survival. They concluded that OS and DFS were significantly higher in patients who had received a radiation dose of greater than or equal to 50Gy than in those who had received a dose of less than 50Gy [49].

The survival rate of 32.22% at the end of 3 years seen in our study is similar to that reported in literature. Various studies have shown a 3-year survival rate of 20% to 45% in esophageal cancer treated with concurrent chemo radiation [13]. An Indian study on clinical outcome in definitive concurrent chemo radiation with weekly paclitaxel and carboplatin for locally advanced esophageal cancer reported 1-year, 2-year, and 3-year survivals of 70%, 47%, and 39%, respectively [33]. Our study showed distant metastases as the most common site of failure followed closely by loco regional recurrence. This is in contrast to most of the studies which have shown loco regional failure as the most common site of treatment failure [50]. This could be because of the fact that baseline PET-CT and CECT scan was available in only 17% and 59% of patients respectively. So, there are chances that asymptomatic distant metastases present at the time of diagnosis were missed. Another reason could be the use of chemotherapy either in neo-adjuvant or concurrent form in only 56% of our patients. Liver was the most common site of distant

metastases seen in our study followed by lung, bone and brain. The pattern reported is similar to that seen in the study by Wu *et al*. analysing pattern of distant metastases in patients with de novo stage IV esophageal cancer at diagnosis identified using the Surveillance, Epidemiology, and End Results database [51].

Before we conclude, it is important to describe the limitations of this study. Being a retrospective analysis, only documented details were available for evaluation. Being a single center study, the sample size was small and heterogeneous. Because of non-availability of PET-CT scan and even CECT scan in few patients, the staging was inadequate in few patients. The patients were treated with a varied combination of chemotherapy and radiation dose. The heterogeneous study population resulted in small sample size for univariate and multivariate subset analyses for any significant predictive factor of loco regional control in esophageal cancer patients treated with radiation with or without chemotherapy. Nonetheless, this real-world data will surely bring forward the issues and outcomes of esophageal cancer patients treated outside clinical trials and may help in designing new studies.

Conclusion

The study showed that squamous cell carcinoma remains the predominant histology in our population with upper esophagus as the most common location. Esophageal cancer continues to be a disease of the elderly. Inadequate nutritional support and presence of co morbidities remains a hindrance for a uniform treatment protocol using concurrent chemo radiation. Both distant metastases and loco regional failure continues to be a matter of concern. Routine use of new imaging modalities like PET-CT scan must be done for adequate staging of these patients to rule out distant metastases at the time of diagnosis. Further improvement in local control must be evaluated by either radiation dose escalation or novel combinations with chemotherapy and immunotherapy in large, multi-centric trial settings.

Ethical Approval

Given the retrospective nature of the study, approval from the Institutional Ethics Committee was not required as a part of institutional protocol of Mahavir Cancer Sansthan, Patna.

Informed Consent

The need for obtaining written informed consent was waived.

Conflicts of Interest

None.

Funding

None.

Author Contributions

RC conceptualized and designed the study and contributed to data collection, data analysis and drafted the original manuscript. VT contributed to data analysis, review and editing the manuscript. RR and US contributed to manuscript editing and revisions.

Data Availability

All data generated or analysed during this study are included in this article.

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