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Clinical Profile, Response to Treatment, and Treatment Toxicities in Patients with Esophageal Cancer at A Tertiary Care Center in Northern India – A Prospective Study

Dr. Nilesh Dhamne[1], Dr. Ashok Vaid[1], Dr Jyoti Wadhwa[1], Dr.Neelam Sharma[1], Dr. Arjun Singh Chib[1], Dr. Shivam Shingla[1], Dr. Bhuvan Chugh[1], Dr. Kiran Tamkhane[1]

1. Department of Medical Oncology, Medanta, the medicity, Gurgaon, Haryana.

Corresponding Author: Dr. Nilesh Dhamne, Department of Medical Oncology, Medanta, the medicity, Gurgaon, Haryana.

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Introduction

Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer mortality in the world.1 In 2020, an estimated 604000 new esophageal cancer cases were diagnosed and 544000 related deaths occurred globally.2 The incidence of esophageal cancer in India is moderately high; According to a data from cancer registries in India, esophageal cancer is the second most common cancer among males and the fourth most common cancer among females.3 There are two major histological types of esophageal cancer, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma dominates globally.4 Incidence rates for adenocarcinoma of the esophagus have been increasing dramatically in several Western countries. Established risk factors for esophageal adenocarcinoma are gastroesophageal reflux symptoms5, obesity6 and tobacco smoking6, while squamous cell carcinoma is mainly associated with tobacco smoking and excessive alcohol intake.7,8 Most esophageal adenocarcinomas arise from a region of Barrett's metaplasia, which is due to gastroesophageal reflux disease (GERD). Other risk factors implicated in carcinoma esophagus are low socio-economic status, diet poor in fruits and nutrition, and tylosis. Epidemiological studies are limited in this malignancy. With this idea, we have conducted a prospective observational study to identify clinical demographics, chemotherapy response and genomic details in patients with carcinoma esophagus at a tertiary care hospital in India.

Material and Methods

The study was carried out at a tertiary care centre - Medanta, the Medicity. Sixty four patients of histologically confirmed newly diagnosed, esophageal cancer who had presented to department of Medical Oncology, Medanta, the Medicity were included in our study. Prospective, Observational study was conducted over a period of 18 months. This was an institute-based study and the available data was collected.

The patients with biopsy proven, newly diagnosed, esophageal and gastro-esophageal junction cancer with age > 18 years were included in the study. Patients who had already taken treatment for esophageal cancer, or having concomitant malignancy, history of previous malignancy were excluded.

Patient’s relevant history was taken along with other required parameters, risk factors, and significant comorbidities etc. They were further evaluated with relevant imaging study and their diagnosis confirmed with biopsy. Histological confirmation via biopsy of the primary neoplasm was preferable, however if

unfeasible, histological confirmation of the metastatic lesion was mandatory before initiation of definitive therapy. Immunohistochemistry markers were applied as per standard practice guidelines. Staging procedures included endoscopic ultrasound (EUS), imaging studies in the form of whole-body Positron Emission Tomography (PET) CECT scan or computerized tomography (CT) of the chest and abdomen. Other tests for functional assessment included complete blood counts, liver function tests, renal function tests, and 2D echocardiogram (Detailed information in data collection form).

The demographic information and relevant histories were taken, which included age of the patient at cancer diagnosis, family history of esophageal cancer, personal history and treatment history and histopathological confirmation was done with Biopsy. After all laboratory and radiological information gathered, TNM staging was done. We also included patients with tumors involving the GEJ in our study [Defined as per AJCC 7th edition]9. Chemotherapy details including toxicities were noted. Patients who had completed planned treatment were eligible for response assessment. Response was evaluated using RECIST 1.1 (Response Evaluation Criteria In Solid Tumors) criteria. Patients who received adjuvant postoperative chemotherapy underwent assessment with CECT chest and abdomen at completion of treatment and were followed for six months to observe for DFS.

Statistical Analysis

Descriptive analysis of parametric parameters were expressed as means and standard deviation. Categorical/Ordinal data was expressed as percentage, median and range. Cross tables were generated, and chi square test was used for comparisons & associations. The assessment of normality of data was tested using the Kolmogorov-Smirnov-Test. Student t- test was used for comparison of quantitative parameters for normally distributed data and Mann Whitney U Test for non-normally distributed data. All statistical tests were two-sided, and P values less than 0.05 will be considered as statistically significant. SPSS software, version 24.0 was used for analysis.

Results

Total 64 patients of carcinoma esophagus were enrolled in our study. 32 (66 %) were males, and 22 (34 %) were females. (Table 1) Males constituted almost twice as females. Age group between 56-70 years constituted the most 34 (56%) of our study population. Mean age of our study population was 60 (+ 11) years. Tobacco as a risk factor was observed in nearly 70% of study population. 80% of SCC patients had tobacco as a risk factor, which was statistically significant. Alcohol consumption was noticed in nearly 50% of patients. More than 50% of SCC patients had alcohol as a risk factor.

Dysphagia was most common presenting symptom 56 (88%) followed by weight loss 28 (44%) and vomiting 16 (25%). Middle one-third thoracic esophagus region was commonest (nearly 50%) location for tumor.

Statistically significant association of vomiting with middle one-third thoracic esophagus and of reflux symptoms with distal esophagus was found. SCC was predominant (nearly 80%) histology type in our study. SCC histology was exclusively present in cervical, upper and middle one-third thoracic esophagus. Distal esophagus was predominated by ADC histology.

Grade 2– moderately differentiated esophagus carcinoma was most common grade of differentiation (Table 2). No significant correlation of HPE grading and tumor location was found. In our study population, T3 was the most common tumor stage and N1 was commonest nodal stage. Males outnumbered females in all stages. Metastatic disease was present in nearly one-quarter of study group. Males constituted predominantly in metastatic disease which was statistically significant.

Stage III (nearly 50%) was the most common stage. Nodal followed by pulmonary was most common site of metastasis. In our study, 94% of the total patients enrolled started on chemotherapy (Figure 1). Regimens used were in accordance to standard practice guidelines. 11 patients received adjuvant chemotherapy and DFS was studied in this study population. Objective response rate (ORR) to first line chemotherapy was studied in 43 (67%) patients. Objective response rate (CR & PR) observed was 80% in definitive concurrent chemo radiation group, 53% in neoadjuvant therapy arm, 66% in perioperative chemotherapy arm and 20% in palliative chemotherapy group (Table 3). Disease control rate (CR, PR and SD) in palliative chemotherapy arm in our study was 53%.

Most common grade 3 or 4 toxicities recorded were mucositis and GI toxicity (diarrhoea or vomiting). Treatment-related deaths observed were 5%.

Gender	Number (n=64)	
F	22 (34.4%)	
M	42 (65.6%)	
Age group (Years)		
< 40	5 (7.8%)	
41 – 55	10 (15.6%)	
56 – 70	36 (56.3%)	
> 70	13 (20.3%)	
Co-morbidities		
DM	18 (28.1%)	
HTN	17 (26.6%)	
CAD	3 (4.7%)	
OTHERS	14 (21.9%)	
Tobacco		
Yes	44 (68.75%)	
No	20 (31.25%)	
Alcohol		
Yes	30 (46.90%)	
No	34 (53.10%)	
Tobacco	**SCC (n=50)**	**Adenocarcinoma (n=14)**
Yes	40 (80.0 %)	4 (28.5%)
No	10 (20.0%)	10 (71.5%)
Alcohol	**SCC (n=50)**	**Adenocarcinoma (n=14)**
Yes	26 (52.0 %)	4 (28.5%)
No	24 (48.0 %)	10 (71.5%)
Symptomatology	**Number (n=64)**	
Dysphagia	56 (87.5%)	
Weightloss	28 (43.8%)	
Vomiting	16 (25.0%)	
Reflux Symptoms	8 (12.5%)	
Cough	7 (10.9%)	
Hoarseness	7 (10.9%)	
Others	8 (12.5%)	
Location (Esophagus)	**Number (n=64)**	
Cervical	5 (7.8%)	
Upper Thoracic	11 (17.2%)	
Middle Thoracic	31 (48.4%0	
Lower Thoracic	12 (18.8%)	
GEJ	5 (7.8%)	

Location	Dysphagia (Number)	Vomiting (Number)
Cervical	5 (8.9%)	0 (0.0%)
Upper Thoracic	10 (17.9%)	0 (0.0%)
Middle Thoracic	29 (51.8%)	14 (87.5%)
Lower Thoracic	9 (16.1%)	1 (6.3%)
Gastroesophageal Junction	3 (5.4%)	1 (6.3%)
Chi square 7.039 Chi square 13.89		
p value 0.134 p value 0.008		
Location	**Reflux symptoms Number**	**Weight loss Number**
Cervical	0 (0.0%)	3 (10.7%)
Upper Thoracic	1 (12.5%)	4 (14.3%)
Middle Thoracic	1 (12.5%)	12 (42.9%)
Lower Thoracic	5 (62.5%)	8 (28.6%)
Gastroesophageal Junction	1 (12.5%)	1 (3.6%)

Histopathology	**Number (n=64)**
SCC	50 (78.1%)
Adenocarcinoma	14 (21.9%)

Location Histopathology	**SCC Number**	**Adenocarcionoma Number**
Cervical	5 (100.0%)	0 (0.0%)
Upper Thoracic	11 (100.0%)	0 (0.0%)
Middle Thoracic	31 (100.0%)	0 (0.0%)
Lower Thoracic	3 (25.0%)	9 (75.0%)
Gastroesophageal Junction	0 (0.0%)	5 (100.0%)

HPE Grade	**Number (n=64)**
Well Differentiated	11 (17.2%)
Moderately Differentiated	38 (59.4%)
Poorly Differentiated	15 (23.4%)

Clinical T Stage	**Female (n=22)**	**Male (n=42)**	**Total n=64 (100%)**
T1	1 (50%)	1 (50%)	2 (100%)
T2	6 (40%)	9 (60%)	15 (100%)
T3	14 (41.2%)	20 (58.8%)	34 (100%)
T4	1 (7.7%)	12 (92.3%)	18 (100%)

Clinical N Stage	Female (n=22)	Male (n=42)	Total n=64 (100%)
N0	3 (33.3%)	6 (66.7%)	9 (100%)
N1	13 (50%)	13 (50%)	26 (100%)
N2	6 (26.1%)	17 (73.9%)	23 (100%)
N3	0 (0.0%)	6 (100%)	6 (100%)
Clinical M Stage	**Female (n=22)**	**Male (n=42)**	**Total (n=64)**
			49 (100%)
M1	2 (13.3%)	13 (86.7%)	15 (100%)

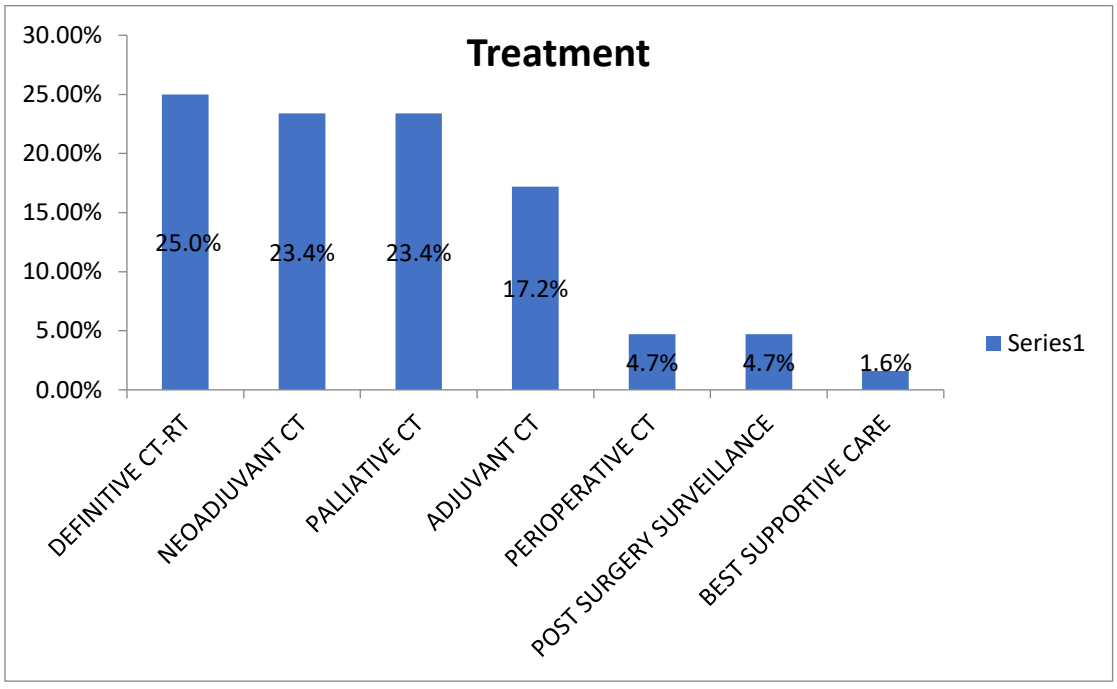
Clinical Stage Collective Impression	Number (n=64)
I	3 (4.7%)
II	14 (21.9%)
III	31 (48.4%)
IV	16 (25.0%)

Location / Stage	I (Number)	II (Number)	III (Number)	IV Number
Cervical	0 (0.0%)	2 (40.0%)	3 (60.0%)	0 (0.0%)
Upper Thoracic	1 (9.09%)	1 (9.09%)	5 (45.45%)	4 (36.37%)
Middle Thoracic	1 (3.23%)	10 (32.3%)	14 (45.16%)	6 (20.31%)
Lower Thoracic	1 (8.33%)	1 (08.33%)	6 (50.0%)	4 (33.34%)
Gastroesophageal Junction	0 (0.0%)	0 (0.0%)	3 (60.0%)	2 (40.0%)

Site of Metastasis	Number (n=16)
Nodal (Non regional)	12 (75.0%)
Pulmonary	7 (75.0%)
Adrenal	4 (25.0%)
Hepatic	4 (25.0%)
Osseous	2 (12.5%)
Peritoneal	2 (12.5%)

Univariate Logistic Regression Analysis (Response to treatment)

	B	S.E.	Odds Ratio	95% C.I.for Odds Ratio		p-value
				Lower	Upper	
Female	1.42	0.74	4.16	0.97	17.77	0.055
Histopathology ADENO	1.19	0.78	3.29	0.71	15.28	0.129
HPE Grade 2	0.44	0.8	1.56	0.32	7.49	0.582
HPE Grade 3	1.41	0.93	4.08	0.66	25.38	0.131
DM	0.15	0.66	1.16	0.32	4.23	0.818
HTN	0.82	0.68	2.26	0.59	8.64	0.233
CAD	0.27	1.45	1.32	0.08	22.41	0.85
Tobacco	0.38	0.63	1.46	0.42	5.04	0.551
Alcohol	0.67	0.6	1.96	0.6	6.39	0.267
Cervical esophagus	1.79	1.29	6	0.48	75.34	0.165
Upper 1/3rd esophagus	0.85	1.21	2.33	0.22	25.24	0.486
Middle 1/3rd esophagus	1.1	1.35	3	0.21	42.62	0.417
Lower 1/3rdesophagus	1.79	1.44	6	0.35	101.57	0.214



Treatment	Number (n=64)
Definitive CT-RT	16 (25.0%)
Neoadjuvant CT	15 (23.4%)
Palliative CT	15 (23.4%)
Adjuvant CT	11 (17.2%)
Perioperative CT	3 (4.70%)
Post-surgery surveillance	3 (4.70%)
Best supportive care	1 (1.6%)
	Number (n=64)
Definitivect-RT	16 (25.0%)
Response	
Complete	10 (62.5%)
Partial	3 (18.8%)
Progressive disease	3 (18.8%)
Neo-adjuvant therapy	15
Nact-RT	13 (20.9%)
Nact	2 (3.1%)
Response	
Complete	3 (20.0%)
Partial	5 (33.3%)
Progressive disease	4 (26.7%)
Death	2 (13.3%)
Perioperative chemotherapy	3 (4.7%)
Response number percent (n=3) (%)	
Complete	0 (0%)
Partial	2 (66.66%)
Progressive disease	1 (33.34%)
Response	Number n=15
Partial	3 (20.0%)
Stable disease	5 (33.3%)
Progressive disease	4 (26.7%)
Death	2 (13.3%)
Chemotherapy discontinued	1 (6.7%)
	Number (n=58)
Myelosuppression	11 (19.0%)
Gi toxicity	13 (22.4%)
Mucositis	14 (24.1%)
Others	4 (06.9%)

Discussion

Our present observational prospective study represents a sample of 64 patients with carcinoma esophagus. These patients were selected from a tertiary care hospital. We studied clinical demographics as well as response to treatment in patients with carcinoma esophagus. Carcinoma esophagus is a disease predominantly present in males. In this study of carcinoma esophagus, males were twice as common as females. It is in accordance with previous studies.10,11 Esophageal cancer is predominantly a disease of the elderly, where nearly one third of the diagnosed patients are more than 75 years of age. Mean age of diagnosis is 67 years.12 However, few previous studies have reported younger age group (41-60 years) also as majority, in their study population.13 Chen M. et.al reported 50-65 years as age of peak incidence of esophageal cancer in their study.14 The majority of patients in our study were between 55 – 70 years of age. Mean age of our study population was 60 (+ 11) years.

The clinical presentations of carcinoma esophagus include dysphagia, weight loss, anorexia, cough and hoarseness of voice. By far, the commonest presentation of this disease condition is dysphagia. The most common presentation in our study was dysphagia (nearly 90%). Tobacco and alcohol use are considered the major contributing factors in the development of esophageal cancer worldwide.15 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. In our study, nearly 70% of patients had history of tobacco exposure in any form. Khan NA et.al found similar rates of tobacco exposure in their study.16 Nearly 50 % of patients had alcohol as a risk factor in our study. Few previous studies reported comparable results13,17. Alcohol and tobacco as etiologic risk factors are linked more with SCC esophagus over ADCs.

SCC still is the predominant histological subtype in Asian nations where most of the cases occur in middle or lower third18. SCC was predominant (nearly 80%) histology type in our study. Out of total 64 patients, only 14 (20%) cases of ADCs were registered in our study population. The majority of squamous cell carcinomas (SCCs) are located in the midportion of the esophagus. In our study, middle one-third of thoracic esophagus was the most common tumor site (nearly 50%). Majority of these tumors were SCCs. Gupta V et.al in their reported middle one third was most common site of tumor location and SCC was most common histopathology.19 SCCs also predominates cervical esophagus cancer. All cases (5/5) of cervical esophagus cancer in our study were SCC. Nearly three-fourths of all ADCs are found in the distal third of esophagus.20 Our study observed all (14/14) cases of ADCs were either in lower one third of esophagus or GEJ.

Early oesophageal cancer is rarely diagnosed, even if its endoscopic aspects are well known. Majority of patients present as locally advanced or metastatic disease. In our study, T3 was most common (>50%) 'T' (tumor) group at presentation. As far as nodal staging is concerned, N1 (40%) followed by N2 (32%) accounted for majority of cases. Stage III was commonest (nearly 50%) TNM anatomic staging at presentation in our study. Mustafa SA et.al also reported stage III as most common stage at presentation in their study.10 Esophagus lack serosal envelope and has rich lymphatic network in submucosa. Early lymph node involvement is common in patients with carcinoma esophagus. In our study 85% patients had lymph node involvement at presentation.

The prognosis for patients with locally advanced esophageal cancer treated with the standard approaches of surgery or radiotherapy alone is poor. The management of local-regional cancer of the esophagus and gastroesophageal junction (GEJ) has undergone a major evolution over the past 15 years. Combined modality therapy, rather than surgery alone, for patients with T3N0, T4aN0, and clinically node-positive thoracic esophageal cancer, regardless of histology is recommended. Concurrent use of chemotherapy and radiotherapy is now a standard of care in the nonsurgical management of locally advanced esophageal cancer.

In our study, 31 patients were planned for preoperative chemotherapy. Out of 31, 16 patients were selected for definitive chemo-radiotherapy eventually. Remaining 15 cases were planned for neoadjuvant chemotherapy followed by surgical resection. 53 % of all patients in NACT arm had either complete or partial response. Three patients had complete metabolic response, of which only one had pathologic CR. The most common regimen used was concurrent chemo-radiotherapy with cisplatin/ 5 FU. Seven patients out of eight patients, who showed response to neoadjuvant chemoradiation, proceeded with surgery. Two patients died during neoadjuvant therapy (one after first cycle and second after 2 cycles). One patient died due to 5-FU induced cardiac toxicity and other succumbed to cisplatin induced nephrotoxicity.

Previous studies have reported response to preoperative chemoradiation in patients with carcinoma esophagus in the range of 40-70%20,21 Kies et. al in their study reported response rate 44% with use of cisplatin/5-FU as preoperative chemotherapy.22 Rizvi et.al observed 78% response to NACT in their study with 45% pathologic CR.23

Perioperative chemotherapy is recommended in locally advanced tumors at GEJ. In patients with operable lower esophageal adenocarcinomas, a perioperative regimen of ECF decreased tumor size and stage and significantly improved progression-free and overall survival.24,25 In our study, three patients at GEJ

received perioperative chemotherapy with ECF. Two patients showed partial response to perioperative chemotherapy and proceeded with surgery. None of our patient (out of two responded) who received perioperative chemotherapy, achieved pathologic CR. One patient showed disease progression while on chemotherapy.

Definitive CRT or neoadjuvant CRT followed by surgery seem to have similar long-term results. Surgery seems to provide a better local control of the tumour, however, no benefit on long-term outcome. Moreover, this benefit is possible at the cost of major surgery and to the subsequent postoperative mortality. In our study, 62% patients had complete metabolic response and nearly 20% had partial response. Less than 20% patients progressed during definitive CT-RT. Continuous infusion cisplatin /5-FU was the most common chemotherapy regimen (50%) used.

Response to definitive CT RT in patients with resectable esophagus cancer ranges from 62-88%26-30

Trial	Histology	Stage	Chemotherapy	Response Rate
JCOG9708[26]	SCC	Ib	Cis/5-FU	87.5%
JCOG9906[27]	SCC	II/III	Cis/5-FU	62.2%
mRTOG (28)[28]	SCC	II/III	Cis/5-FU	70.6%
JCOG0604[29]	SCC	II/III	S-1	59.5%
PRODIGE5[30]	SCC, AC	I-IV A	Cis/5-FU	41.3%

Mucositis was common toxicity, likely due to infusional 5- FU. Although, no treatment related death was observed during definitive CT-RT.

Nearly 50% of patients with a diagnosis of esophageal cancer present with overt metastatic disease, and chemotherapy is the mainstay of palliation in this setting. Response to palliative chemotherapy ranges from 10-40% in various studies)31-37. It is higher for combination chemotherapy as compared to single agent. 15 patients (25%) were enrolled to assess the response to palliative chemotherapy. However, chemotherapy was discontinued for one patient due to poor general condition. Two patients died during study period. One patient developed TOF and eventually succumbed to aspiration pneumonia, while other patient died due to neutropenic sepsis. Our study showed 20 % response rate to palliative chemotherapy. One third of all patients with stage IV disease in our study group had stable disease after first line of palliative chemotherapy. However, 27% patients progressed during chemotherapy. Nabpaclitaxel–

carboplatin was the most common regimen (32%) followed by PCF (25%). Failure to maintain dose density due to poor tolerance is a significant contributor to poor response to palliative chemotherapy.

Adjuvant chemotherapy after neoadjuvant chemoradiation and esophagectomy is associated with improved survival in patients with residual nodal disease.37 For patients with completely resected, node-positive or node-negative, pathologic T3 or T4 esophageal adenocarcinomas who have not received neoadjuvant therapy, high-risk pathologic T2N0 adenocarcinomas, and resected SCC with positive margins, some form of postoperative therapy is recommended (as per NCCN), in an attempt to improve outcomes. For patients with SCC, postoperative chemoradiation is recommended only in case of positive resection margins. However, in case of lymphovascular or perineural invasion or high pathologic nodal disease, postoperative chemoradiation is suggested to improve outcome (reference). We studied adjuvant chemoradiation in 11 patients. Disease free survival (DFS) was observed at 6 months postoperative period. DFS was present in more than 80% of patients. Less than 20% of patients who received adjuvant chemotherapy progressed within 6 months. Concurrent chemo-radiotherapy with cisplatin– 5 FU was the most common regimen (64%) used in adjuvant settings.

Toxicities of chemotherapy especially in combination regimen is a significant concern in treatment of patients of carcinoma esophagus. Cisplatin, 5-FU, paclitaxel, carboplatin, anthracyclines are main agent used in treatment of carcinoma esophagus. Concurrent administration of radiotherapy adds to chemotherapy toxicity. Main toxicities of above-mentioned chemotherapy agents used either alone or in combination are mucositis, myelosuppression, gastrointestinal toxicity cardiotoxicity, nephrotoxicity and skin toxicity. We did not study skin toxicity in our study group. Mucositis and myelosuppression were main toxicities in our study. Mucositis was commoner toxicity, probably due to infusional use of cisplatin/ 5 FU as a primary regimen. Three treatment - related deaths (5%) were noticed during study. One patient died due to cisplatin induced nephrotoxicity, another due to 5 FU induced cardiotoxicity and third patient succumbed to neutropenic sepsis. Aroori S et. al studied use of low dose continuous 5-FU and cisplatin as NACT in patients with carcinoma esophagus to minimize toxicity.38 It was concluded in their study that low dose regimen is well tolerated with minimal toxicity. Histopathological response rates and survival figures are comparable with the more toxic neoadjuvant chemotherapeutic regimens.

We hereby report a study in patients with carcinoma esophagus at a tertiary care hospital. We included patients of both histologies (SCC and ADC), of all locations (from cervical esophagus to GEJ) and studied management of all stages in carcinoma esophagus. Sample size was smaller in our study group. As study

duration was limited, parameters like PFS and OS were not studied. Study with a larger sample size and for longer duration is needed to address above limitations. We studied only two risk factors - alcohol and tobacco. Other risk factors like nutritional and socioeconomic status, obesity etc. were not studied. Another limitation of our study was diverse chemotherapy regimens used. This is bound to happen in routine clinical studies where consecutive patients are enrolled and not all of them can be administered the standard treatment regimens due to underlying co-morbidities or performance status.

The strengths of our study were its prospective nature, robust data collection and use of standard protocols for diagnosis and staging. This is impressive in a resource limited country such as ours. In majority we could administer chemotherapy in accordance to standard practice guidelines.

References

1. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15 ;127(12):2893–917.

2. Sung H, Ferlay J, Siegel RL, Laversanne M. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.

3. Gajalakshmi V, Swaminathan R, Shanta V. An Independent Survey to Assess Completeness of Registration: Population Based Cancer Registry, Chennai, India. Asian Pac J Cancer Prev. 2001 ;2(3):179–83.

4. Cook MB. Editorial: Non-Acid Reflux: The Missing Link Between Gastric Atrophy and Esophageal Squamous Cell Carcinoma? Am J Gastroenterol. 2011 Nov 7 ;106(11):1930–2.

5. Lagergren J, Bergström R, Lindgren A, Nyrén O. Symptomatic Gastroesophageal Reflux as a Risk Factor for Esophageal Adenocarcinoma. N Engl J Med. 1999 Mar 18;340(11):825–31.

6. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2008 Feb 1;57(2):173–80.

7. Morris Brown L, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, et al. Excess Incidence of Squamous Cell Esophageal Cancer among US Black Men: Role of Social Class and Other Risk Factors. Am J Epidemiol. 2001 Jan 15;153(2):114–22.

8. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of alcoholic beverages. Lancet Oncol. 2007 Apr ;8(4):292–3.

9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann Surg Oncol. 2010 Jun 24;17(6):1471–4.

10. Mustafa SA, Banday SZ, Bhat MA, Patigaroo AR, Mir AW, Bhau KS. Clinico-Epidemiological Profile of Esophageal Cancer in Kashmir. Int J Sci Study. 2016;3(11).

11. Sehgal S, Kaul S, Gupta BB, Dhar MK. Risk factors and survival analysis of the esophageal cancer in the population of Jammu, India. Indian J Cancer. 2012;49(2):245–50.

12. Enzinger PC, Mayer RJ. Esophageal Cancer. N Engl J Med. 2003 Dec 4 ;349(23):2241–52.

13. Bathija GV, Itagimath SR, Bant DD, Lokhare L. Study on Socio-Demographic and Associated Risk Factors for Oesophageal Cancer in Karnataka Institute of Medical Sciences Hospital, Hubli, Karnataka. Sch J Appl Med Sci . 2014;2(2C):706–10.

14. Chen M-F, Chen P-T, Lu M-S, Lee C-P, Chen W-C. Survival benefit of surgery to patients with esophageal squamous cell carcinoma. Sci Rep. 2017 Apr 6;7:46139.

15. Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, et al. Cancer survival in Africa, Asia, and Central America: a population-based study. Lancet Oncol. 2010 Feb;11(2):165–73.

16. Khan NA, Teli MA, Mohib-Ul Haq M, Bhat GM, Lone MM, Afroz F. A survey of risk factors in carcinoma esophagus in the valley of Kashmir, Northern India. J Cancer Res Ther. 2011;7(1):15–8.

17. Chitra S, Ashok L, Anand L, Srinivasan V, Jayanthi V. Risk factors for esophageal cancer in Coimbatore, southern India: a hospital-based case-control study. Indian J Gastroenterol. 2004 ;23(1):19–21.

18. Eroğlu A, Aydin Y, Altuntaş B, Gündoğdu B, Yilmaz Ö. Turkish Journal of Medical Sciences The increasing incidence of esophageal squamous cell carcinoma in women in Turkey. Turk J Med Sci. 2016 ;46:1443–8.

19. Gupta V, Bhardwaj S, Bhagat OK. Pattern of esophageal cancer in tertiary care hospital in North India: a clinicopathological study. Int J Res Med Sci. 2017 Mar 28 ;5(4):1405.

20. Posner M, Minsky B, and Ilson D. Cancer of the Esophagus. In: DeVita V, Lawrence

T, Rosenberg S by Cancer. 10th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2015)

21. Ilson D, Wadleigh R, Leichman L, Kelsen D. Paclitaxel given by a weekly 1-h infusion in advanced esophageal cancer. Ann Oncol. 2007 Feb 14 ;18(5):898–902.

22. Kies MS, Rosen ST, Tsang TK, Shetty R, Schneider PA, Wallemark CB, et al. Cisplatin and 5-fluorouracil in the primary management of squamous esophageal cancer. Cancer. 1987 Nov 1;60(9):2156–60

23. Rizvi FH, Syed AA, Khattak S, Rizvi SSH, Kazmi SA, Khan MQ. Complete pathological response after neoadjuvant treatment in locally advanced esophageal cancer predicts long term survival: A retrospective cohort study. Int J Surg. 2014 Jun 1;12(6):621–5.

24. Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol. 1997 Jan;15(1):261–7.

25. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.

26. Kato H, Sato A, Fukuda H, Kagami Y, Udagawa H, Togo A, et al. A Phase II Trial of Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol. 2009 Oct 1 ;39(10):638–43.

27. Kato K, Muro K, Minashi K, Ohtsu A, Ishikura S, Boku N, et al. Phase II Study of Chemoradiotherapy With 5-Fluorouracil and Cisplatin for Stage II–III Esophageal Squamous Cell Carcinoma: JCOG Trial (JCOG 9906). Int J Radiat Oncol. 2011 Nov 1;81(3):684–90.

28. Kato K, Eguchi Nakajima T, Ito Y, Katada C, Ishiyama H, Tokunaga S -y., et al. Phase II Study of Concurrent Chemoradiotherapy at the Dose of 50.4 Gy with Elective Nodal Irradiation for Stage II-III Esophageal Carcinoma. Jpn J Clin Oncol. 2013 Jun 1 ;43(6):608–15.

29. Wang H, Li G, Chen L, Duan Y, Zou C, Hu C. Definitive concurrent chemoradiotherapy with S-1 and cisplatin in elderly esophageal squamous cell carcinoma patients. J Thorac Dis. 2017 Mar ;9(3):646–54.

30. Conroy T, Galais M-P, Raoul J-L, Bouché O, Gourgou-Bourgade S, Douillard J-Y, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol. 2014 Mar ;15(3):305–14.

31. Van Hagen P, Hulshof MCCM, Van Lanschot JJB, Steyerberg EW, Henegouwen MI van B, Wijnhoven BPL, et al. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med. 2012 May 31;366(22):2074–84. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst. 1994 Jul 20;86(14):1086–91.

32. Muro K, Hamaguchi T, Ohtsu A, Boku N, Chin K, Hyodo I, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. Ann Oncol Off J Eur Soc Med Oncol. 2004 Jun;15(6):955–9.

33. Kies MS, Rosen ST, Tsang TK, Shetty R, Schneider PA, Wallemark CB, et al. Cisplatin and 5-fluorouracil in the primary management of squamous esophageal cancer. Cancer. 1987 Nov 1;60(9):2156–60.

34. Bleiberg H, Conroy T, Paillot B, Lacave A., Blijham G, Jacob J., et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer. 1997 Jul 1 ;33(8):1216–20.

35. Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol. 1998 May;16(5):1826–34.

36. Ilson DH, Forastiere A, Arquette M, Costa F, Heelan R, Huang Y, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer J.;6(5):316–23.

37. Burt BM, Groth SS, Sada YH, Farjah F, Cornwell L, Sugarbaker DJ, et al. Utility of Adjuvant Chemotherapy After Neoadjuvant Chemoradiation and Esophagectomy for Esophageal Cancer. Ann Surg. 2017 Aug;266(2):297–304

38. Aroori S, Parshad R, Kapoor A, Sd G, Kumar A, Tk C. Neoadjuvant Chemotherapy in Squamous Cell Carcinoma of the Esophagus using Low Dose Continuous Infusion 5-Fluorouracil and Cisplatin : Results of a Prospective Study. :3–7