



ESOPHAGEAL CANCER IN SOUTH INDIA; AN INSTITUTIONAL 5-YEARS RETROSPECTIVE ANALYSIS ON ITS CLINICOPATHOLOGY AND RISK FACTORS OF DISTANT METASTASIS

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ABSTRACT

Context: Esophageal cancer (EC) is highly fatal malignancy with considerable geographical variation in its distribution, etiologies, histopathological subtypes, and mortality. **Methods:** A retrospective analysis was performed to study the clinicopathology, and risk factors of distant metastasis (DM) among 255 cases of EC treated between January 2015 and December 2019 in a tertiary cancer center in south India. **Statistical analysis:** Chi-square test and multivariate analysis (MVA) were used for analysis. $P < 0.05$ was considered significant. **Results:** The median age at diagnosis of EC was 57 years, higher for male. Younger EC patients (≤ 40 years) constituted 8.2%, and were commonly female, non-smoker, non-alcoholic, squamous cell carcinoma (SCC). Male: female ratio was 1.67:1. Lower thoracic esophagus was the commonest site. SCC was the commonest histology. Adenocarcinoma (ADC) was common among older age, male, esophagogastric junction (EGJ), high grade tumor, and carried higher risk of DM. ADC had higher propensity for liver metastasis, whereas SCC for lung metastasis. MVA showed the risk factors associated with DM were poor performance status (PS), delayed diagnosis, EGJ tumor, ADC histology, high grade tumor. **Conclusion:** Lower thoracic esophageal location and SCC histology remains the commonest type of EC in southern part of India. Younger EC patients are commonly female, nonsmokers, non alcoholic, SCC. ADC is common in male, older age. EGJ tumor are commonly ADC, high grade, and carries higher risk of DM, which warrants early diagnosis, aggressive systemic therapy in this subset of patients for improving the survival.

KEYWORDS : Clinicopathology, distant metastasis, esophageal cancer, risk factors

INTRODUCTION:

Worldwide esophageal cancer (EC) remains the seventh most common cancer and sixth most common cause of cancer mortality, whereas in India it is the fourth most common cause of cancer mortality.^[1] Considerable geographical variation exists in its distribution, etiologies, histopathological subtypes, and mortality.^[2,3] EC is diagnosed more frequently among men. The two most common histopathological types of EC are squamous cell carcinoma (SCC) and adenocarcinoma (ADC). The countries with higher socioeconomic development have greater ADC: SCC ratio. The SCC is most common globally and in low human development index (HDI) countries; whereas in high HDI countries like USA, the ADC is following an increasing trend.^[1,3,4] EC is a highly fatal disease and carries poor survival with the 5 year survival ranges from 15-25%.^[5] Whereas, previous studies have reported the trend of improved survival in EC is related to early diagnosis and availability of multimodal treatment protocols.^[6,7] The age adjusted incidence and mortality of EC is following a decreasing trend in high HDI countries like USA, which could be due to increased awareness, preventive measures, early detection and treatment. Whereas, it is still a major health problem in low HDI countries like India and carries a poor prognosis.^[11] Hence, understanding the epidemiology, clinicopathology of the disease can help in awareness, primary prevention, early detection, and effective treatment to improve the survival outcome in EC patients of this geographical area. We conducted an institutional retrospective analysis to study the current clinicopathological characteristics, the risk factors of distant metastasis in EC patients.

SUBJECTS AND METHODS:

The present study was a retrospective analytical study, conducted in a tertiary cancer centre in south India. The study population included, all histopathologically confirmed cases of EC treated between January 2015 and December 2019. The data was retrieved from the hospital cancer registry, after obtaining the institutional ethical committee permission. Patients were classified into two age groups; i.e the younger (≤ 40 years), the intermediate and older (> 40 years) age groups. Tumors were classified into five subgroups based on the location: cervical (16-20cm from incisors), upper thoracic (20-25cm from incisors), middle thoracic (25-30cm from incisors), lower thoracic (30-40cm from incisors, not involving the esophagogastric junction i.e EGJ) and EGJ (tumor involving EGJ). Diagnostic evaluation for all patients included histopathological confirmation, endoscopic evaluation, computed tomography of thorax and abdomen, whereas endoscopic ultrasonography or magnetic resonance imaging was not performed routinely. The staging of EC was done by using American Joint Committee on Cancer (AJCC) staging 8th edition. IBM SPSS statistics software for windows, version 21.0 (Armonk, NY: IBM Corp) was used for data analysis. The frequency distribution and association among different clinicopathological variables was evaluated by Chi-square analysis, and the risk factors of distant metastasis were evaluated by multivariate analysis ($P < 0.05$ and confidence interval of 95%)

RESULTS:

In the present study, the mean age at diagnosis was 57.2 ± 11.7

years. Male patients were more common than female, with male: female ratio of 1.67: 1 [table 1]. The frequency of performance status of patients at presentation was in the order of ECOG II > ECOG I > ECOG III > ECOG IV [table 1]. Frequency of smokers and alcoholic in the study were 45.9% and 39% respectively, with majorities (99%) of each were male. Most common symptom at presentation was progressive dysphagia (96.8%) and most of the cases (59.6%) were diagnosed with duration of symptoms between 1 to 4 months [table 1]. Lower thoracic esophagus was the most common subsite of tumor location, followed by middle thoracic esophagus and EGJ tumors [table 1]. The distal esophageal tumors (particularly the EGJ tumors) were found commonly among male (male: female ratio being 3:1, whereas male: female ratio for overall EC was 1.67: 1), ADC histology (62.5%), barrette's pathology (in two cases), more frequently high grade tumors, and carried higher rate of distant metastasis (47.5%) at initial diagnosis. In the present study, the most common histopathology of EC was SCC, with SCC: ADC ratio of 7.6: 1. Younger patients (≤ 40 years) constituted 8.2% of the study population, and were commonly found among female (male: female ratio 0.5:1 vs. 1.85:1 for ≤ 40 years and > 40 years old patients respectively, $P = 0.004$), non-smokers (19% vs. 48.3% smokers among ≤ 40 years and > 40 years respectively, $P = 0.012$), non-alcoholics (19% vs. 41% alcoholic among ≤ 40 years and > 40 years respectively, $P = 0.05$), SCC histology (95.2% vs. 86.3% among ≤ 40 years and > 40 years old patients respectively, $P = 0.118$) with absence of ADC histology among younger patients. Subgroup analysis revealed the ADC histology to be common in older age, male, distal esophageal location, greater frequency of high grade tumors [table 2], and higher rate of distant metastasis [table 3]. The regional nodal metastasis was found increasingly among male (47.2% vs. 35.4% among male & female respectively, $P = 0.06$), ADC histology (72.4% vs. 37.8% in ADC & SCC respectively, $P = 0.000$), high grade tumors (79.5% vs. 35.8% vs. 31.3% among high grade, intermediate grade & low grade tumors respectively, $P = 0.000$), EGJ (72.5%) > cervical (52.9%) > lower thoracic (41.8%) > upper thoracic (35.7%) > mid thoracic tumors (27.8%) with $P = 0.000$. The most common sites of distant metastasis were, liver, followed by distant nodes and lung [table 1]. A trend towards increased rate of lung metastasis was found among SCC histology ($P = 0.22$), whereas liver metastasis in ADC histology ($P = 0.148$). Multivariate analysis revealed the risk factors of distant metastasis in EC in the present study were; poor performance status, longer duration of symptoms, distal esophageal location, ADC histology, high grade of tumor [table 3].

Table 1: Frequency distribution of different parameters among the study population

Parameters	Number (%)
Age (years)	
Median	57
Range	22-86
Sex	
Male	159 (62.4)
Female	96 (37.6)
Performance status (ECOG)	
1	100 (39.2)
2	122 (47.8)
3	30 (11.8)
4	3 (1.2)
Smoking	
Smoker	117 (45.9)
Non smoker	128 (50.2)
Unknown	10 (3.9)
Alcohol	
Alcoholic	100 (39.2)
Non alcoholic	143 (56.1)
Unknown	12 (4.7)

Symptoms	
Progressive dysphagia	247 (96.8)
Weight loss	98 (38.4)
Vomiting	14 (5.5)
Malena	3 (1.2)
Neck swelling	3 (1.2)
Pain abdomen	4 (1.6)
Breathing difficulty	2 (0.8)
Duration of symptoms	
< 1 month	43 (16.9)
1-2 months	89 (34.9)
2-4 months	63 (24.7)
> 4 months	60 (23.5)
Subsites	
Cervical	17 (6.7)
Upper thoracic	28 (11.0)
Middle thoracic	72 (28.2)
Lower thoracic	98 (38.4)
EG junction	40 (15.7)
Endoscopy findings	
Scope negotiable	178 (69.8)
Scope non-negotiable	77 (30.2)
Histopathology	
SCC	222 (87.1)
ADC	29 (11.4)
UDC	4 (1.5)
Grade	
I	32 (12.5)
II	179 (70.2)
III	44 (17.3)
TEF	
Present	4 (1.6)
Absent	251 (98.4)
Nodal status	
Positive	109 (42.7)
Negative	146 (57.3)
Distant metastasis	
Metastatic	45 (17.6)
Non metastatic	210 (82.4)
Site of distant metastasis	
Liver	21 (8.2)
Distant nodes	15 (5.9)
Lung	9 (3.5)
Bone	5 (2.0)
Adrenal	4 (1.6)
Peritoneal	4 (1.6)
Brain	1 (0.4)

Abbreviations: ECOG: Eastern cooperative oncology group, EG junction: Esophagogastric junction, SCC; Squamous cell carcinoma, ADC: Adenocarcinoma, UDC; Undifferentiated carcinoma

Table 2: Association of different epidemiological parameters with histopathological subtypes

Parameters	Histopathology (%)			P value
	SCC	ADC	UDC	
Age				
≤ 40 years	9.5	0	25	0.040
> 40 years	90.5	100	75	
Sex				
Male	59.9	79.3	75	0.111
Female	40.1	20.7	25	
PS (ECOG)				
I	40.7	27.6	0	0.024
II	48.9	37.9	0	
III	9.5	31	25	
IV	0.9	3.4	75	
Smoker				
Yes	46.8	34.5	75	0.215
No	50	55.2	25	
Unknown	3.2	10.3	0	

Alcoholic				
Yes	39.6	37.9	25	0.559
No	56.3	51.7	75	
Unknown	4.1	1.4	0	
Subsites				
Cervical	100	0	0	0.000
Up thoracic	100	0	0	
Mid thoracic	95.8	2.8	1	
Low thoracic	96.9	2	1	
EG junction	32.5	62.5	5	

Abbreviations: PS: performance status, ECOG: Eastern cooperative oncology group, EG junction: Esophagogastric junction, SCC; Squamous cell carcinoma, ADC: Adenocarcinoma, UDC: Undifferentiated carcinoma

Table 3: Risk factors for distant metastasis in esophageal cancer evaluated by multivariate analysis (95% level of significance)

Parameters	Metastases (%)	P value
Age		
≤40 years	23.8	0.447
>40 years	17.1	
Sex		
Male	17	0.693
Female	18.8	
Performance status (ECOG)		
I	8.1	0.000
II	18	
III	46.7	
IV	33.3	
Smoking		
Smoker	14.5	0.394
Non-smoker	21.1	
Alcohol		
Alcoholic	17	0.906
Non-alcoholic	18.9	
Unknown	25	
Symptoms		
Weight loss	44.7	0.229
Dysphagia	15.8	
Vomiting	76.9	
Neck swelling	100	
Pain abdomen	50	
Breathlessness	50	
Duration of symptoms		
< 1 month	7	0.022
1-2 months	13.5	
2-4 months	16.6	
>4 months	35.1	
Endoscopy findings		
Scope negotiable	24.7	0.805
Scope non-negotiable	25.3	
Subsites		
Cervical	0	0.000
Upper thoracic	7.1	
Mid thoracic	6.9	
Lower thoracic	19.4	
EG junction	47.5	
Histopathology		
SCC	13.1	0.000
ADC	44.8	
UDC	75	
Grade		
I	6.3	0.000
II	11.2	
III	52.3	
Nodal status		
Node positive	24.8	0.011
Node negative	12.3	

Tracheo-esophageal fistula		
Present	25	0.702
Absent	17.5	

Abbreviations: ECOG: Eastern cooperative oncology group, EG junction: Esophagogastric junction, SCC: Squamous cell carcinoma, ADC: Adenocarcinoma, UDC: Undifferentiated carcinoma

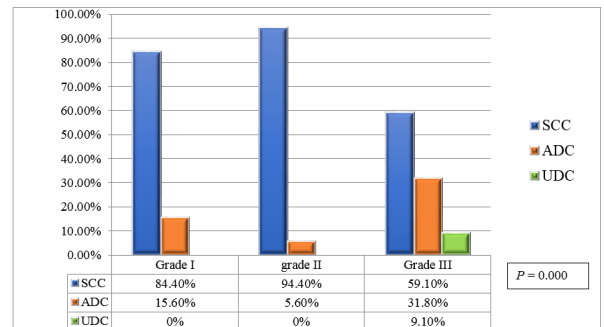


Figure 1: Association of histopathological subtypes with grades of esophageal tumor

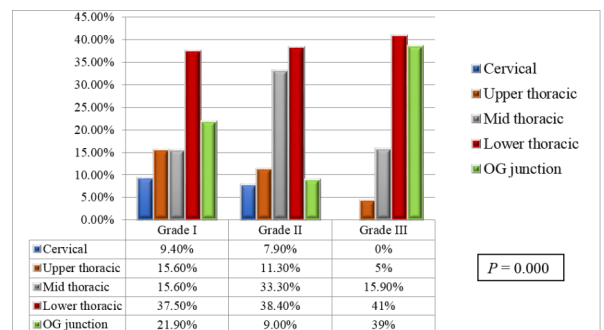


Figure 2: Association of different tumor subsites with grades of esophageal tumor

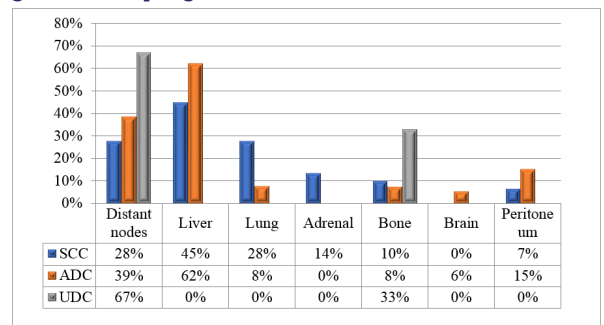


Figure 3: Different sites of distant metastasis in esophageal cancer

DISCUSSION:

The present study was conducted to study the epidemiology, the pattern of distant metastasis and the risk factors of distant metastasis in EC, which can guide in early detection and effective multimodality treatment planning to improve the survival. The incidence of EC peaks in the sixth decade of life in most part of the world,^[8] a similar incidence pattern was observed in the present study, where the first peak was found in the sixth decade, followed by second peak in the seventh decade (37% and 22% respectively). The mean age at presentation among males was relatively higher than among females (59.1±10.9 years vs. 54±12.1 years respectively), which was in concordance with previous Indian study report.^[9] EC among younger patients (≤40 years) comprised 8.2% of the total study population, with greater predilection for female. The male: female ratio among younger patients (0.5:1) in the present study found lower than the previous study report of 1.4:1.^[10] Whereas, the male: female ratio for overall patients

in the study (1.67:1) was higher than the previous report from north western India (1.15).^[11] Risk factors for SCC of oesophagus include excess tobacco and alcohol consumption,^[12] poor socioeconomic status, low intake of dietary fruits, vegetables,^[13,14] hot beverages,^[15] poor oral health,^[16] whereas in addition to smoking, alcohol, other risk factors for ADC are obesity, GERD, barrette's oesophagus.^[17] In the present study, prevalence of smokers and alcoholics were 45.9% and 39% respectively, whereas it was lesser i.e. 19% each among younger patients (≤ 40 years), 48.3% respectively among older patients (> 40 years) which was similar to the previous study report.^[10] Among smokers and alcoholics, majorities belonged to male (99%), but had not shown to have predilection for histopathology or subsites. Globally and in developing countries, SCC constitute the most common histopathological subtype of EC followed by ADC,^[1,18] a similar histopathological distribution pattern was found in the present study, where the SCC and ADC subtypes constituted 87.1% and 11.4% respectively, which was also in concordance with previous Indian study report.^[9] Incidence of EC has been reported to be more common among men than women, with male: female ratio of 2:1,^[11] a similar pattern of higher incidence among men was observed in the present study with male: female ratio of 1.67: 1, which was higher than the report of previous study from north-west India (male: female ratio of 1.15:1).^[10] In the present study, ADC histological subtype was found more frequent among male as compared to female (male: female ratio of 1.49:1 vs. 3.83:1 among SCC and ADC respectively, with $P = 0.05$), which was in concordance with previous study reports.^[19] Whereas, the mean age of diagnosis of ADC was relatively higher than SCC in the present study (60.9 ± 11.4 years vs. 56.9 ± 11.6 years respectively), and there was no cases of ADC observed among ≤ 40 years in the present study, which supports the hypothesis of the endocrine status in pre- and peri- menopausal females act as protective factor against esophageal adenocarcinoma with an increasing rate among older post menopausal females.^[20] The present study finding contradicts the previous Indian study report of higher incidence of ADC among younger age group with the mean age in fourth decade of life.^[9] SCC represents most common histopathology of EC, with a higher incidence of ADC in the distal esophageal location.^[21] Similarly, in the present study, SCC constituted the most common subtype of EC and also in the proximal esophageal location (cervical and thoracic esophagus), whereas ADC constituted most common histological subtype (86.2%) among the EGJ tumors. SCC of esophagus were most frequently diagnosed with intermediate grade tumors (75.9%), whereas ADC were most frequently diagnosed with high grade tumors (48.3%) with higher rate of distant metastasis at diagnosis compared to SCC histology (62.1% vs. 18.9% respectively). Lower thoracic esophagus constituted the most common location of EC in the present study, which was contradictory to the previous Indian study report of middle thoracic esophagus as the most common site of EC.^[22] In the present study, distal esophageal tumors were commonly found to have adenocarcinoma histology, high grade tumors, and higher rate of distant metastasis.

Incidence of metastatic EC at presentation is 32.7% as reported in the previous study from China,^[23] whereas it was found 17.6% in the present study. Previous studies have reported the most common sites of distant metastasis in EC follows the order of liver, distant lymph nodes, lungs respectively.^[24] A similar pattern of distant metastasis was observed in the present study. ADC of esophagus was reported to be associated with higher rate of liver and brain metastasis, whereas lower rate of lung metastasis compared to SCC. Distant lymph node and bone metastasis were reported to be independent of histopathological subtype of EC.^[24] In the present study, distant nodal and bone metastasis

was similar in both histopathological subtypes, ADC histology was found to have greater propensity for distant metastasis at diagnosis, relatively higher predilection for liver metastases, whereas SCC had higher predilection for lung metastases. The present study found the risk factors associated with distant metastasis were poor performance status, delayed diagnosis, distal esophageal tumor location (EGJ and lower thoracic esophagus), ADC histology, and high grade tumor.

CONCLUSION:

The EC is more common in male and the median age at diagnosis is higher for male than female. SCC remains the commonest type and lower thoracic esophagus is the commonest site of EC. Younger EC patients were commonly female, non-smoker, non-alcoholic, SCC histology. ADC was common in older age, male, EGJ location and high grade tumor, carries increased risk of DM. Other risk factors of DM in EC are EGJ location, poor PS, delayed diagnosis. The present study has highlighted important clinicopathological characteristics of EC and risk factors of distant metastasis, which can help clinicians for early diagnosis and appropriate multimodal treatment planning to optimize the survival outcome.

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