CLINICAL, ENDOSCOPIC, HISTOPATHOLOGIC FEATURES AND TREATMENT OF ESOPHAGEAL CARCINOMA PATIENTS

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ABSTRACT

Significance: Esophageal carcinoma is one of the most severe tumors worldwide. Even so, there is a paucity of data in the Philippines. The aim of this study if to describe the demographics, clinical characteristics, diagnostic findings, staging and treatment of esophageal cancer and compare characteristics of the different types.

Methodology: Retrospective cross-sectional study of all esophageal CA patients from 2010-2015

Results: Among 31 patients, mean age was 58.5 years with male predominance (83.9%). Majority were smokers (24.5 pack years). Most common complaints were dysphagia (87.1%) and weight loss (45.2%). 54.8% were found to have SCC while 45.2% had adenocarcinoma. Atrophic gastritis was higher in adenocarcinoma (28.6% vs 0%, p value 0.032). SCC was found more proximally (52.9% vs 0%, p value 0.001) while adenocarcinoma, distally (92.9% vs 35.3%, p value 0.002). Majority (67.7%) had masses greater than 5cm. Majority had advanced disease (38.7% stage IV). Majority (38.7%) had chemoradiotherapy. 25.8% had CROSS protocol treatment. The cumulative survival using Kaplan-Meier in 6 months and 12 months were 39% and 24%, respectively. Expectedly, survival was statistically different between the different stages of disease (p= 0.001) with median survival of 3 months for stage IV disease.

Conclusion: Esophageal carcinoma is a vicious disease with high mortality with a 6 and 12 month survival of 39% and 24% and median survival of 3 months for stage IV disease. Clinical characteristics were similar from previous studies. SCC was slightly higher than adenocarcinoma with SCC seen more proximally and adenocarcinoma more distally. Atrophic gastritis was seen more commonly with adenocarcinoma.

Key words*: Retrospective,* Esophageal carcinoma, Esophageal mass, Squamous cell carcinoma, Adenocarcinoma

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INTRODUCTION

Esophageal carcinoma is one of the most severe tumors worldwide owing to its rapid progression and fatal outcome. It is the eight most common cancer and the sixth leading cause of cancer mortality worldwide. The incidence of this disease varies widely with high incidences noted in South Africa and Northern China as compared to its Western counterparts.1 It accounts for about 5% (407,000 deaths) of all deaths due to cancer annually. It remains to be a highly lethal malignancy with overall 5-year survival rate of only less than 20 %. The aim of this study if to describe the demographic profile, risk factors, clinical presentation, usual diagnostic findings and treatment outcomes of esophageal cancer patients in the Philippines.

OBJECTIVES

Describe the demographic profile, clinical features, diagnostic findings and treatment of esophageal cancer patients in UST Hospital

Specific Objectives:

1. Describe the following: a. mean age of presentation, b. gender predilection, c. associated risk factors, d. clinical features
2. Discuss the endoscopic and imaging findings of esophageal carcinoma
3. Determine the histopathologic type of disease
4. Determine the staging of disease
5. Discuss the different treatment options
6. Determine the mortality rate of esophageal cancer patient

REVIEW OF RELATED LITERATURE

Esophageal carcinoma is one of the most destructive neoplasms in the gastrointestinal tract due to its late diagnosis, older age of onset and accompanying nutritional disorders due to esophageal obstruction.2 It has a diverse incidence, with high indices noted in Asian countries.3,4 Esophageal cancer is more frequent in older male individuals, ingestion of caustic substances, Barrett Esophagus (BE), megaesophagus and human papiloma virus infection.5

Esophageal cancer is classified histologically as squamous cell carcinoma (SCC) or adenocarcinoma (AC). During the past 30 years, multiple investigators have demonstrated that the incidence of adenocarcinoma in the US, Europe and other Western countries has significantly increased compared with esophageal squamous cell carcinoma.6 Presently, Esophageal AC is the predominant type in the West while SCC is still the most prevalent type in Eastern countries including Asia. SCC results from the formation of non-keratinized stratified squamous epithelium and is more common in developing countries. The preferential area of growth of SCC are the middle and upper thirds of the esophagus.2,7 Adenocarcinoma, on the other hand, usually occurs in the lower third of the esophagus and results from intestinal metaplasia (Barrett's), due to chronic gastric reflux.8

For esophageal SCC, the two most common risk factors are cigarette or tobacco smoking and excessive alcohol consumption.9 When combined, they also form a

synergistic effect further leading to increased risk. The highest risk has been reported in tobacco smoking but other forms such as Asian betel quid have also been linked to its progression. Alcohol has a slightly lower risk compared to smoking with a risk of about 3 to 5 fold, but greatly increasing when the alcohol intake is beyond 140g/week. Nutritional deficiencies have also been implied as having a strong relationship. This includes Vitamin A, C and E deficiency. HPV, specifically serotypes 16 and 18, and achalasia and its associated chronic mucosal irritation have also been linked to esophageal SCC. Patients with other esophageal disorders such as esophageal webs have also increased risk for SCC.10

Esophageal adenocarcinoma is believed to be 8 times more common in men than in women and has been linked to high socioeconomic status unlike SCC which is more commonly seen in SCC.1,11 Like SCC, tobacco smoking increases the risk for AC, but alcohol does not seem to be a prominent risk factor for this type. GERD leading to Barrett's esophagus seem to be the most important risk factor for adenocarcinoma.10 Obesity has been also found as a risk factor with a 2 to 3 fold increase in risk.12,13 H. pylori infection, on the other hand, has been found to be inversely related to AC due to reduction in gastric acidity.10

Patients with esophageal carcinoma, whether SCC or AC, have similar clinical presentation. Most patients are asymptomatic in the early stages. With time, weight loss and progressive dysphagia have been found to be the most common symptoms of disease.6 Dysphagia is seen initially with solids but progresses to liquids at the later

stages. Other symptoms may include odynophagia, chest pain, abdominal pain, hoarseness, etc.

Imaging studies are helpful in diagnosing and staging the disease. The diagnosis is mainly done through endoscopy with biopsy as this has the highest yield for diagnosis. Barium contrast esophagography is also a helpful tool in detecting the mass, but this has fallen out of favor due to the ease in utilizing endosocopy. CT scan and MRI can detect wall thickening/ irregularity, strictures and the intraluminal mass and can help in staging the disease.10

There are different treatment approaches for patients with esophageal carcinoma. If deemed potentially curable, a multidisciplinary approach should be instituted to discuss all the options of treatment. For the longest time, surgery has been considered as the standard of care for T1a, T1b and T2 cancers without nodal involvement or distant metastasis. A multimodal approach which includes surgery is indicated for T1 to T4a staging with lymph node metastasis.14 The reported rate of esophagectomy varies widely. In England, it is estimated to be at 26% while in Japan, it is estimated to be at 75%. In the Philippines, there is still a lack of data with regards to resection rates. According to previous studies, the 5-year survival rate for patients who undergo an esophagectomy ranges from 20% to 50%, but rarely exceeds 35%. Esophagectomy is associated with postoperative mortality rates that range from 1% to 13% in high-volume centers, and this may increase to 20% in low volume centers. It also has a high

postoperative morbidity ranging from 40-50%, and a substantial impact on the quality of life [8-13].

Because of the relatively high mortality and morbidity rate, several studies have been performed examining different methods such as neoadjuvant chemotherapy and/or radiation therapy in improving treatment outcomes.[14-17]. One of the largest trials that was recently published was the chemoradiotherapy for oesophageal cancer followed by surgery study or CROSS trial. This randomized trial compared neoadjuvant chemoradiotherapy (nCRT) plus surgery to surgery alone. This study concluded that the addition of neoadjuvant therapy significantly increased the survival rates of patients from a median overall survival of 24 months to 49 months. Because of this, neoadjuvant chemoradiotherapy plus surgery has become the standard treatment in Netherlands and several other countries for potentially curable esophageal carcinoma (T2-3N0-3M0 and T1N1-3M0).14

In the Philippines, because of the result of the CROSS trial, majority have adapted this standard of treatment although there is still a paucity of data in the country in terms of treatment outcomes.

This study will give us knowledge on esophageal cancer patients in the Philippines and determine the profile, risk factors, common histologic type, clinical presentation, usual diagnostic findings and treatment outcomes of this disease.

MATERIALS AND METHODS

Study Design and Participants

This is a retrospective cross-sectional study which included all adult patients, aged 18 years and above, diagnosed with esophageal carcinoma during the period from January 2010 to December 2015. Data will be retrieved by review of the medical records from the endoscopic database of the section of Gastroenterology and the patient database of the section of Medical Oncology and Radiation Oncology. Diagnosis of esophageal carcinoma will be confirmed by histopathology and the demonstration of typical findings in the endoscopy, CT or MRI. The demographic profile, risk factors, diagnostic findings, type of carcinoma, staging, mortality, and different treatments will be determined.

Outcome Measures

The demographic profile of the patients were retrieved such as age, gender, risk factors and comorbid conditions. Results of the imaging tests such as endoscopy, CT, and MRI were retrieved. The type of carcinoma, location, size and staging were determined. Interventions done to the patient were also studied including outcomes of the different treatment modalities.

Privacy and Confidentiality

All the data from the patients were kept private and confidential. Only the authors had access to the names of the patients and the data being presented.

Benefits

Data from this paper can be used to improve current practices on treating esophageal carcinoma.

Risk

There were no risks involved in the study.

Compensation and Expenses

The expenses of data collection, computer usage, printing were shouldered by the authors.

Conflict of Interest

All the investigators do not have financial and commercial affiliations.

Statistical Analysis

Data were encoded using MS Excel and data analysis was done using SPSS Statistics version 22. Quantitative variables were summarized and presented as mean, range and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. Categorical variables were tested using the fisher's exact test or chi-square test, where applicable.

RESULTS

During the period of the study, a total of 31 patients were included. The mean age was 58.5 years with a range of 24 to 78 years old. The patients were predominantly male (83.9%). Majority (77.8%) of patients had a smoking history, 58.4% of which were previous smokers while 19.4% were current smokers with a mean of 24.5 pack years. 31% had a history of tobacco use and 6.7% had a history of chewing betel nut as well. 42% earned less than 100,000 while 22.6% earned more than 200,000 pesos per year.

In terms of symptoms, the most common complaints were dysphagia (87.1%) and weight loss (45.2%). An endoscopy was done in all patients with biopsy of lesion for histopathology. 11(35.5%) patients each were found to have well and moderately differentiated carcinoma while 9(29%) had poorly differentiated carcinoma. 54.8% were found to have squamous cell carcinoma (SCC) while 45.2% had adenocarcinoma as histopathologic diagnosis.

4 (12.9%) patients were found to have atrophic gastritis and all of these were in the adenocarcinoma group. Hence, the presence of atrophic gastritis was found to be significantly higher in adenocarcinoma (28.6% vs 0%, p value 0.032). In terms of location of the lesion, 9 (29%) were found in the proximal esophagus and all of these were found to be squamous cell carcinoma. Majority (92.9%) of the adenocarcinoma group, on the other hand, were found either in the distal esophagus or in the gastroesophageal junction. This difference in location was statistically significant with SCC found in more proximal areas (52.9% vs 0%, p value 0.001) while adenocarcinoma was found more commonly in

the distal esophagus (92.9% vs 35.3%, p value 0.002). Majority (67.7%) of the patients had masses greater than 5cm in size during endoscopy.

In terms of staging of esophageal carcinoma, majority had advanced disease upon diagnosis with 38.7% having stage IV carcinoma. 25.8% had stage IIIa, 3.2% had stage IIIb and12.9% had stage IIIc. There were no patients classified as stage I during diagnosis.

For treatment, majority (38.7%) had chemoradiotherapy for treatment. 8 patients (25.8%) had neodjuvant chemoradiotherapy with surgery (CROSS protocol). 12.9% had radiotherapy only as treatment. 6.5% had surgery only while another 6.5% had no treatment done.

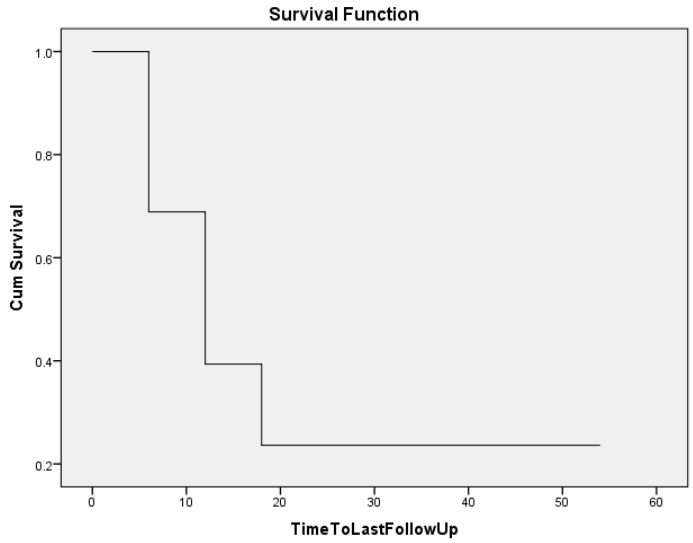
Table 1 Baseline characteristics of study population

	Total	Squamous Cell Carcinoma n= 17 (54.8%)	Adenocarcinoma n= 14 (45.2%)	p value
Age Mean Median	58.5 (24-78) 61	56.6	60.9	0.359
Gender Male (n/%) Female (n/%)	26 (83.9) 5 (16.1)	14 (82.3) 3 (17.7)	12 (85.7) 2 (14.3)	0.800
Smoking History Never Previous Current Pack years	 6 (19.4%) 18 (58.4%) 6 (19.4%) 24.5	 2 (12.5) 9 (56.3) 5 (31.3) 24.9	 4 (28.6) 9 (64.3) 1 (7.1) 24.1	0.523
Use of tobacco? Yes No	Data= 29 9 (31%) 20 (69%)	 3 (20) 12 (80)	 6 (42.9) 8 (57.1)	0.170

History of chewing Betelnut?	Data= 30			0.171
Yes	2 (6.7%)	2 (12.5)	0	
No	28 (93.3%)	14 (87.5)	14 (100)	
Socioeconomic status				
Less than 50,000/year	3 (9.7%)	1 (5.9)	2 (14.3)	0.798
50,000-100,000/year	10 (32.3%)	5 (29.4)	5 (35.7)	
100,000-200,000/year	11 (35.5%)	7 (41.2)	4 (28.6)	
>200,000/year	7 (22.6%)	4 (23.5)	3 (21.4)	
Clinical Presentation				
Dysphagia (n/%)	27 (87.1%)	15 (88.2)	12 (85.7)	0.835
Weight Loss (n/%)	14 (45.2%)	7 (41.2)	7 (50)	0.623
Odynophagia (n/%)	2 (6.5%)	0	2 (14.3)	0.107
Abdominal pain (n/%)	5 (16.1%)	2 (11.8)	3 (21.4)	0.467
Chest pain (n/%)	1 (3.2%)	1 (5.9)	0	0.356
Hoarseness (n/%)	2 (6.5%)	1 (5.9)	1 (7.1)	0.887
Loss of appetite (n/%)	2 (6.5%)	0	2 (14.3)	0.107
Globus (n/%)	0	0	0	
Melena (n/%)	1 (3.2%)	0	1 (7.1)	0.263
Endoscopic Finding	4 (12.9)	0	4 (28.6)	0.018
Atrophic gastritis (n/%)	3 (9.7)	1 (5.9)	2 (14.3)	0.431
H. pylori positive (n/%)				
Location	9 (29)	9 (52.9)	0	0.007
Proximal (n/%)	3 (9.7)	2 (11.8)	1 (7.1)	
Mid (n/%)	11 (35.5)	4 (23.5)	7 (50)	
Distal (n/%)	8 (25.8)	2 (11.8)	6 (42.9)	
GE Junction				
Size	0	0	0	
< 2 cm (n/%)	10 (32.3)	5 (29.4)	5 (35.7)	
2-5 Cm (n/%)	21 (67.7)	12 (70.6)	9 (64.3)	
>5 cm (n/%)				
Degree of Differentiation				
Well	11 (35.5)	8 (47.1)	3 (21.4)	
Moderate	11 (35.5)	7 (41.2)	4 (28.6)	0.079
Poor	9 (29)	2 (11.7)	7 (50)	
Staging of Disease			0	
IA	0	0	0	
IB	0	0	1 (7.1)	
IIA	2 (6.5)	1 (6.3)	3 (21.4)	
IIB	4 (12.9)	1 (6.3)	3 (21.4)	
IIIA	8 (25.8)	4 (25)	0	
IIIB	1 (3.2)	1 (6.3)	2 (14.3)	
IIIC	4 (12.9)	2 (12.5)	5 (35.7)	

IV	12 (38.7)	7 (43.8)		
Treatment				
None (n/%)	2 (6.5)	0	2 (14.3)	
Surgery (n/%)	2 (6.5)	3 (18.8)	5 (35.7)	
nCRT plus Surgery (n/%)	8 (25.8)	10 (62.5)	2 (14.3)	
Surgery plus Adj RT (n/%)	1 (3.2)	1 (6.3)	0	
Surgery plus Adj Chemo (n/%)	2 (6.5)	1 (6.3)	3 (21.4)	
CRT (n/%)	12 (38.7)	0	2 (14.3)	
RT (n/%)	4 (12.9)	1 (6.3)	0	

In this series, the median follow up time is 5.8 ± 9.3 months. The cumulative survival using Kaplan-Meier in 6 months and 12 months are 39% and 24%, respectively.



There were no significant differences in survival among SCC or AC (p= 0.506) and those who received treatment following the CROSS protocol or those who did not (p= 0.083). Expectedly, survival was statistically different between the different stages of disease (p= 0.001). The median survival of patients with stage IV disease was 3 months.

DISCUSSION

The demographic profile, clinical features, endoscopic and histopathologic findings, staging and treatment were analyzed in this study. The age of patients were similar from previous studies that showed a greater incidence in those that were greater than 50 years old with no difference between SCC and AC.5 In the present study, the mean patient age was 56.6 for SCC and 60.9 for AC with no difference between them (p value 0.359). Both groups showed a predominance of male patients (82.3% for SCC, 85.7% for AC, p value 0.8) that was the same as previous studies.1,5

One of the major risk factors of esophageal carcinoma is smoking which was seen in our study with a mean of 24.5 pack years. Other risk factors such as tobacco use (31%) and chewing of betel nut (6.7%) were seen in the patients. In some studies, it was shown that patients who had SCC were in the lower socioeconomic class as compared to AC which was better seen in the higher socioeconomic class but this was not shown in our study.10 There was no statistical difference seen among the 2 groups.

The common clinical symptoms of esophageal carcinoma in our study were the same as previous studies.11

For the EGD findings, there were 4 patients who had atrophic gastritis and all of them were in the AC group. Only 3 patients tested positive for H. pylori and the results were not statistically different between the groups. Most lesions in the SCC group were found in the proximal esophagus while most lesions in the AC group were found in the

more distal areas (p value 0.007). This was consistent with results from previous studies. Majority of lesions in the study were already greater than 5 cm and this may be attributed to the late stage upon diagnosis of patients in the study.

Most patients were diagnosed as stage IV disease while there were no diagnosed Stage 1 disease. This further emphasizes the need for fast work-up and diagnosis as this is a rapidly worsening disease with nonspecific symptoms that is usually diagnosed late in the spectrum of disease. Majority of the patients were only given chemotherapy and this may be because of the late stage of diagnosis of disease. But it is important to note that there is an increasing number of patients, especially in the most recent years, who underwent neoadjuvant chemoradiotherapy followed by surgery which is the current standard of treatment for esophageal CA patients with noted excellent results.15 All of the patients who underwent neoadjuvant chemoradiotherapy followed by surgery were still alive up to the present although because of the relatively new guidelines on the CROSS protocol, length of follow up is still not enough to determine statistical difference.

Overall survival analysis was found to be low further emphasizing the severity of esophageal carcinoma. This high mortality is similar to previous studies.

There are several limitations to the study. First is the small population size of participants. It would be better to analyze the different factors and include survival analysis if there were more patients included in the study. Also, because this is a retrospective study, some of the data such as other risk factors, cannot be retrieved from

the databases and charts. The authors would like to recommend a prospective study on esophageal cancer and/ or a follow up retrospective study with longer duration of years to include more patients.

CONCLUSION

Esophageal carcinoma is a vicious disease with high mortality with a 6 and 12 month survival of 39% and 24% and median survival of 3 months for stage IV disease. It is usually diagnosed late in the disease spectrum. Demographic and clinical characteristics were similar from previous studies. SCC was slightly higher than adenocarcinoma with SCC seen in the proximal areas and adenocarcinoma in the distal areas. Atrophic gastritis was seen more commonly with adenocarcinoma. An accurate history, examination and reliable endoscopic and imaging findings are important for early detection and diagnosis leading to effective treatment.

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