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ORIGINAL ARTICLE

DISTAL OESOPHAGEAL CANCER AND ITS HISTOLOGICAL PATTERN: A FIVE YEARS RETROSPECTIVE REVIEW AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM

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ABSTRACT

Background: *Esophageal carcinoma is a significant cause of morbidity and mortality among cancer patients in Tanzania. Squamous cell carcinoma is the most predominant subtype encountered. But the adenocarcinoma might also occur, especially in the distal third of the esophagus. Risk factors and treatment of these two histological subtypes vary significantly. Hence it is important to understand the true prevalence of Distal oesophageal cancer and that of adenocarcinoma. This study aimed to understand the prevalence of Distal oesophageal cancer and that of adenocarcinoma.*

Methods: *This was a retrospective chart review for patients treated with oesophageal cancer from April 2013 to April 2017 at Muhimbili National hospital. Patients with Distal oesophageal cancer were identified and their socio -demography, Takita's dysphagia grade, tumor length from the upper incisor teeth, endoscopic tumor morphology, histology and stage of the disease was abstracted. Data was analyzed using SPSS where descriptive statistics were computed. Associations were determined using chi-square test with significance set at <5%. Ethical approval was obtained from Muhimbili University Institutional Review Board.*

Results: *Distal oesophageal cancer made 34.1% of all esophageal cancers, with no variations over the five-year review. The mean age of patients with Distal oesophageal cancer was 59.7 years with female predominance at 2:1 for men. Adenocarcinoma was the most predominant histological subtype at 3:1 for squamous cell carcinoma. Low socio-economic status, alcohol drinking, smoking cigarettes and positive history suggestive of Gastro Oesophageal Reflux Disease were common among these patients. Most of the tumors are fungating with late presentation judged clinically with dysphagia as the most common presentation.*

Conclusion: *Clinicians and researchers should be aware of the higher incidence of Distal oesophageal cancer presenting with adenocarcinoma. Failure to recognize this unique entity in a region where squamous cell carcinoma is the most predominant type might result in misinterpretation of data and misallocation during treatment and prognostication.*

Keywords*: Distal oesophageal cancer; Distal esophageal cancer; esophageal adenocarcinoma; gastro esophageal cancer; esophageal cancer trend*

INTRODUCTION

Oesophageal Cancer (EC) ranks seventh globally in incidence and sixth in mortality accounting for 1 in 20 of all cancer-related mortality in 2018 (1). EC exhibits geographical variations with rates reported to be higher in Eastern Asia and Eastern Africa regions including in Tanzania (2). Two commonly encountered histological subtypes also show significant geographic variation: oesophageal Squamous Cell Carcinoma (ESCC) is predominant in many Low – and – Middle-Income settings (LMICs) and oesophageal adenocarcinoma (EAC), typically occurring in the distal oesophageal , is predominant in the High-Income Countries (HICs) settings (3).

Therefore, to properly understand EC in any region, it is important to take into consideration this histological variability as they have different risk factors to address. The synergistic effect of heavy drinking and smoking has been responsible for risk factors for ESCC in the HICs while the risk factors in LMICs are still elucidated (4). The increasing prevalence of obesity and waist circumference, GERD, and the decline in H.pylori infection due to improvements in hygiene are speculated to be responsible for the increase in EAC in the HICs (5). With rapid westernization in many LMICs, how these factors shape the histological subtype in the distal oesophageal had remained unknown.

Furthermore, the treatment classification and outcomes measures differ significantly between the two histological groups just as is their aetiology (6). In Tanzania, EC ranks 5th by contributing to 2,516 cases and is 3rd in mortality by 2,486 cancer-related deaths in 2018 alone (7). The true impact of westernization on distal oesophageal cancer, which should be predominantly EAC, has remained unknown and unattended. This has led to misclassification of patients with

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EC by grouping them as a similar entity of disease by the clinicians. Understanding distal oesophageal cancer burden and its histological subtype hence became a necessity to address the disparities in research and treatment among patients with EC in Tanzania and the region, which this study aimed to address. This study will add value to the on-going case-control studies in this region and also address outcomes among these patients.

METHODS

Study design and setting
This was a hospital-based retrospective study conducted at Muhimbili National Hospital (MNH) and Ocean Road Cancer Institute (ORCI) from April 2013 to April 2017. The two hospitals, both located in Dar es Salaam, provide comprehensive cancer management in Tanzania. MNH offers diagnostic and surgical care to EC patients, and ORCI offers chemotherapy and radiation therapy services to the same patients.

Study population
Patients who presented with dysphagia and were diagnosed to have EC during the study period were involved. Cases were included if they had histological confirmation of EC from MNH pathology laboratory, and had endoscopically detected lesions at or below 30cm from upper incisor teeth. Patients of all sexes and age groups were included.

Subjects identification
The Muhimbili National hospital histopathology registry was examined to identify all patients with a diagnosis of oesophageal cancer during the period under review. Hospital registration numbers, names and sex were collected in an excel spread sheet identifying 1200 cases. Since some patient might have reached ORCI without going through MNH histopathology registry, similar exercise was repeated by collecting all the hospital registration numbers, names and sex on a separate excel spread sheet identifying 1056 cases. The two excel spread sheets were merged to remove duplicates whereby 1000 patients with oesophageal cancer remained in the final excel spread sheet. The 1000 case notes were reviewed to identify EC patients with an endoscopic diagnosis of distal EC. The two lists were compared for similarity and where discrepancy arose, an independent abstractor was assigned to repeat the abstraction process for the individual case.

Study power
With 34.1% of patients having distal oesophageal carcinoma, the study had the power of 80% to detect the difference of less than 5% with 95% confidence interval of between 0.3116 and 0.3713.

Variables collected
Variables collected from the case notes included demography of the patients: age in years, occupation of the patient, level of education, Risk factors include: smoking, alcohol intake, reported a family history of oesophageal cancer, features of GERD. Clinical features including the modified Takita's dysphagia score, the endoscopic tumour location from the upper incisor teeth and tumour morphology, the histological tumour type, and stage of the disease.

Data analysis
Data were checked for completeness, de-identified, coded, and entered into Statistical Package for Social Scientists (SPSS) software version 26 for analysis. Categorical variables were summarized as proportions while continuous variables were summarized as means with standard deviation. Tumour location was sub-grouped as at 35cm, 35 to 36cm, and at 37cm and compared by the two histological subtypes. Significant differences in histology by the length from the upper incisor were considered when the p-value was less than 5%. Patients were grouped as young (< 40years), middle-age (40 – 60years), and elderly (> 60 years of age). The proportion of patients with the common risk factors was computed among those in whom they were reported. The trend over five years was computed by comparing the proportion of distal EC over total EC during each year and plotted on a line curve.

Ethics approval
The study protocol was reviewed and approved by the Institutional Review Board of the Muhimbili University of Health and Allied Sciences and permission to conduct the study was obtained from Muhimbili National Hospital and Ocean Road Cancer Institute administration. No direct patient identifiers were used during data analysis following the de-identification process.

RESULTS

We identified 1000 case notes of patients with a histological diagnosis of oesophageal cancer of which 341 were found by endoscopy to have a distal oesophageal cancer giving an incident rate of 34.1%. In **Table I** below, we describe the socio-demography and risk factor profile of patients with distal EC. They had a mean age of 57.9±13.7 (29 – 92) years and the majority were 40 years and older. Females were the majority with a female to male ratio of 2:1. Most patients had low socioeconomic status characterized by a primary level of education in 260 (76.3%) and peasant as occupation in 189(55.4%).

Table I: Demography, risk factor profile and year of diagnosis of patients with distal oesophageal carcinoma at MNH 2013-2017

Variable	Frequency (%)
Age groups (years)	
< 40	39 (11.4)
40 to 60	152 (44.6)
> 60	150 (44.0)
Sex	
Male	112 (32.8)
Female	227 (66.6)
Education level attained	
Primary	260 (76.3)
Secondary	68 (19.9)
Secondary and above	13 (3.8)
Occupational status	
Peasant	189 (55.4)
Employed	117 (34.3)
Not employed	35 (10.3)
Family history of EC (n=321)	
Yes	40 (12.5)
No	281 (87.5)
Alcohol (n=321)	
Yes	227 (66.6)
No	114 (33.4)
Smoking cigarette (n=273)	
Yes	132 (48.4)
No	141 (51.6)
History of GERD (n=321)	
Yes	200 (60.4)
No	131 (39.6)

Of the assessed risk factors, alcohol information was available in all the patients of which 66.6% reported having used it. Family history was positive in 12.5% of 321 cases. GERD presentation was collected in 331 with 60.4% reporting positive history. Cigarette smoking was reported in 48.4% of the 273 patients.

In Table II, we present the clinical presentation as dysphagia grade assessed by modified Takita's grading system summed in four groups with combined Grade five and six. A majority had grade three dysphagia in 163 (47.8) followed by grade II dysphagia in 123 (36.1). The most predominant endoscopic morphology was that of a Fungating tumor seen in 288(84%) of the patients followed by that of ulceration in 38(11.1%). Histologically, tumors were either adenocarcinoma or squamous cell carcinoma with the former being the most predominant type in 249(73%).

An overwhelming majority of the patients were reported to have a locally advanced disease clinically in 290 (85%).

The mean tumor location from the upper incisor for the distal adenocarcinoma was 35.7±2.8 (32 – 40) cm. We grouped tumors as below 35cm, from 35 to 36cm, and at 37cm and beyond. Adenocarcinoma was predominantly present at all intervals of the distal oesophageal when compared to oesophageal carcinoma. This dominance was significantly increasing downwards (p=0.0001). [**Fig. 1**]

Table II: Clinical presentation, endoscopic tumor morphology, histologic type and stage at diagnosis for distal oesophageal cancer at MNH 2013-2017.

Variable	Frequency (%)
Modified Takita's dysphagia grade	
Grande 2	123 (36.1)
Grande 3	163 (47.8)
Grande 4	30 (8.8)
Grade 5 and above	25 (7.3)
Tumor endoscopic morpholo-gy	
Fungating	288 (84.5)
Ulcerative	38 (11.1)
Stricturing	9 (2.6)
Infiltrative	4 (1.2)
Not documented	2 (0.6)
Histological type	
Adenocarcinoma	249 (73.0)
Squamous cell carcinoma	92 (27.0)
Stage at diagnosis	
Locally advanced	290 (85.0)
Metastatic	46 (13.5)
Not documented	5 (1.5)

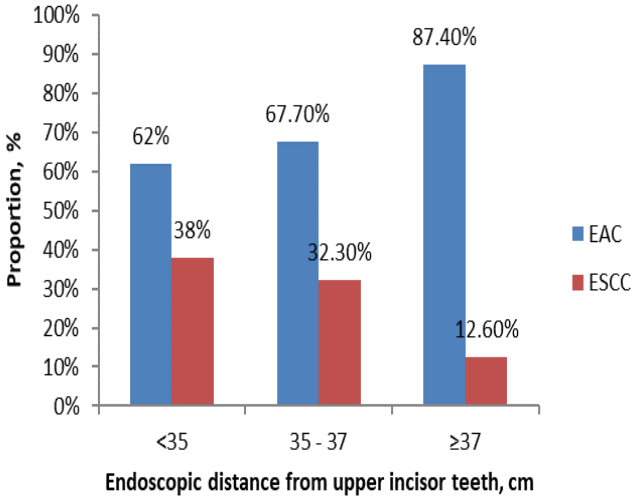

Figure 1: Columns showing three distance categories from upper incisors teeth stratified by histologic diagnosis for distal EC.

We finally evaluated to see if distal oesophageal carcinoma has been increasing over the five years. **Fig. 2** depicts a near stable pattern whereby distal oesophageal cancer constitutes about 30% of oesophageal cancer. There was an almost 9% drop in 2015 but a steady rise was seen in 2016 continuing through to 2017.

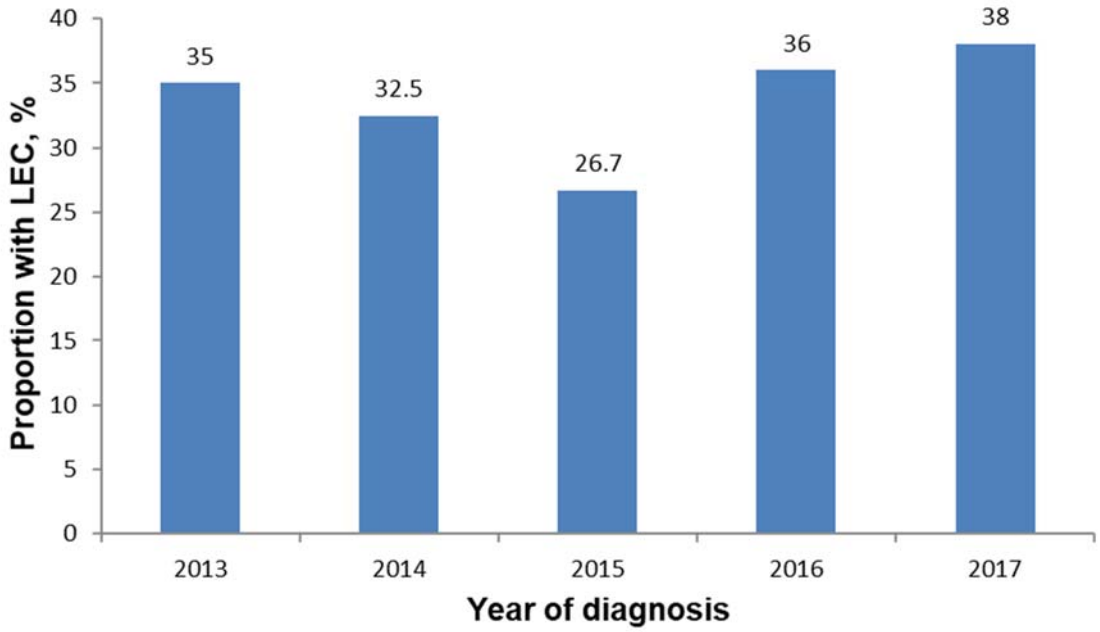

Figure 2: Bar chart showing five year trend of distal oesophageal cancer in Dar-es-Salaam from 2013 – 2017.

DISCUSSION

Incidence of distal cancer

This is the first study that looked at distal EC in a region recognized globally as a high-risk belt for EC in general.

We report a predominance of adenocarcinoma (AC) in the distal oesophageal in a geographic region where the usual predominant subtype has been SCC: 1 in 3 histological subtypes identified were of EAC. However, the prevalence of SCC in the same region was still high when compared to the picture seen in Europe and the US (8, 9). Overall, SCC is still the most predominant cancer globally with EAC now constituting about 40%, up from 10% 4 decades ago (10). The predominance of distal EAC in the west has been linked to the rise of risk factors such as obesity, gastroesophageal reflux, and Barrett's oesophageal (11). The exact risk factors for EAC in this setting remain unknown, likewise that of ESCC. Current risk factor studies have focused on SCC, but with this picture of a similarly higher prevalence of EAC, there is a need to not forget that the risk factors might be different. Segregation of data based on histology cannot be avoided to get accurate data on EC risk in this region with a high incident case.

Alcohol, Smoking, and GERD

Two fifth of patients with distal EC had a positive history of smoking and 2 in 3 of the patients had reported being taking alcohol. Both cigarette smoking and alcohol intake are known to be strong risk factors for ESCC with little conclusion on their role on EAC of the oesophageal (12). The confounding effect of other factors responsible for the development of distal oesophageal malignancies needs to be further explored in this setting. The just -completed case-control study on EC in Tanzania, carried out at MNH, focused only on ESCC.

Gastroesophageal Reflux Disease (GERD) has long been known to be a predisposing factor for the development of Barrett's oesophageal (13). GERD is not properly investigated in our setting but a prolonged history of heartburn was taken as a surrogate for GERD.

However, racial differences in the occurrence of GERD were seen in the US with a distal incidence among black when compared to whites (14). This was despite other studies showing the similar prevalence of heartburn, of all severities, among races (15). But, with more than half of our patients with distal EC reporting a positive history of heartburn, the role of GERD should not be underrated. Identifying patients with GERD in society and treating them has been shown to reduce the incidence of AC of the oesophageal and oesophago-gastric junction (EGJ) in the west (16). Studying the prevalence of GERD in Tanzania and instituting medical treatment and follow up therefore has the potential to address EAC in the distal oesophageal.

Smoking and features suggestive of GERD together with obesity have long been known to be causative of distal EAC of the oesophageal (17). In Tanzania, obesity is not anticipated among people of low socio-economic status unlike in the High- Income countries (18). In Tanzania, obesity has been noted to be more prevalent among high socioeconomic status groups, especially among women (19, 20). Looking at academic status and employment status, most of the patients we reviewed here had low socioeconomic status. This makes the potential role of obesity, though not studied, doubtful but still probable in our setting. A comprehensive study, evaluating all the currently known risk factors for distal oesophageal EAC is urgently needed as there is the potential to intervene.

Gender disparities

While it is known that EC, both EAC, and ESCC, is a male predominated disease (21), our findings suggest a higher prevalence of distal EC among the female sex in the Tanzanian population. Hypothesis towards the male predominance in the West was linked to the protective role of oestrogen among females, lost as they attain menopausal status (22). Oestrogen receptors are known to induce oesophageal cell apoptosis, hence preventive for both ESCC and EAC in western populations (23). The endogenous oestrogen effect is lost following menopausal attainment. Being a retrospective study, the menopausal status of EC patients is not routinely captured hence was not studied. But it is known that African women reach menopause almost a decade or earlier compared to western counterparts (24). Women in Africa might therefore not have these oestrogen protective effects against oesophageal cancer. But this selectively higher female prevalence in the distal oesophageal needs further scrutiny.

Genetic predisposition

About 1 in 10 of our patients had a documented history of having a family relatedness that had developed EC. Genetic predisposition is unusual except with palmar and plantar keratosis (tylosis) where up to 95% of victims will develop EC by age 65 (25). It is important to study these patients further during the clinical assessment to document the presence or absence of palmar and plantar keratosis. This familial clustering, though rare, is shown to occur at a relatively young age and is associated with a poor prognosis (26). Quantifying the number of family members affected is needed among these patients to rule out the possibility of chance alone (27). The involvement of two or more first-degree family members with EC had up to 10-fold increased risk for cancer (28). There is a possibility of genetic risk that is based on the Nucleotide Excision Repair pathway which is exacerbated by ever-smoking, overweight/obesity, male sex, and ever drinkers (29). Epidemiological studies properly assigning genetics risks coupled with targeted genetic studies among younger victims of EC are needed in the African population.

Management implications

The two histological subtypes demand different management approaches hence every effort should be made to have this clear to practicing clinicians and oncologists. The recently launched Tanzania National Cancer treatment guideline did not make this distinction. Even though occurring in the same location, EAC and ESCC are staged differently (with regards to primary tumour status and tumour grade for stage I – IIIb) hence the need to pay attention to this histological difference in the distal oesophageal (30). Failure to properly stage these patients might result in misplacement in treatment category suitability. EAC in the distal stomach might be categorized as gastric cancer or EC according to Siewert-Stein classification for Gastroesophageal junction tumours.

Tumour location was only provided as the distance of the upper margin from the upper incisor teeth. This is contrary to the current requirement by the 8th edition of the AJCC staging system for all EC to be reported from the epicentre of the tumour and be assigned c (31). This is important for treatment planning and can either be obtained endoscopically if no complete obstruction or by chest computed tomography. Similarly, knowing the epicentre is more important for adenocarcinoma of the distal oesophageal as it can reclassify them as either oesophageal cancer or gastric cancer according to Siewert-Stein's classification. Distal adenocarcinomas with epicenters no more than 2cm from the gastric cardia are classified as oesophageal carcinoma while the rest are adenocarcinomas. (32)

Management of EC has significantly evolved over the years with the introduction of neoadjuvant Carboplatin and Taxol plus 41.1Gys concurrent therapy followed by surgery. This study demonstrated significant benefits for the ESCC and only marginal benefits for EAC (33). It is important to follow current evidence when managing patients with distal oesophageal cancers. This can only be realized if patients are properly assigned a proper histological diagnosis and further sub-categorization of the EAC groups into the three Siewert groups.

Conclusion

Distal oesophageal cancer is not uncommon in Tanzania, affecting 1 in 3 patients with EC. We have demonstrated a higher predominance of oesophageal adenocarcinoma over squamous cell carcinoma occurring in these patients. Failure to recognize this unique entity in a region where squamous cell carcinoma is the most predominant type had led to misinterpretation of data and misallocation during treatment and prognostication. This present study highlights the urgent need to consider this entity of patients in the case-control studies and treatment strategies. Further research is needed to fully expose the aetiology of oesophageal adenocarcinoma in Tanzania.

List of abbreviations

AJCC	America Joint Committee on Cancer
EAC	Oesophageal Adenocarcinoma
EC	Oesophageal Cancer
ESCC	Oesophageal Squamous Cell Carcinoma
GERD	Gastro oesophageal Reflux Disease
HIC	High Income Country
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
LMIC	Low and Middle Income Country
SPSS	Statistical Package for Social Sciences

Declarations

Ethics approval and consent to participate

MUHAS IRB approved this study in accordance with the declaration of Helsinki and waiver of consent was provided.

Consent for publication

MUHAS IRB provided consent for publication

Availability of data and materials

Data that gave this report shall be available on fair request to the corresponding author's institution.

Competing interests

All authors have completed the ICMJE uniform disclosure form (available at: http://dx.doi.org/10.21037/aoe-2020-geja-01). The authors have no conflict of interest to declare.

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Authors' contributions

(I) Conception and design: LO Akoko, FM Sudai; (II) Administrative support: LO Akoko; (III) Provision of study materials or patients: None; (III) Collection and assembly of data: FM Sudai, NE Kivuyo; (IV) Data analysis and interpretation: LO Akoko, and R Khamis; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors.

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Authors' information (optional)

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