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ORIGINAL RESEARCH

Clinico-Pathological Findings and Spatial Distributions of Esophageal Cancer in Arsi Zone, Oromia, Central Ethiopia

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Purpose: Arsi Zone is one of the esophageal cancer endemic areas and is reported to have a high incidence of esophageal cancer in Ethiopia. This study assessed clinicopathological patterns and spatial distributions of esophageal cancer in Arsi Zone, Oromia, Central Ethiopia.

Methods: A cross-sectional study design was carried out by abstracting data of 403 patients treated from January 2015 to January 2019. Data were collected by using a structured data collection form and Geographical Positioning System software. The collected data were summarized in the form of tables, figures, means, and standard deviations. Statistical data analysis was done using SPSS software version 21.0 while geospatial analysis was conducted using the Arc-GIS 10.1 software.

Results: The disease was prominent among individuals aged 50 to 59 years. The mean age of females and males was 52.2 (SD±10.41) and 56.94 (SD ±12.27) years respectively. The vast majority (98.3%) of cases had squamous cell carcinoma. Dysphagia with weight loss accounted for 87.6% of the presenting symptoms. A large proportion (42.9%) of patients had a tumor located at the lower thorax. The majority (62%) of patients were from the eastern and north-eastern parts of the Arsi zone.

Conclusion: Dysphagia with weight loss was the major symptom during the first visit. Squamous cell carcinoma was the predominant histopathological type. Eastern and the northeastern parts of the Zone are the most affected regions. Future studies should focus on the determinants of esophageal cancer and precise areas with high incidences by using the population and/or facility-based cancer registry systems.

Keywords: esophageal cancer, clinical pattern, geographical distribution, Arsi, Ethiopia

Introduction

Esophageal cancer (EC) is a malignant tumor that develops inside the esophagus as the result of alteration in epithelial linings.[1] It is the 7th cancer in incidences and the 6th cause of cancer mortality in the world.[2] World Health Organization (WHO) identified Squamous Cell Carcinoma (SCC) and Adenocarcinoma (AC) as the major tissue types of esophageal cancer.[3] Adenocarcinoma is more prevalent in developed countries such as in the United States, United Kingdom, Scandinavia, France, Switzerland, Denmark, Italy, Slovakia, Netherlands, Australia, and New Zealand.[4]

Esophageal cancer has distinct geographical distributions within the country and across the globe.[5] In Canada, rural parts of the Quebec region have higher incidences of EC than other parts.[6] Similarly, considerable geographical variations were

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seen in the northeast and Midwest regions of America.[7] Corresponding variations were observed in different regions of France, Denmark, and the Netherlands.[8] Squamous cell carcinoma is the predominant type of EC in developing countries.[9] Eastern Turkey, northeastern Iran, Kazakhstan, and northern and central China are the hot spot areas in Asia's EC belt.[10]

Projection of cancer in Africa anticipated staggering increases in cancer corresponding to 1.27 million new cases and 0.97 million deaths in 2030.[11] The incidences of EC were rare until the 1930s in East, Central, and Southern Africa.[12] With gradual increases over time, eastern and southern Africa became the epicenter of esophageal carcinoma.[5,13–15] Concentrations of EC cases were notably observed in rural and Eastern Cape provinces of South Africa,[16] western parts of Kenya,[17,18] among Darfurian tribes in Sudan,[19] and populations living in Kilimanjaro areas in Tanzania.[20]

In Ethiopia, there is no reliable data on incidences of EC so far. Cancers of different organs account for about 5.8% of total national mortality.[21] Arsi Zone was one of the EC endemic areas in Africa's esophageal cancer belt for years,[22] and a constantly reported high incidence area of EC in Ethiopia.[23,24] An epidemiological study in the Oromia region showed that 68% of EC patients were from Arsi and neighboring Zone.[25]

Identifying a cluster of cases of EC within the endemic area is crucial in highlighting high-risk populations and generating hypotheses about the potential risk factors associated with that disease.[23,24] Yet, except few observational studies at country and regional levels,[23,25,26] no study has ever been conducted to assess the clinicopathological patterns and spatial distributions of esophageal cancer in esophageal cancer endemic areas in Ethiopia.

Therefore, this study was conducted to determine the clinicopathological patterns and spatial distributions of esophageal cancer in Arsi Zone, Oromia, Central Ethiopia.

Materials and Methods

Setting

Arsi Zone is found in the central part of the Oromia Regional State in central Ethiopia. Asella is the capital city of Arsi Zone located 175 Kilometers South East of Addis Ababa (the capital city of Ethiopia). Data were collected from surgical, oncology, endoscopy, and pathology units of seven referral hospitals and four clinics that render diagnostic services, consultations, and cancer treatments (Additional File 1). The data collection period covers from January 1 to February 30, 2019.

Study Design

A cross-sectional study design was carried out by abstracting data of 403 patients treated from January 2015 to January 2019.

Source Population

All EC patients from Arsi Zone who visited the selected health facilities during the study period were considered as source populations.

Study Population

The study populations constituted radio-graphically diagnosed and pathologically confirmed EC patients from Arsi Zone.

Inclusion and Exclusion Criteria

Endoscopy and pathologically confirmed esophageal cancer patients with complete data were included. Records of 85 patients (78 documents with no endoscopy findings and 7 patients with incomplete address) were excluded from the study.

Data Collection Instrument and Procedures

Data were collected by five trained BSc nurses using close-ended questionnaires (checklists) that comprised demographic characteristics (age, sex, and residence), clinical, histopathological type of cancer, tumor location, degree of tumor differentiation, cancer stages, and the primary residences of the patients. The severity of dysphagia was graded as follows: grade 1: normal swallowing; grade 2: difficulty in swallowing solids; grade 3: difficulty in swallowing semisolids; grade 4: difficulty in swallowing liquids; grade 5: difficulty in swallowing own saliva. The clinical staging was performed using TNM (American Joint Committee on Cancer (AJCC) cancer staging manual); this is a staging system that is an expression of the anatomical extent of the disease based on the extent of the primary tumor (T), absence or presence of and extent of regional lymph node metastasis (N) and absence or presence of distant metastasis (M).[27] The administrative units, geographical locations, and agro-climatic divisions were gathered from the Arsi Zone finance and economic development office while the topologies of the study area were

collected by using Geographical Information System (GIS) obtained from the agriculture departments of Arsi Zone (Additional file1 2).

Data Processing and Analysis

Questionnaires were checked daily for accuracy, consistency, and completeness by supervisors. Furthermore, the supervisor and the principal investigator gave feedback and correction on daily basis. Patients were categorized into highland, midland, and lowland agro-climatic divisions. The information related to administrative units (Districts) was extracted from the map of Arsi Zone with a scale ratio of 1:1200. The extracted demographic information on spatial locations was geo-tagged to the database containing administrative districts from where patients came.

The categorical variables of the cases were analyzed by descriptive statistical methods and presented in the form of tables and figures. Continuous variables were summarized using means and standard deviations. Statistical data analysis was done using SPSS software version 21.0 (SPSS, Inc, Chicago, IL, USA).

Categorical attributes of the number of males and females were identified and the coordinates of the point were taken using Geographical Positioning System (GPS) at the district level. The number of EC patients per district was used for delineating and mapping the distributions of EC per district in the Arsi Zone. Arc-GIS 10.1 software was used to automatically mark out and map the burden of cancer s per districts by incorporating CSI, 2013 Ethio- GIS administrative data. Finally, different types of colors were used to indicate the burden of EC cancer per district based on the following category: Red color for the districts which had 31 and above patients, Pink color for the districts which had 21 to 30 patients yellow color for the districts which had 11 to 20 patients and Green color for the districts which have 1 to 10 patients.

Results

Patients' Characteristics

Out of 403 patients whose cards were reviewed, 388 (96.3%) were rural residents. Two hundred nine (51.8%) patients were females. The male to female ratio was 0.93:1.0 with no statistically significant difference. The majority of patients (72.2% females vs 50.5% males) were below the age of 60 years. The overall mean age was 54.5 (SD±11.6) years. The mean age of female patients was 52.2 (SD±10.41) years which ranges from 25 to 85 years. The corresponding mean age for males was 56.94 (SD ±12.27) years with the age ranging from 19 to 88 years (Table 1).

Clinico-Pathological Characteristics

Concerning histopathological subtype, 396 (98.3%) cases had squamous cell carcinoma. The tumor was located at the lower thorax, mid thorax, and Gastroesophageal Junction (GEJ) among 42.9%, 26.1%, and 23.8% of patients, respectively. Furthermore, 168 (41.7%) of patients had moderately differentiated tumors while there were no conclusive reports on the degree of tumor differentiation for 47 (11.7%) cases. A greater number of patients (87.6%) had dysphagia and weight loss during the first visit. The majority (42.4%) of patients were at the third stage of cancer while cancer staging was not determined for 76 (18.9%) of patients (Table 2).

The Magnitude of Esophageal Cancer in the Arsi Zone

Cases of EC were recorded from 25 (96.2%) of the existing 26 districts of Arsi Zone. The majority of the patients were from Robe,[28] Jaju,[17] and Diksis[29] districts followed by 21 to 30 patients being from Doddota, Sude, Zuway-Dugda, Lode-Hetosa, and Shirka districts. Seven districts (Amigna, Sire, Munessa, Merti, Chole, Lemu-Bilbilo, and Tiyo) accounted for 11 to 20 cases during the study period. The remaining ten districts (Bale, Guna, Gololcha, Honkolowabe, Hetosa, Seru, Tena, Aseko, Bekoji, and Digalu-Tijo) contributed one to 10 patients (Figure 1).

Table 1 Socio-Demographic Characteristics of EC Patients in Arsi Zone, Oromia, Ethiopia, 2020

Variables	Sex of the Participants		
	Male	Female	Total
	No. (%)	No. (%)	No. (%)
Residence			
Urban	8 (4.1)	7 (3.3)	15 (3.7)
Rural	186 (95.9)	202 (96.7)	388 (96.3)
Age of the participants			
≤19 years	1 (0.5)	0 (0)	1 (0.2)
20–29 years	2 (1.0)	3 (1.43)	5 (1.2)
30–39 years	8 (4.12)	15 (7.2)	23 (5.7)
40–49 years	31 (16.0)	49 (23.4)	80 (20.0)
50–59 years	56 (28.9)	84 (40.2)	140 (34.7)
60–69 years	60 (30.9)	46 (22)	106 (26.3)
70–79 years	30 (15.5)	9 (4.3)	39 (9.7)
≥80 years	6 (3.1)	3 (1.4)	9 (2.2)

Table 2 Clinico-Pathological Characteristics of Esophageal Cancer Patients in Arsi Zone, Oromia, Ethiopia, 2020

Variables	Sex of the Participants		Total
	Male	Female	
	No. (%)	No. (%)	
Histopathological types			
Squamous cell carcinoma	191 (98.5)	205 (98.1)	396 (98.3)
Adenocarcinoma	4 (1.9)	3 (1.5)	7 (1.7)
Tumor location			
Cervical	2 (1)	0 (0)	2 (0.5)
Upper thorax	15 (7.7)	12 (5.7)	27 (6.7)
Mid thorax	48 (24.7)	57 (27.3)	105 (26.1)
Lower thorax	89 (45.9)	84 (40.2)	173 (42.9)
Gastro Esophageal Junction	40 (20.6)	56 (26.8)	96 (23.8)
Degree of tumor differentiation			
Well differentiated	53 (27.3)	47 (22.5)	100 (24.8)
Moderately differentiated	77 (39.7)	91 (43.5)	168 (41.7)
Poorly differentiated	44 (22.7)	44 (21.1)	88 (21.8)
Report not conclusive	20 (10.3)	27 (12.9)	47 (11.7)
Presenting symptoms			
Dysphagia and weight loss	171 (88.1)	182 (87.1)	353 (87.6)
Vomiting	23 (11.9)	27 (12.9)	50 (12.4)
Cancer stage			
Stage 1	7 (3.6)	7 (3.3)	14 (3.5)
Stage 2	17 (8.8)	28 (13.4)	45 (11.2)
Stage 3	81 (41.8)	90 (43.1)	171 (42.4)
Stage 4	48 (24.7)	49 (23.4)	97 (24.1)
Not graded	41 (21.1)	35 (16.7)	76 (18.9)

Spatial Distribution of Oesophageal Cancer

In this study, 141 (35%) of patients were from the Eastern parts of the Zone. The northeast, southeast, and northern parts of the zone had a total of 108 (26.8%), 47 (11.7%), and 31 (7.7%) patients respectively. Additionally, Asella town-and surrounding district (Tiyo) contributed to a total of 30 (7.4%) patients while 27 (6.7%) and 17 (4.2%) cases were found to be the residents of the western and south-west parts, in that order (Figure 2). Out of the total cases, 178 (44.2%), 137 (34.0%), and 88 (21.8%) patients were from the districts located in the highland, midland, and lowland agro-climatic divisions, respectively.

Discussion

In this study, we attempted to review the clinicopathological patterns and spatial distributions of esophageal cancer in the Arsi Zone. Accordingly, vast proportions of the patients were rural residents similar to preceding studies that reported predominance of EC in rural areas.[16,23,27,29] A high proportion of EC among rural residents may be attributed to exposure to various environmental and occupational carcinogens.[17,29,30] Furthermore, Patel et.al. (2013) argued that the predominance of EC among rural populations is linked to infection from fungi and bacteria that replicate in grass-thatched houses.[17] Moreover, inadequate nutrient intakes and lower socioeconomic status could be another risk factor associated with increased incidences of EC among the rural populations.[31,32]

In the present study, 7.1% of patients were ≤ 39 years of age and the youngest male and female patients were diagnosed at the age of 19 and 25 years, respectively. This is contradictory to the pathogenesis of EC that usually increases with age and attaining a climax after 70 years.[1] Some studies in Africa also found increases in the proportion of young patients as early as 12 years of age.[18,33] The proportion of youngest patients in this study is greater than the findings in Ethiopia,[25] and Kenya.[18] Observing EC among younger populations may indicate early childhood exposure to the carcinogens that may alter the natural pathogenesis of the disease.

Dysphagia with weight loss accounted for 87.6% of the presenting symptoms. Besides, the majority of the patients were at advanced stages of cancer. Dysphagia and late presentations became the cardinal presentations of EC patients in Ethiopia,[23,25,26] Africa,[16,17,30,34–36] and elsewhere.[43,37,39,40] The reason could be that the esophagus has a remarkable capability to stretch until significantly blocked by a tumor.[38] Besides, presenting at a late stage of cancer with dysphagia could be linked to failure to understand the early symptoms associated with esophageal carcinoma.

Squamous cell carcinoma was the dominant (98.3%) histo-pathological type similar to previous studies in Ethiopia.[23,25,26,39] The finding is very conceivable since squamous cell carcinoma is the leading histopathological type of EC in developing countries.[1,40,41] The lower thorax was the commonest anatomical site for a tumor followed by mid thorax and GEJ with no significant differences between male and female patients. The finding is similar to the studies that found the lower thorax as the commonest anatomical site of esophageal cancer[34,39] but contrary to the studies that identified the middle thorax as a major cancer location in Ethiopia,[23,26] Uganda,[34] Tanzania,[27] Ghana,[28] and Pakistan.[42] The inconsistencies in tumor locations can be explained by differences in the

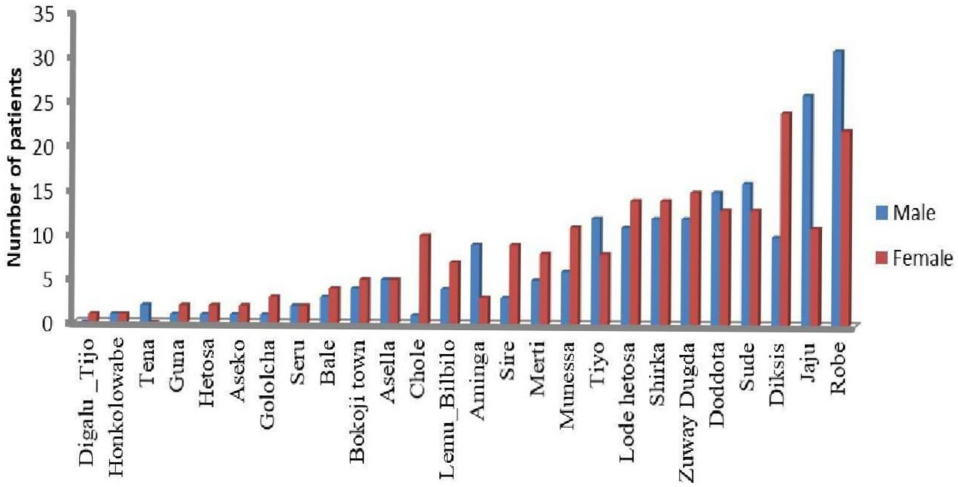

Figure 1 The number of esophageal cancer patients per district in Arsi Zone, Oromia, Ethiopia, 2020.

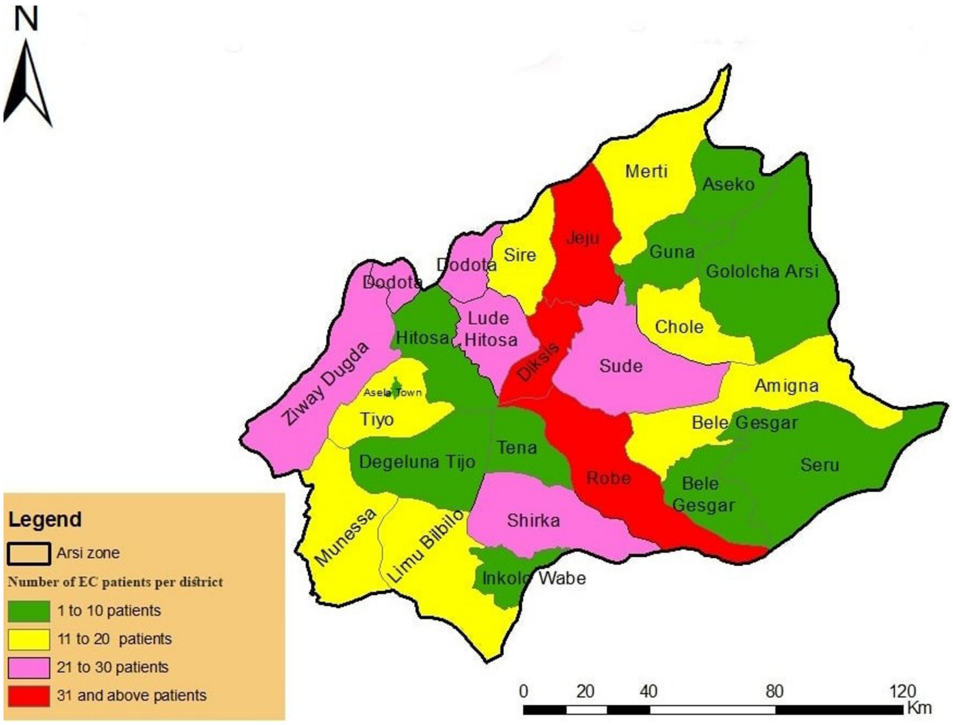

Figure 2 Map showing the spatial distribution of esophageal cancer cases in Arsi Zone, Oromia, Ethiopia, 2020.

classification of the anatomic sites. In this study, tumor locations were based on Watanabe et.al, of five (Cervical, upper, mid, lower, and GEJ) anatomical sites for the carcinogenesis of EC[3] contrary to other studies that used three (upper, mid, and lower) anatomical classifications.

The majority of the patients in this study had a moderately differentiated tumor differently from studies that found well-differentiated tumors among EC patients.[23,31] The disparities might be because of lower inconclusive results in this study (11.7%) than the rate of undetermined pathological results (62.7%) in the aforementioned studies.

The geographical distribution of EC in the Arsi Zone showed asymmetrical patterns. About 62% of patients were from the eastern and north-eastern parts. The majority of the patients were from the Robe district followed by Jaju, Disksis, and Sude districts. Additionally, Doddota, Zuway-Dugda, Lode-Hetosa, and Shirka were

succeeding districts in an increased number of cases. Besides, 44.2% of the cases were from the highland agro-climatic zone. The finding is in agreement with the study that reported high altitude areas as the main location of EC in the Arsi Zone.[35] The predominance of EC in those areas seems to be related to the population sizes because the eastern, north-eastern, and highland agro-ecological zone are the most populated areas in Arsi Zone.[43,44] In stratified analysis though, the effect of population sizes was not observed. For instance, the Robe district which had the highest number of cases encompasses equivalent population size (6.2% of the zonal population) to Munessa district that had only 4.2% of the total cases. Whereas, Jaju and Diksis districts that have lower populations had a higher number of patients than the Munessa district. Conversely, the 6th populated district (Digalu-tijo district) contributed to a single esophageal cancer patient.

Remarkably, greater numbers of patients were from contiguous districts that are located farther from the main referral hospital in the Zone. The clustering of EC at demarcated areas and the disparities between and within geographical locations are the peculiar characteristics of EC in Africa, Asia, and elsewhere.[10,22,45,46] High prevalence of EC in geographically adjacent areas may signal the existence of potentially harmful factors in high burden areas than areas with a lower prevalence of esophageal cancer. Nevertheless, there is no established evidence whether the routinely reported "hot wheat porridge consumption" is widely practiced in higher burden districts of Arsi Zone. In the wake of increasing chronic diseases in developing countries like Ethiopia,[11] the identified clinico-pathological findings and high-risk geographical areas can be used as the baseline for exploring the potential risk factors and designing preventive strategies.

Limitations

Being the retrospective study and absence of proper cancer registry systems influenced retrieving important sociodemographic and clinical information which might provide better perspectives to our study. Besides, identification of the patients' residents at the district level may not exactly locate the patient's exact agro-climatic areas due to existing overlapping in agro-ecological zones within the districts.

Conclusion

Dysphagia with weight loss was the major symptom during the first visit. Squamous cell carcinoma was the predominant histopathological type. Eastern and northeastern parts of the Arsi Zone are the most affected areas. The discrepancies in the geographical distribution of EC in the Arsi Zone may be primarily linked to differences in dietary practices, lifestyles, genetics, and exposure to environmental carcinogens. Education on early symptoms associated with EC and the benefit of timely seeking health care should be provided using various education channels. Future studies should focus mainly on the eastern and the northeastern parts of the Zone by using prospective studies through the population and/or facility-based cancer registry systems.

Abbreviations

AC, Adenocarcinoma; AJCC, American Joint Committee on Cancer; EC, Esophageal cancer; GEJ, Gastroesophageal junction; GIS, Geographical Information System; GPS, Geographical Positioning System; IRB, Institutions Research Board; REC, Research Ethical Committee; SCC, Squamous Cell Carcinoma; WHO, World Health Organization.

Data Sharing Statement

The datasets supporting the conclusions of this article are included in the article.

Ethics Approval and Consent to Participate

The study was approved by the Institutions Research Board (IRB) of Jimma University and it was conducted in accordance with the Declaration of Helsinki. The study participant's consent was waived by the review board as the study was conducted through a review of medical records. Permission to collect data was secured from respective health facilities. Confidentiality of the information was maintained by excluding personally identifiable information on the questionnaires.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and

interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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