RESEARCH ARTICLE

Patterns of Esophageal Cancer in the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012

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Abstract

Background: Esophageal cancer (EC) is among the most common malignancies in Eastern Africa, but the occurrence of EC in Sudan has rarely been described in the scientific literature. This paper reports the results of a consecutive case series of all EC patients who visited one of the two public cancer treatment centers in the country in 1999-2012, providing a first description of this disease in a treatment center located in central Sudan. Materials and Methods: Clinical and demographic data for all EC patients who visited the Department of Oncology of the National Cancer Institute at the University of Gezira (NCI-UG) from 1999 to the end of 2012 were abstracted and tabulated by sex, tumor type and other characteristics. Results: A total of 448 EC patients visited NCI-UG in 1999-2012, and the annual number of EC cases increased steadily from 1999. Squamous cell carcinoma (SCC) was the predominant EC tumor type (90%), and adenocarcinoma (ADC) was reported in 9.4% of the EC cases. The overall male-to-female ratio for EC was 1:1.8, but the ratio was tumor type-dependent, being 1:2 for SCC and 2:1 for ADC. Only 20% of EC patients reported having ever used tobacco and/or alcohol, and the vast majority of these patients were male. At the time of EC diagnosis, 47.3% of the patients resided in Gezira State. Some EC patients from Gezira State seek out-of-state treatment in the national capital of Khartoum instead of visiting NCI-UG. Conclusions: The annual number of EC patients visiting NCI-UG has increased in recent years, approximately half of these patients being from Gezira State. Although this consecutive series of EC patients who visited NCI-UG was complete, it did not capture all EC patients from the state. A population-based cancer registry would provide more complete data required to better understand EC patterns and risk factors.

Keywords: Esophageal cancer - case series - hospital-based - Gezira State - Sudan

Asian Pac J Cancer Prev, **16 (15)**, 6481-6490

Introduction

Esophageal cancer (EC), including squamous cell carcinoma (SCC) and adenocarcinoma (ADC), has a poor prognosis in the great majority of cases(Rustgi and El-Serag, 2014). Its global incidence has increased markedly in recent decades, representing the most rapid increase among major malignancies, with geographical differences in EC incidence exhibiting the greatest variability among cancers (Al-Samawi and Aulaqi, 2014). The esophagus is among the most common cancer sites in Eastern Africa (Bray et al., 2013). In contrast, in Western Africa, EC is very rare (Cook, 1971; Jemal et al., 2011). EC is estimated to be the fourth most common cancer in Sudan(Elamin et al., 2015), with an estimated age-standardized rate (ASR) of incidence of 5.3 cases per 100,000 people and a high ASR of mortality: 5.0 deaths per 100 000 people(Bray et al., 2013). This incidence rate was estimated based on 2001-2002 incidence rates from Aswan, Egypt, partitioned by cancer site, sex and age group using proportions obtained from the cancer registries of Gezira State (2006) and the city of Khartoum (2007). The mortality rate was calculated from the estimated national cancer incidence for 2012 and modeled survival (Bray et al., 2013). A study conducted at the Gezira Center for Gastroenterology and Laparoscopic Surgery (GCGLS) showed that in Gezira State, a greater proportion of women than of men were diagnosed with EC (3.3:1) (Mohammed et al., 2012). However, established risk factors for EC such as tobacco use (smoking or smokeless tobacco use) and alcohol consumption are rarely reported among women in Sudan (Idris et al., 1998).

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In the existing scientific literature, information about the occurrence of EC in Sudan is limited. Boulos and ElMasri (1977) analyzed the histopathological reports of 135 EC tumor specimens received in the Central Research Laboratory in Khartoum in1965-1974 (Boulos and El Masri, 1977), and Babekir et al. (1989) described 226 EC cases seen in 1979-1989 at the University Hospital and Radiation and Isotopes Center, Khartoum (RICK) (Babekir et al., 1989). Both studies showed that the disease affected males and females equally. In 2010, a cross-sectional study of 114 patients who underwent endoscopy in the endoscopy unit of Soba University Hospital in Khartoum found that 40% of the patients had EC (Mudawi et al., 2010). There are no population-based cancer registries in Sudan.

Typically, the referral process for EC patients in Sudan starts at a health center in the patients' village or district or at the nearest hospital, when symptomatic patients seek medical care. Patients are then referred by the attending physician to a hospital or private clinic for endoscopy with tissue biopsy and histopathology. The results of endoscopy and positive histopathology, along with a clinical report, are usually then transmitted to a cancer treatment center (the National Cancer Institute at the University of Gezira [NCI-UG] and RICK) at the time of referral of EC cases by the endoscopist. Some EC patients receive full coverage of diagnosis costs and partial coverage of treatment costs from government medical insurance. In addition, several companies provide private medical insurance, and some patients are willing to pay more than the cost of the government insurance for more comprehensive treatment coverage. This financial support from both public and private insurance providers helps encourage patients to seek health care and treatment.

There are only two public cancer treatment centers in Sudan: RICK, which was established in 1959, and NCI-UG, which was established in 1999 as the Institute of Nuclear Medicine and Molecular Biology and Oncology to provide cancer treatment (chemotherapy and radiation). A private center was established in 2010 in the city of Khartoum, in Khartoum State. In Gezira State, endoscopy is performed at the Center for Laparoscopic Surgery and Endoscopy in the Wad Medani Teaching Hospital, which belongs to the Federal Ministry of Health and cooperates with the University of Gezira. A total of seven clinicians perform endoscopy in the center and in private clinics. Histopathological evaluation is performed by the referral histopathology laboratory (which belongs to the University of Gezira's Department of Histopathology) and by private laboratories in the Gezira State capital of Wad Medani. These facilities in Wad Medani also serve patients from neighboring states, because the city is located relatively close to several state borders.

This paper reports the results of a consecutive case series of all EC patients who visited NCI-UG in 1999-2012, providing the first description of EC in patients visiting a treatment facility in Sudan. These results may also be representative of the disease characteristics of EC within the population of eastern Sudan in general.

Materials and Methods

Setting

NCI-UG, located in Wad Medani, began treating cancer patients in 1999. Only patients in whom cancer has been histopathologically confirmed receive treatment at NCI-UG. The NCI-UG's Department of Oncology serves about 4 million inhabitants of Gezira State and additional patients from nearby states, such as Sennar, Alqadarif and Kassala, which are connected to Wad Medani by a highway that runs between these states and Khartoum. The cancer treatment modalities available at NCI-UG include radiotherapy, chemotherapy and palliative. A complete clinical workup (ultrasound, X-rays, blood tests and tumor marker analysis) is carried out at NCI-UG after confirmation of a cancer diagnosis.

Patients with dysphagia, weight loss and other symptoms can seek health care either at the nearest public health care center or at a private clinic, and this choice often depends on patients' socioeconomic status. Patients may also seek treatment from traditional healers. Private clinics are relatively expensive but can provide a diagnosis more quickly than the public health care centers or hospitals covered by government health insurance. Within the public institutions, patients are referred by the medical officer to a referral teaching hospital when more-specialized investigations (such as endoscopy and histopathology) are needed. The endoscopist then refers patients to the cancer treatment center upon confirmation of malignancy.

Demographic and clinical data abstraction

A hospital-based study was initiated in 2013 to determine the number of EC patients who visited NCI-UG's Department of Oncology between 1999(when the center became operational) and the end of 2012, and to abstract these patients' demographic and clinical characteristics. These data, which are typically collected during the first patient visit and were abstracted from clinical records, include date of the first visit to NCI-UG, age at diagnosis, sex, ethnicity (specifically tribal background), place of birth or origin of the patient's family, place of residence at the time of treatment at NCI-UG, marital status and occupation. The town nearest to the patient's home and the patient's state of residence were also obtained from the hospital records. The clinical record also noted whether the patient had ever used tobacco or/and consumed alcohol, and for how long.

Information on the clinical presentation and symptoms (such as dysphagia and difficulty swallowing) present at the time of seeking treatment were available, as was the elapsed time between onset of symptoms and diagnosis or the visit with the clinician who referred the patient for endoscopy (in the patient's clinical history).The results of the first endoscopy and the name of the facility where it was conducted were also included in the hospital records for the majority of patients. The GCGLS was one of the main facilities that provided endoscopy services. Biopsy samples were evaluated by a pathologist. When cancer

was present, the tumor type (SCC, ADC or other rarer morphologies), grade of differentiation (well, moderately or poorly differentiated) and other histomorphological criteria were reported and available for data abstraction.

Ethical considerations

Ethical approval to abstract the data from clinical records was obtained from NCI-UG's ethical committee on January 30, 2011, as part of a proposed pilot study of EC in Gezira State. A waiver to request patients consent was obtained.

Statistical analysis

Abstracted demographic and clinical data were tabulated to determine counts and percentages by sex, tumor type and other characteristics using SAS 9.1 (SAS Institute Inc., Cary, NC, USA). The mean, standard deviation, range and median are reported for all continuous variables as appropriate. The mean distance between the cities in which EC patients underwent endoscopy and NCI-UG in Wad Medani was calculated using the website Gosur.com. This information was useful for estimating the distances that patients must travel to obtain medical care and for defining NCI-UG's catchment area.

Results

Demographic and other patient characteristics

A total of 448 EC patients were treated at NCI-UG in 1999-2012, and the annual number of EC patients increased steadily from 1999 (Figure 1). The male-to-female ratio was 1:1.8. Demographic and other patient characteristics are presented overall and by sex in Table 1. The age distribution of the patients (Figure 2) shows an increase in the number of EC cases with increasing age, peaking around 60-69years of age and then decreasing at older ages. The median patient age was 60 years, and patients aged 35 years or younger(n=27)constituted6.0% of the total number of patients, with similar proportions among females (5%) and males (8%).

The majority of EC patients were married (84.8%). Most female patients were housewives (94.1%), and46.3% and 36.4% of male patients were farmers and manual laborers, respectively (Table1). The patients were of various ethnicities; Guhaina was the most prevalent tribal origin (42.2%), followed by Jaali (23.9%; mostly concentrated in central Sudan), Beja (11.2%; in eastern Sudan), Darfurian (5.6%;in western Sudan) and others, as shown in Table 1.At the time of diagnosis, 47.3% of the EC patients resided in Gezira State and 20.8% resided in neighboring Alqadarif State. Relatively few patients resided in other parts of the country, such as Red Sea State, Kurdufan and River Nile State, as shown in Figure 3.

Nearly all of the cases (99.3%) were histopathologically confirmed. SCC was the predominant morphology type, diagnosed in 90.6% of cases, and ADC was diagnosed in 9.4% of cases. SCC was also the most common tumor type (diagnosed in 96.3% of cases) among the patients aged 35 years or younger at diagnosis. The male-to-female ratio was 1:2 for SCC and 2:1 for ADC. As shown in Table 1, only about 20% of the EC patients reported having

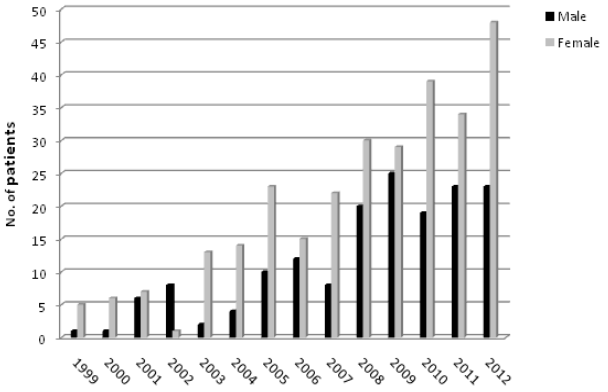

Figure 1. The Number of Esophageal Cancer Patients (N=448) who Visited the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, each Calendar Year from 1999 to 2012, by Sex

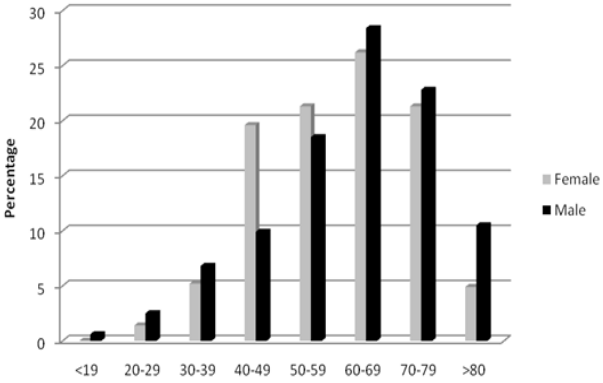

Figure 2. Age Distribution of Esophageal Cancer Patients (N=448) who Visited the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012, by Sex

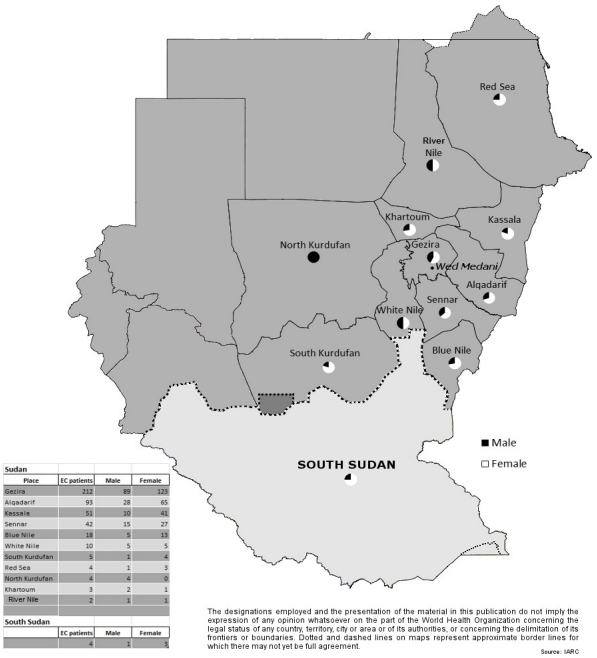

Figure 3. The Number of Female and Male Esophageal Cancer Patients who Visited the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012, by State of Residence

Table 1. Demographic and other Characteristics of the 448 Esophageal Cancer Patients who Visited the National CancerInstituteat the University of Gezira, in Gezira State, Sudan, in 1999-2012

	Both sexes		Males		Females	
	n	%	n	%	n	%
	448	100	162	36.2	286	63.8
Marital status						
Married	380	84.8	145	89.5	235	82.2
Widowed	42	9.4	4	2.5	38	13.3
Unmarried	17	3.8	9	5.5	8	2.8
Divorced	8	1.8	4	2.5	4	1.4
Information missing	1	0.2	0	0	1	0.3
Occupation						
Housewife	269	60	0	0	269	94.1
Farmer	81	18.1	75	46.3	6	2.1
Manual laborer	62	13.8	59	36.4	3	1
Office worker	17	3.8	13	8	4	1.4
Nomad	10	2.2	10	6.1	0	0
Student	1	0.2	1	0.6	0	0
Information missing	8	1.7	4	2.5	4	1.4
Ethnicity						
Guhaina	189	42.2	61	37.7	128	44.8
Jaali	107	23.9	43	26.7	64	22.4
Beja	50	11.2	12	7.4	38	13.3
Darfurian	25	5.6	15	9.3	10	3.5
Bagara	19	4.2	4	2.4	15	5.2
Red Sea	13	2.9	2	1.2	11	3.9
Nubian	11	2.5	5	3.1	6	2.1
Funj	11	2.5	6	3.7	5	1.8
Nigerian	10	2.2	7	4.3	3	1
Nilotic	9	2	5	3.1	4	1.4
Eritrean	1	0.2	1	0.6	0	0
Turkish	1	0.2	0	0	1	0.3
Information missing	2	0.4	1	0.6	1	0.3
State of residence at the time of diagnosis						
Gezira	212	47.3	89	54.9	123	43
Alqadarif	93	20.8	28	17.3	65	22.7
Kassala	51	11.4	10	6.2	41	14.3
Sennar	42	9.4	15	9.3	27	9.4
Blue Nile	18	4	5	3.1	13	4.6
Other	32	7.1	15	9.2	17	5.4
Tumor type						
Squamous cell carcinoma	403	90	133	82.1	270	94.4
Adenocarcinoma	42	9.4	28	17.3	14	4.9
Information missing	3	0.6	1	0.6	2	0.7
Ever tobacco use and/or alcohol consumption						
No	355	79.2	81	50	274	95.8
Yes	89	19.9	79	48.8	10	3.5
Information missing	4	0.9	2	1.2	2	0.7
Lifestyle behaviors (everuse/consumption)						
No tobacco use or alcohol consumption	355	79.2	81	50	274	95.8
Smoking only	30	6.7	25	15.4	5	1.8
Snuff use only	14	3.1	13	8	1	0.3
Alcohol consumption only	6	1.3	5	3.1	1	0.3
Snuff use and smoking	9	2	8	4.9	1	0.3
Snuff use and alcohol consumption	9	2	8	4.9	1	0.3
Smoking and alcohol consumption	10	2.2	9	5.6	1	0.3
Snuff use, smoking and alcohol consumption	11	2.5	11	6.8	0	0
Information missing	4	0.9	2	1.2	2	0.7

ever used tobacco and/or consumed alcohol(48.8%of the male patients and only 3.5% of the female patients). For1.2% and 0.7% of the male and female EC patients, respectively, this information was missing. A total of 60EC patients (13.5%)-53 male (33.1%) and 7 female (2.5%)- reported having ever smoked, either exclusively or in addition to having ever used snuff and/or consumed alcohol. A total of 43 patients (9.7%)-40 male (24.7%) and 3 female (1.0%) - reported having ever used snuff, either exclusively or in addition to having ever smoked and/or consumed alcohol. A total of 36 patients (8.0%)-33 male (20.6%) and 3 female (1.0%) - reported having

Table 2. Clinical Picture of the Esophageal Cancer Patients who Visited the National Cancer Institute at the University of Gezira (NCI-UG), in Gezira State, Sudan, in1999-2012

	All patients*		Squamous cell carcinoma				Adenocarcinoma			
			Males		Females		Males		Females	
	n	%	n	%	n	%	n	%	n	%
	445	100	133	33	270	67	28	66.6	14	33.4
Mean age(years) ± SD (range)	58.7±14.0 (16-95)		59.6±14.7 (16-95)		57.8±13.5 (25-90)		64.6±15.8 (35-90)		55.7±12.2 (40-75)	
Place of endoscopy										
WadMedani (where NCI-UG is located)	283	63.6	88	66.2	170	63	16	57.1	9	64.3
Khartoum (~185 km from NCI-UG)	79	17.8	26	19.5	42	15.6	9	32.1	2	14.3
Alqadarif (~175 km from NCI-UG)	57	12.8	10	7.5	42	15.6	2	7.1	3	21.4
Elmanagil (~69.9 km from NCI-UG)	6	1.3	4	3	2	0.7	0	0	0	0
Kassala (~382 km from NCI-UG)	3	0.7	0	0	3	1.1	0	0	0	0
Port Sudan (~940 km from NCI-UG)	2	0.4	1	0.8	1	0.3	0	0	0	0
Sennar State	1	0.2	0	0	1	0.3	0	0	0	0
Outside Sudan	3	0.7	2	1.5	1	0.3	0	0	0	0
Information missing	11	2.5	2	1.5	8	3	1	3.6	0	0
Clinical symptoms and conditions										
Dysphagia	415	93.3	126	94.7	253	93.7	23	82.1	13	92.9
Epigastric pain	21	4.7	5	3.8	11	4.1	5	17.9	0	0
Back pain	2	0.4	0	0	1	0.3	0	0	1	7.1
Information missing	7	1.6	2	1.5	5	1.9	0	0	0	0
Location of the tumor in the esophagus										
Lower third	121	27.2	36	27.1	47	17.4	27	96.4	11	78.6
Middle third	253	56.8	75	56.4	175	64.8	1	3.6	2	14.3
Upper third	65	14.6	21	15.8	43	15.9	0	0	1	7.1
Information missing	6	1.3	1	0.7	5	1.9	0	0	0	0
Degree of tumor differentiation										
Well differentiated	208	46.7	57	42.9	140	51.8	7	25	4	28.6
Moderately differentiated	146	32.8	48	36.1	91	33.7	5	17.9	2	14.3
Poorly differentiated	76	17.1	27	20.3	34	12.6	9	32.1	6	42.8
Report not conclusive on degree of differentiation	15	3.4	1	0.7	5	1.9	7	25	2	14.3

*Information on tumor type was missing for three patients

ever consumed alcohol, either exclusively or in addition to having ever used tobacco (Table 1).

Clinical picture of the esophageal cancer patients who visited NCI-UG

Table 2 presents the patients' diagnoses and various characteristics by tumor type and sex. Tumor diagnosis was made by histopathological evaluation of multiple mucosal biopsies obtained during upper GI endoscopy. Most of the endoscopies were done in Gezira State, and approximately 64% of them were done in the city of Wad Medani, where NCI-UG is located. The most common clinical presentation was dysphagia, reportedin 93.3%of the EC patients, with a median duration at the time of diagnosis of120 days (range: 7-720 days). Information on the severity of the dysphagia was not always provided, so it was not possible to subdivide this category according to the degree of obstruction determining impediment to swallowing solids or liquids. The mean duration of dysphagia in male and female patients was similar:138±108.9 days with a median of 120 days (range:7-270 days) in males and136.2±100.9 days with a median of 120 days (range: 10-720 days)in females. The duration of dysphagia in patients from surrounding states ranged from 30 to 480 days, with a median of 120 days; in patients from Gezira State it ranged from7to720 days, with amedian of 90 days. A small number of patients reported other symptoms: epigastric pain (4.7%) and back pain (0.4%). Proportionally, epigastric pain was more frequently reported by males with ADC (17.9%) than by males or females with SCC (3.8% and 4.1%, respectively).

In general, most of the tumors included in the case series we report were located in the middle third of the esophagus (56.8%), followed by the lower third (27.2%).However, most ADCs were located in the lower third (Table 2). Among the patients with SCC, well-differentiated tumors were most common, in both males (42.9%) and females(51.8%). Among the patients with ADC, poorly differentiated tumors were predominant, constituting 32.1% and 42.8% of the ADCs in male and female patients, respectively, as shown in Table 2.

Tobacco use and alcohol consumption

Among the male EC patients included in this case series, the subgroup of manual laborers had the highest proportion of ever tobacco use and/or alcohol

Table 3. Demographic and other Characteristics of the 448 Esophageal Cancer patients who Visited the National Cancer Institute at the University of Gezira, in Gezira State, Sudan, in 1999-2012, by Sex and Lifestyle Behaviors

		Males Tobacco use and/or alcohol consumption					Females Tobacco use and/or alcohol consumption				Information missing
	Total	No		Yes		Total	No		Yes		N
		n	%	n	%		n	%	n	%	
	160	81	50.6	79	49.4	284	274	96.5	10	3.5	4
Occupation											
Housewife	0	0	0	0	0	267	260	97.4	7	2.6	2
Farmer	75	47	62.7	28	37.3	6	5	83.3	1	16.7	0
Manual laborer	59	20	33.9	39	66.1	3	1	33.3	2	66.7	0
Office worker	12	6	50	6	50	4	4	100	0	0	1
Nomad	9	7	77.8	2	22.2	0	0	0	0	0	1
Student	1	1	100	0	0	0	0	0	0	0	0
Information missing	4	0	0	4	100	4	4	100	0	0	0
Ethnicity											
Guhaina	60	26	43.3	34	56.7	127	122	96.1	5	3.9	2
Jaali	43	23	53.5	20	46.5	63	61	96.8	2	3.2	1
Beja	12	8	66.7	4	33.3	38	38	100	0	0	0
Darfurian	15	10	66.7	5	33.3	10	10	100	0	0	0
Bagara	4	3	75	1	25	15	15	100	0	0	0
Red Sea	2	1	50	1	50	11	11	100	0	0	0
Nubian	4	1	25	3	75	6	6	100	0	0	1
Funj	6	3	50	3	50	5	5	100	0	0	0
Nigerian	7	4	57.1	3	42.9	3	3	100	0	0	0
Nilotic	5	0	0	5	100	4	1	25	3	75	0
Eritrean	1	1	100	0	0	0	0	0	0	0	0
Turkish	0	0	0	0	0	1	1	100	0	0	0
Information missing	1	1	100	0	0	1	1	100	0	0	0
State of residence at the time of seeking treatment at the National Cancer Institute											
Gezira	88	37	42	51	58	121	114	94.2	7	5.8	3
Alqadarif	28	16	57.1	12	42.9	65	64	98.5	1	1.5	0
Kassala	10	6	60	4	40	41	41	100	0	0	0
Sennar	15	11	73.3	4	26.7	27	27	100	0	0	0
Blue Nile	4	1	25	3	75	13	13	100	0	0	1
Other	15	10	66.7	5	33.3	17	15	88.2	2	11.8	0
Tumor type											
Squamous cell carcinoma	132	69	52.3	63	47.7	268	259	96.6	9	3.4	3
Adenocarcinoma	28	12	42.9	16	57.1	14	13	92.9	1	7.1	0
Information missing	0	0	0	0	0	2	2	100	0	0	1
Location of the tumor in the esophagus											
Lower third	63	31	49.2	32	50.8	58	54	93.1	4	6.9	0
Middle third	75	39	52	36	48	175	172	98.3	3	1.7	3
Upper third	21	10	47.6	11	52.4	44	41	93.2	3	6.8	0
Information missing	1	1	100	0	0	7	7	100	0	0	1
Degree of tumor differentiation											
Well differentiated	64	31	48.4	33	51.6	143	138	96.5	5	3.5	1
Moderately differentiated	52	24	46.2	28	53.8	92	90	97.8	2	2.2	2
Poorly differentiated	36	23	63.9	13	36.1	40	37	92.5	3	7.5	0
Report not conclusive on degree of differentiation	8	3	37.5	5	62.5	7	7	100	0	0	0
Information missing	0	0	0	0	0	2	2	100	0	0	1

consumption (66.1%), followed by the office workers (50%) and farmers (37.3%) (Table 3). Ever tobacco use and/or alcohol consumption was more common among male patients from Blue Nile State (75%) than among patients from other states. Ever tobacco use and/or alcohol consumption was most common among patients of Nilotic tribal background (n=9), for both males(100%) and females (75%), followed by patients of Nubian and Guhaina tribal backgrounds (Table 3). Ever tobacco use and/or alcohol consumption was more frequently reported by males with either ADC (57.1%) or SCC (47.7%) than by their female counterparts.

Esophageal cancer in Gezira State

Through collaboration with RICK, we determined the number of EC patients from Gezira State who visited the center between 2000 and 2012. RICK is the only other public cancer treatment center in Sudan. Figure 4 shows the numbers of EC patients from Gezira State treated exclusively at NCI-UG or RICK per calendar year. The

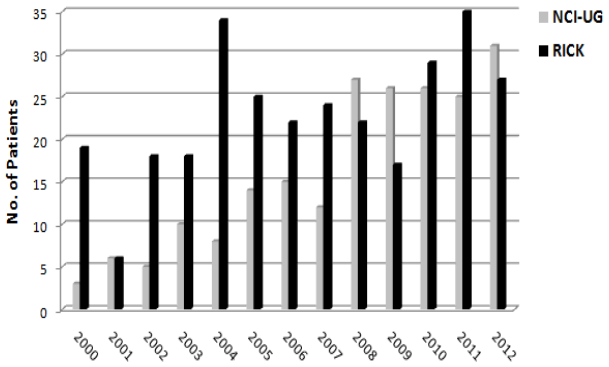

Figure 4. The Numbers of Esophageal Cancer Patients from Gezira State, Sudan, (N=448) Treated Exclusively at the National Cancer Institute at the University of Gezira (NCI-UG) or the Radiation and Isotopes Center, Khartoum (RICK) Each Calendar Year from 2000 to 2012

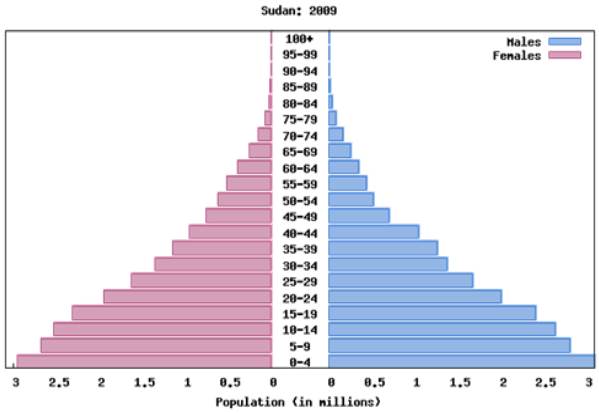

Figure 5. Population Pyramid of Sudan, 2009. Source: http://commons.wikimedia.org/wiki/File:Population_Pyramids_for_Sudan.png

annual number of patients from Gezira State visiting NCI-UG increased markedly starting in 2008, whereas there was less fluctuation over time in the annual number of patients from Gezira State visiting RICK. In the most recent years, similar numbers of patients visited each center.

Discussion

The annual number of EC patients visiting NCI-UG has increased in recent years, probably due to the increased availability of endoscopy. In this paper, we have described a complete consecutive case series of 448 EC patients who visited NCI-UG for treatment in 1999-2012. However, even the total number of Gezira State EC cases treated at NCI-UG and RICK together is unlikely to fully capture the true burden of EC in the state, since not all patients with cancer seek care within the conventional health care system.

As has been reported previously in other African populations(Hendricks and Parker, 2002), SCC was the predominant histological type of EC in patients who visited NCI-UG(diagnosed in 90% of the cases). Among the EC patients with SCC, the male-to-female ratio was 1:2, while among ADC patients it was 2:1, resulting in an overall ratio of 1:1.8. Al-Samawiet al. (2014) reported similar findings in Yemen(Al-Samawi and Aulaqi, 2014). As in most of the few published studies from Sudan (Babekir et al., 1989; Idris et al., 1994; Mohammed et al., 2012), a higher prevalence of EC was observed in females than in males, whereas in hospital case series from other African countries, such as Ethiopia (Bane et al., 2009), Tanzania (McHembe et al., 2013), Kenya (Wakhisi et al., 2005; Dawsey et al., 2010) and South Africa (Tettey et al., 2012), the male-to-female ratio for EC was closer to2:1. To our knowledge, there are no sex differences in healthcare-seeking behavior in Sudan; however, there are several differences in the typical daily activities of Sudanese men and women. This situation is exemplified in the Beja population, in which women are exclusively involved in indoor (inside-the-tent) activities, such as cooking, grinding sorghum, making butter from camel milk, making mats from palm leaves and weaving wool carpets. With the exception of harvesting and sawing, Beja men are mainly involved in animal herding(Jacobson, 1998). This sharp division of labor could result in distinct exposure profiles in men versus women. In our case series, more female than male EC patients visited the NCI-UG.

Babiker et al. (1989) found that 49% of SCCs were located in the middle third of the esophagus (Babekir et al., 1989). In the EC case series reported here, the proportion was higher, at62%. Several studies have found that SCC was most commonly located in the lower third of the esophagus, such as studies conducted in Ghana (84.9%) (Tettey et al., 2012) and Pakistan (62.2%) (Afridi et al., 2000). In our case series, only 21% of the SCC tumors were located in the lower third of the esophagus. In the United States and most other Western countries, the incidence of esophageal and esophagogastric junction ADCs increased rapidly in the second half of the 20th century (Keeney and Bauer, 2006; Wheeler and Reed, 2012). In our case series, ADC was found in 9.4% of EC patients who visited NCI-UG, a proportion similar to that observed for this histology in other African EC case series (Tettey et al., 2012).

Sudan has a predominantly young age structure, as shown in Figure 5. A wide age range was observed among the EC patients seeking treatment at NCI-UG; 6.2% of the EC patients were aged 35 years or younger. In Kenya, EC was found to be relatively common among people aged less than 30 years (Dawsey et al., 2010; Parker et al., 2010). In Yemen, Al-Samawi et al.(2014) found that the mean age of patients with SCC was 60 years, with a range of 23-100 years, while for ADC the mean age was 65 years with a range of 27-90 years(Al-Samawi and Aulaqi, 2014). In the448 patients in our case series, the mean age was 58.7 years (58.4 years for SCC and 61.7 years for ADC) as shown in Table 2.

Throughout Sudan, patients often have advanced disease at the time of presentation at the hospital. Patients are often dehydrated and malnourished, making emergency rehydration and feeding an important initial step in their clinical management (Ahmed, 1993). In our study, most of the EC patients reported dysphagia, with the reported duration ranging from 7 days to 2years and a median duration of 120 days. This long duration of

dysphagia may indicate that patients tend to seek or receive care only at a very late stage, when they start suffering from disease complications.

Sudan is a multiethnic country with a wide variety of ethnically specific cultures and traditions. NCI-UG's hospital-based records showed that most of the EC patients came from three states: Gezira, Alqadarif and Kassala. Each of these states has a different ethnic composition, with varying cultural and lifestyle behaviors; yet it is also conceivable that these populations may share common risk factors. In our EC case series, the most prevalent tribal backgrounds were Guhaina and Jaali (from central Sudan),followed by Beja (from eastern Sudan). These cultural and lifestyle behaviours include the consumption of hot beverages, use of tobacco and alcohol, dietary habits, and burning of wood for cosmetic purposes.

Sudanese have a common habit of drinking hot beverages; specifically tea and coffee. Coffee, which in Sudan is usually prepared with ginger, can irritate the esophageal mucosa if consumed in large amounts, and drinking tea at high temperatures has been associated with increased EC risk in high-risk areas in Iran (Islami et al., 2009; Marjani et al., 2010). Unfortunately, we lack information about the tea and coffee drinking habits of the patients included in the EC case series reported here. The consumption of hot tea and spicy ginger-containing coffee are common habits in the Sudanese population. Several studies have suggested that coffee consumption may reduce overall cancer incidence, and that it also has an inverse association with some types of cancers (such as esophageal, oral/pharyngeal, colon and bladder cancers) (Tavani et al., 2003; Turati et al., 2011; Yu et al., 2011). However, a study published by Tverdal et al. (2011) does not support an association between coffee consumption and incidence of cancer of the mouth or esophagus (Tverdal et al., 2011).

The International Agency for Research on Cancer (IARC) has summarized the scientific evidence available on the causal associations between tobacco use and alcohol consumption and cancer of the esophagus(Secretan et al., 2009; IARC, 2012). In the northern part of Sudan, the population is predominantly Arab Muslim, and in this part of the country alcohol is considered a vice and is prohibited by Muslim society. Nevertheless, alcohol consumption does occur in the region, and there are locally brewed alcoholic beverages, although alcohol is not consumed in public (Ahmed, 2013b). It is difficult to obtain accurate data on alcohol consumption in Sudan, and there are no epidemiological studies on the relationship between alcohol consumption and cancer in the country (Ahmed, 2013a).Proportionally, the EC patients in our case series with a Nilotic tribal background (n=9) were more likely to have ever used tobacco or consumed alcohol(88.9%) than were the patients with other ethnic backgrounds. Most Sudanese of Nilotic tribal origin are not Muslim.

Several risk factors may contribute to EC in Sudanese men and women. Our data showed that a greater proportion of male patients (48.8%) than female patients (3.5%) had a history of tobacco use and/or alcohol consumption. Idris et al.(1998) reported tobacco use in a house-to-house cross-sectional survey of 21 648 Sudanese residents (a 92.6% response rate). In the healthy adult population (aged 18 years or older), the prevalence of the use of toombak (a local smokeless tobacco product) and cigarette smoking were 34% and 12% among male respondents and 2.5% and 0.9% among female respondents, respectively(Idris et al., 1998). Some of this difference might be accounted for by underreporting by women, since it is customary in Sudan that women deny these behaviors, while the same behaviors among men are more socially acceptable (Idris et al., 1998). However, even taking underreporting into account, tobacco use among Sudanese women is believed to be much less common than among Sudanese men.

Most of the EC patients who visited NCI-UG had occupations typically associated with low socioeconomic status and may have had low intake of fresh fruits and vegetables, a known risk factor for esophageal SCC (Kamangar et al., 2009). Low consumption of fruits and vegetables has also been associated with a small but significant increase in the risk of cancers of the upper aerodigestive tract in European studies (Boeing et al., 2006; Sapkota et al., 2008). The consumption of fruits and vegetables is overall very low in Sudan(Mahgoub and Adam, 2012). It is not known whether general malnutrition, specific nutrient deficiencies or certain dietary habits contribute to EC in Sudan. In this case series, the majority of EC patients resided in the states of Gezira, Alqadarif, Kassala and Sennar, each of which has distinct traditions and customs related to nutrition. Kassala is located in eastern Sudan, where childhood malnutrition has been studied (Elbushra and Eltom, 1988; Grandesso et al., 2005; Mahgoub and Adam, 2012). The low average socioeconomic status in this area may contribute to insufficient nutritional supply through low food intake and poor diet. Low intake of fresh fruits and vegetables and low socioeconomic status have been associated with a higher risk of esophageal SCC (Mao et al., 2011).

Pernicious anemia is an established risk factor for stomach cancer, and a link between pernicious anemia and increased risk of EC has been studied in Sweden (Hsing et al., 1993; Ye and Nyren, 2003), revealing a significantly higher risk of esophageal SCC in the presence of pernicious anemia (standardized incidence ratio: 3.3; 95% confidence interval:2.4-4.4). Pernicious anemia in Sudan was studied by Abu-Sin and Ahmed (1978), but the study only included three affected patients, so little could be determined about the frequency of the condition among the Sudanese population in general (Abu-Sin and Ahmed, 1978). More recent studies have reported a high prevalence of anemia and folate deficiency among pregnant women in Gezira State and eastern Sudan (Ali et al., 2011; Abdelgadir et al., 2012). Iron deficiency may play a role in the occurrence of EC in Sudan, an effect that may be exacerbated in women of reproductive age through blood loss during menstruation and pregnancy. In our study, parity information was available for only 64% of the female patients, who had a mean of 5children (standard deviation: 2.8), ranging from 1 to 14 children, with a median of 6 children. In 2012, the average fertility rate in Sudan was 4.1 children born per woman(http://www.indexmundi.com/sudan/). The life expectancy at

birth in Sudan is about60 years: 61 years for females and 58 years for males.

Polycyclic aromatic hydrocarbons (PAHs) are produced by incomplete combustion and have been identified as carcinogenic agents, in particular benzo[*a*] pyrene (B[*a*]P) (IARC, 2010). A recent study in Iran found significantly higher levels of B[a]P biomarkers in non-tumoral esophageal epithelium from patients with SCC than in samples from control subjects, suggesting a role of PAHs in esophageal carcinogenesis (Abedi-Ardekani et al., 2010). In Sudan, smoke produced by burning acacia (*Acacia nilotica*) wood is commonly used for cosmetic purposes by married women. The wood is usually burned in an enclosed space, with the women sitting in close proximity to the coals to "bath" in the perfumed smoke. It is not known whether this acacia smoke bath plays any role in carcinogenesis by exposing women to inhalation of PAHs in the smoke. Acacia bark has in fact been studied for its apparent anticancer properties (Meena et al., 2006; Salem et al., 2011), but to our knowledge, the effects of burning the wood have never been investigated.

In conclusion, the annual number of EC patients visiting NCI-UG has increased in recent years, and about half of the patients come from Gezira State. SCC was the most common histological type of EC in this case series, and was more common in females than in males. The male-to-female ratio for EC was tumor type-dependent, being 2:1 for ADC and 1:2 for SCC. Ever tobacco use and/or alcohol consumption was reported by less than half of the male EC patients and by very few of the female patients. No etiological studies have ever been conducted in Sudan to identify the causes of EC. Before such a study can be undertaken, a better understanding of the true burden of disease of EC in Sudan is needed. Although this consecutive series of EC patients who visitedNCI-UG (the main cancer treatment center in Gezira State) is a complete hospital-based series, it certainly did not capture all patients with EC in the state's population.

A population-based cancer registry would provide the more complete data required to better understand EC patterns and risk factors within the population of Gezira State. The results of this descriptive case series suggest that a population-based representative survey of suspected and established risk factors should be conducted.

Acknowledgements

The Radiation and Isotopes Center, Khartoum (RICK) provided general data on the number of ECs seen at the center in patients from Gezira State. The work reported in this paper was undertaken during a fellowship awarded to Dr N. Gasmelseed by the Union for International Cancer Control (through a Yamagiwa-Yoshida Memorial international study grant). The analysis and manuscript writing were carried out while she was at the International Agency for Research on Cancer (IARC). We are grateful to Gilles Ferro at IARC for his assistance in generating the map displayed in Figure 3. We thank Dr AbediArdekani for very useful discussions on EC.

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