Oesophageal squamous cell cancer in a South African tertiary hospital: a risk factor and presentation analysis

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Background: Squamous carcinoma of the oesophagus (SCO) is the most common form of oesophageal cancer in South Africa (SA). Risk factors include male gender, smoking, alcohol consumption and low socio-economic status (SES). This study assessed the risk factors for SCO in KwaZulu-Natal.
Methodology: Information on patients managed at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa, between 1 October 2013 and 31 December 2014 was retrieved from a prospective database of Oesophageal Cancer (OC). Data collected included demographics, risk factors, symptoms and clinical findings.
Results: One hundred and fifty-nine patients (159) with SCO were identified. The site of tumour location was in the middle 96 (60.4%), distal 42(26.4%) and proximal 17(10.6%) oesophagus. The male to female ratio was 1:1 with an age range of 22-93 years (mean 60.6; SD±12.1). Females were significantly older than males ($p = 0.018$). Eighty-eight per cent were Black African. Dysphagia was reported in 158 (99.4%) of patients and loss of weight in 149(95.5%). Thirty-six patients were HIV positive (age 52.8; SD±9.7) and significantly younger than those without HIV infection (age 61.2; SD±11.5). Most patients had low SES and poor dental health. Male patients were significantly more likely to use tobacco ($p < 0.001$; Odds Ratio (OR) 7.8) and consume alcohol ($p < 0.001$; OR 7.7) than females who were 2.5 times more likely to report a family history of cancer ($p = 0.017$; OR 2.6).
Conclusion: An equal gender distribution was observed. Male patients with SCO reported the expected risk factors; however these were not observed amongst women. SES may contribute to the development of SCO. Poor dental health may be a surrogate marker for low SES and a possible risk factor for SCO. HIV positive individuals present a decade younger when compared with HIV negative patients.
Key words: Oesophageal cancer, squamous cell cancer, HIV, dental hygiene, socioeconomic status, South Africa, esophageal cancer, risk factors

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Background

Oesophageal cancer is the eighth most common cancer worldwide and ranks fifth in terms of mortality.[1] The most common form of oesophageal cancer in the developed world is adenocarcinoma (AC) and this has a well described pathogenesis.[2] In South Africa (SA) squamous carcinoma of the oesophagus (SCO) is the most common form of oesophageal cancer and is associated with late referral and advanced stage at presentation.[3] In contrast to AC, the pathogenesis of SCO is poorly understood. The traditional risk factors believed to be associated with the development of SCO are male gender, smoking, alcohol consumption and low socio-economic status (SES).[4, 5]

Previous local studies have identified alcohol, and tobacco use and the ingestion of maize meal as risk factors for development of SCO amongst men in KwaZulu-Natal.[6] These studies assumed the subjects to be of poor socio-economic standing but did not control for this in their analyses. The definition of SES is contentious and a number of parameters must be considered. Most definitions of low SES are

multifaceted and include educational level, occupation and income. All these factors impact indirectly on health status and health seeking behaviour.[7-9] A number of authors have suggested that dental health may be used as a surrogate marker of low SES.[10,11] In addition, poor dentition has been identified as a contributing and possible etiological factor in the development of squamous carcinoma of the oropharynx and the oesophagus.[12,13] The use of dental health as marker of poor SES has not been assessed in SA and its association with the development of SCO has not been evaluated. Most studies from SA have also been exclusively on men with SCO and little has been written about SCO in women.

The aim of this study was to assess the risk factor profile of patients presenting with SCO in KZN and better define its relationship to low SES and poor dental health.

Methodology

Patients with proven SCO managed at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa between 1 October 2013 and 31 December 2014 were included in the study. IALCH is a quaternary hospital, receiving patients from the entire eastern seaboard of South Africa. Patients lacking a histological diagnosis were excluded. The University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) supplied class approval for the creation of a comprehensive prospective database for presenting oesophageal cancer patients. Demographic data collected included: age at diagnosis, race, gender, residential area, level of schooling, income and occupation. Risk factor data were collected for smoking, alcohol consumption, family history of cancer, maize storage and socio-economic status. Low SES was defined as either illiteracy or schooling up to grade 7 or a household income less than the minimum basic wage of R2000/month (US$ 150). High SES was defined as a school graduate and a household income of more than R10 000/month and medium SES ranged between these categories. Dental health was assessed by the principal investigator (PI) at first consultation and classified as good if no dental caries or tooth loss was noted, poor if less than 3 visible dental caries with or without missing teeth, very poor if more than 3 visible caries and missing teeth and lastly, no teeth at all or dentures. In the absence of a clinician-based screening scoring system, a grading score of oral health based on the above three variables was adopted by the PI. Information on anthropometric data and clinical presentation were also collected. The dataset was more than 90% complete.

The performance status was graded according to the Eastern Cooperative Oncology Group (ECOG) classification. Dysphagia grading: 0- no dysphagia, 1- tolerating normal diet avoiding certain foods such as raw apple and steak, 2- tolerating semi-solid diet, 3- tolerating fluids only, and 4- complete dysphagia for even liquids.[14,15] Clinician assessment of loss of weight (LOW) involved asking about changes in clothing size since most patients do not have access to scales. Adequate staging was based on a Computed Tomography (CT) scan and either an endoscopic ultrasound (EUS) or Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18F-FDG). Other investigations necessary to confirm the presence of local invasion and metastasis, for example bronchoscopy and biopsy, were also performed as indicated. Patients were staged according to the 7th American Joint Committee on Cancer (AJCC) on Tumor-Node-Metastasis (TNM) cancer staging system.[16]

Statistical methodology

Data was analysed using *Stata 13.0* (StataCorp. 2013). Continuous data was summarised using mean (standard deviation) or median (interquartile range) if the data were skewed. Comparison of continuous variables by dichotomous classification was assessed using the Students t-test. If the normality assumption was not upheld, then the Wilcoxon rank-sum (Mann-Whitney) test was used instead. One-way analysis of variance (ANOVA) was used to compare means across three or more groups. The non-parametric equivalent, namely the Kruskal-Wallis equality-of-populations rank test, was used if the assumptions of the ANOVA were not met. Association between two categorical variables (i.e. contingency tables) was analysed using the Pearson chi-squared (χ^2) test. If an expected cell count was fewer than 5 observations, then the Fishers exact test was used instead. Bivariate logistic regressions were also employed to estimate magnitude of association (effect size) between selected risk factors and gender for example. A p-value of < 0.05 was used to define statistical significance. Missing data was controlled for in the analysis where applicable.

Results

A total of 180 patients with oesophageal tumours were identified of which 159 with SCO were included in the final analysis. Tumours excluded from analysis were adenocarcinoma (AC, 12), neuro-endocrine tumour (NET, 1), adenosquamous (1), muco-epidermoid cancer (1) and 6 patients without histological confirmation of cancer. Tumours were located in the middle 96 (60.4%), distal 42 (26.4%) and proximal 17 (10.6%) oesophagus. Table 1 describes the demographic and symptom data. The age ranged from 22–93 years with a mean age of 60.6 (SD±12.1) years. Females were significantly older than the males (62.9 (SD±12.7) vs. 58.3 (SD±11.0) years) ($p = 0.018$). The majority of patients were Black African (141 or 88.7%), followed by Asian (13 or 8.2%), Mixed ethnicity (3 or 1.9%) and White (2 or1.3%). The mean ECOG score was 1.54. There were 80 male patients giving a male to female ratio of 1:1. There was no significant difference in age by race group ($p = 0.952$). The mean BMI at presentation was 20.0 (SD±5.8) and did not significantly vary by race group ($p = 0.994$).

The most predominant symptom at presentation was dysphagia occurring in 158 patients (99.4%). One hundred and forty-nine patients (95.5%) reported LOW. Hoarseness, cough and halitosis were less frequent symptoms (42, 40 and 37%

Table 1: Socio-demographic characteristics of the study population

Demographics	n	%
Male sex	79	49.7
Age (SD) [range]	60.6 (12.1) [22-93]	
Race		
Black	141	88.7
Indian	13	8.2
Mixed ethnicity	3	1.9
White	2	1.3
ECOG score		
1	83	52.2
2	38	23.9
3	29	18.2
4	9	5.7
Dysphagia score		
Grade 0	1	0.6
Grade 1	57	35.8
Grade 2	74	46.5
Grade 3	22	13.8
Grade 4	5	3.1
BMI (SD)	19.7 (6)	
HIV status		
Negative	94	59.1
Positive	36	22.6
Declined testing	29	18.2
Symptoms		
Dysphagia	158	99.4
Loss of weight	149	95.5
Hoarseness	65	42.2
Cough	61	39.6
Halitosis	57	37.0
Family history of cancer	35	22.9
Haematemesis	25	16.1

of cases respectively). Among the 130 patients who consented to HIV testing, 36 (28%) were HIV positive. The mean age of HIV positive patients was significantly younger than that of HIV negative patients (52.8 years (SD±9.7) compared to 61.2 years (SD±11.5) respectively ($p < 0.001$).

The socio-economic characteristics of the patients are summarised in Table 2. For patients with observed SES almost all were classified as low or medium according the definition used. Ninety-seven patients (64.2%) were classified as literate. The dental health was classified as poor (37%), very poor (44.1%) or no teeth (4.7%), while only 18 (14%) had good dental health. The relationship between SES and dental care rating was not statistically or epidemiologically meaningful

Table 2: The Socio-economic factors associated with low socio-economic status

	n	%
Socio-economic Status		
Low	56	35.2
Medium	94	59.1
High	1	0.6
Unknown	8	5.0
Source of income		
The patient as breadwinner	81	52.2
Household dependent on pension or grant income	93	58.5
Education		
Illiterate	53	35.5
Primary school	63	42.0
High school	34	22.6
Dental health		
Good	18	14.2
Poor	47	37.0
Very poor	56	44.1
No teeth or dentures	6	4.7

Table 3: Differences in risk behavior by gender

	Male n (%)	Female n (%)	P value; CI; OR
Tobacco use	55 (69.6)	9 (11.3)	<0.001 ; 7.8; 18.1
Alcohol consumption	49 (62.0)	11 (13.8)	<0.001 ; 7.7; 10.2
Family history of cancer	11 (14.7)	24 (30.8)	0.017 ; 0.17; 0.39

($p = 0.63$); however a significant difference in dental care rating by gender was noted. Males scored more poorly on the rating scale ($p = 0.04$).

The relationship between alcohol consumption, smoking, family history and patient sex is presented in Table 3. Male patients were significantly more likely to use tobacco ($p < 0.001$; Odds Ratio [OR] 7.8) and consume alcohol ($p < 0.001$; OR 7.7). Female patients were 2.5 times more likely to report a family history of cancer ($p = 0.017$; OR 2.6).

Discussion

Late presentation of SCO was the norm in this series and was similar to other SA studies where advanced dysphagia, LOW and significant malnutrition is typical.[1] The traditional view of SCO in SA that this disease predominantly affects African

males of low SES, who regularly consume alcohol and smoke tobacco holds true in KwaZulu-Natal. However, this study found an equal male to female ratio among patients with SCO along with a significantly lower frequency of tobacco smoking and alcohol use amongst females and a stronger reported family history of cancer. These findings cast doubt in the etiological role of alcohol and tobacco as the major contributors in developing SCO in this study population.

Low SES is often cited as a risk factor for SCO but standardised models of assessing and classifying SES are lacking.[7,8] Low SES as assessed by education and income alone may be insufficient to define SES in our setting.[9] A number of authors have suggested that poor dental health may be used as a surrogate marker for low SES, since SES is a difficult concept to define, but requires further studies to support this.[12,13] Our study showed that, based on the conventional definition of SES, most of the patients had low or medium SES (78–94%). When dental health was assessed, 86% of our patients were shown to have poor dental health. Our data therefore suggests that poor dentition is indeed a marker of low SES and may well be a pragmatic proxy marker of low SES. The association between low SES and SCO is complex and any pathogenic mechanism almost certainly multi-factorial. Further studies are required to establish the validity of the role of using dental health as a marker for SES and to look for specific etiological factors associated with low SES and poverty.

The lack of alcohol consumption and tobacco smoking amongst women with SCO suggests that there are other risk factors for the development of SCO. Dental health has been described as a risk factor for oropharyngeal carcinoma and SCO both in Europe and Kashmir, India.[12,13] This may still be an independent risk factor not yet described in SA. There is data to suggest that poor dental health results in alteration in the oral flora and this may well play an etiological role in oncogenesis through an inflammatory process.[13] The increased incidence of SCO amongst women may reflect bias toward health seeking behaviour. Similarly, the positive family history of cancer observed amongst women may reflect recall bias affecting knowledge of the specific cancer. The need for an ongoing cancer registry in SA is highlighted by these findings.

The high incidence of HIV in KZN was also reflected[18] and a new finding was that the age at which SCO was diagnosed amongst HIV positive patients was a decade younger than the rest of the study population. This follows a previously described pattern in a similar population group with predominantly squamous cell carcinoma of the anus.[19] Further research is required to explain the specific role immune-suppression plays and the impact that anti-retroviral therapy will have on cancer outcomes.

The lack of a national cancer registry in South Africa is a major limitation. Without such a system, the divided and segmented nature of South African health care makes it difficult to gain an overview of any disease process. The state sector generally serves lower SES patients whilst those with access to private insurance are predominantly seen in the private sector. Currently data from the private sector is maintained by private insurers and accessing this data may allow for a comparison between groups of patients based on a number of parameters which would include age, sex, race and SES.

Conclusion

The study demonstrated an equal gender distribution of SCO. However, the traditional risk factors differed significantly between men and women with the disease. The different social histories between male and female patients casts doubt on some of the traditional theories about oncogenesis of SCO. There is an association between low SES and SCO and further work is needed to identify specific etiological factors associated with poverty. It seems that poor dentition may well be a good proxy marker of low SES, however whether poor dentition on its own is an etiological factor in the development of SCO is unclear. HIV positive individuals present on average a decade younger when compared with HIV negative patients. The role of HIV in oncogenesis requires further research.

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