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Oesophageal cancer in Area 2 of Kwazulu-Natal: predictors of late presentation

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Background: There are limited prospective data sets on clinical characteristics, stage of presentation and treatment of patients with Oesophageal Squamous Cell Carcinoma (OSCC) in South Africa. This study aimed to assess the frequency and severity of clinical characteristics associated with late presentation of patients with OSCC presenting to a cancer referral centre in KwaZulu-Natal, South Africa.

Methods: A prospective consecutive series of patients presenting with confirmed OSCC treated at Greys Hospital in 2016/2017 were enrolled. Data collected included: age, gender, home language, referral centre, clinical and laboratory characteristics: dysphagia score, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), serum albumin, tumour pathology and treatment administered.

Results: One hundred patients were analysed. Ninety four percent spoke isiZulu. The mean age was 61 with a male to female ratio of 1.5:1 Ninety percent had palliative treatment as their overall assessment precluded curative treatment. Five patients underwent curative treatment. The age standardised incidence (ASR) was 25.2 per 100 000. The factors associated with late presentation and their frequency were: advanced dysphagia grade (>/=2 in 68%), malnutrition (BMI <18.5kg/m² in 49%), hypoalbuminaemia (serum albumin < 35 g/l in 70%), poor performance status (ECOG>/=2 in 50%) and moderate to poor tumour differentiation in 95% of patients.

Conclusions: OSCC in Kwazulu-Natal has double the ASR of South Africa and places a significant burden on the region's health care system. Factors associated with late presentation occur in the majority and alone or in combination preclude curative therapies. The frequency of these factors serve as a benchmark for comparison, and reduction in their frequency may indicate effectiveness of interventions designed to improve awareness and access to proper care.

Introduction

Oesophageal cancer is the eighth most common cancer in the world.[1] The highest incidence is reported in East and South-East Asia. Sub-Saharan Africa has the second highest incidence worldwide.[1, 2] The estimated Age Standardised Rate (ASR) in Southern Africa is 13.7 and 6.7 per 100 000 in men and women respectively.[1] Squamous cell carcinoma and adenocarcinoma are the two main histological subtypes.[2] The former is the predominant subtype in South Africa where the Eastern Cape has the highest documented incidence.[3-5] Oesophageal squamous cell carcinoma (OSCC) is generally associated with a poor prognosis.[6] This is particularly true in South Africa where most patients with oesophageal cancer present late with debilitating symptoms and incurable disease.[7,8] The majority of patients are not suitable for curative treatment at the time of diagnosis.[6,9] This disease can have a devastating effect on quality of life and five-year survival is low.[4,10]

Retrospective studies provide limited information on the patient profile, clinical presentation and treatment of squamous cell carcinoma of the oesophagus in KwaZulu-Natal (KZN). Many of these studies are based only on patients who reach health institutions and reflect the referral bias due to limited and regionally variable access to more sophisticated levels of care. Epidemiological studies are hampered by lack of awareness of the symptoms of the disease as well as the variable data sets coming from sub-Saharan Africa.[1,11,12] Consequently it is probable that the incidence of oesophageal
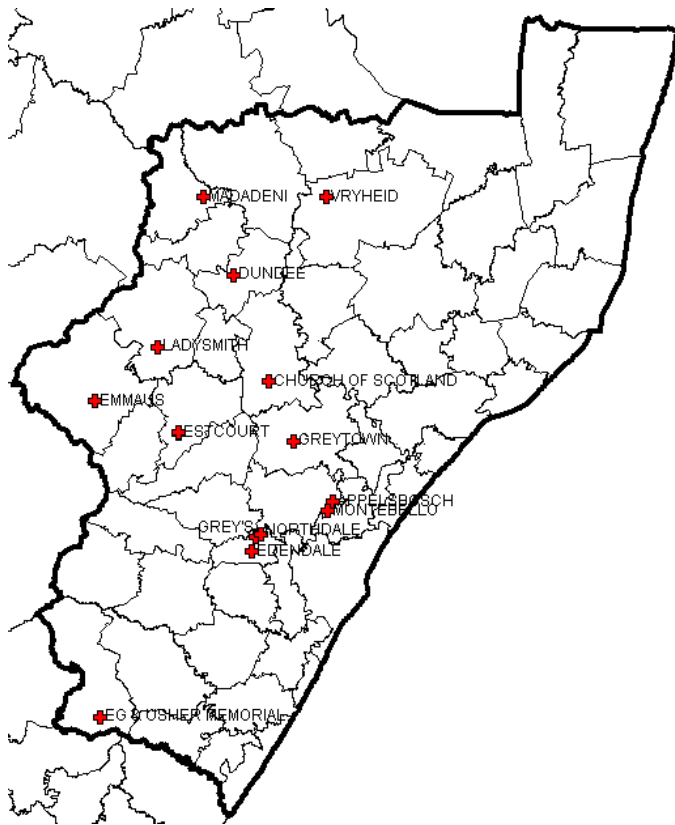
Figure 1. Referral centres from Area 2 (Greys catchment area)

squamous cell carcinoma may be underestimated in the region and that a lack of awareness of this disease may be contributing to the late presentation and poor prognosis.

To gain a better understanding of the clinical profile of patients diagnosed with OSCC and the frequency of factors associated with advanced disease at the time of diagnosis we prospectively collected and analysed data from patients presenting to a tertiary hospital in KZN.

Methods

Study design

This study employed a prospective case series design. All patients with a suspected or confirmed diagnosis of OSCC presenting to Greys Hospital between April 2016 and March 2017 were entered into the study. Greys hospital is a tertiary hospital in KZN providing care to patients from Area 2, which is a large area comprising urban and rural populations covering the western part of KZN, with a population of about three million and 20 referring hospitals.[13,14] Data collected included demographic data, symptom severity, body mass index (BMI), serum albumin levels, performance status, tumour pathology and treatment administered. Significant weight loss was defined as weight loss resulting in a change in the size of the clothing they could wear comfortably. The BMI was defined as normal if it was between 18.5 and 25. A BMI above 25 was classified as overweight and below 18.5 as underweight. A BMI of less than 16 was classified as severely underweight. Patients in whom the diagnosis of

OSCC could not be confirmed histologically were excluded from the analysis.

We assessed severity of dysphagia using the Mellow and Pinkas dysphagia score.[15] This is a 5-scale grading system where grade 0 denotes the ability to swallow normally: grade 1 dysphagia to normal solids, grade 2 dysphagia to soft solids, grade 3 dysphagia to liquids and solids and grade 4 inability to swallow saliva.

Performance status was measured using the Eastern Cooperative Oncology Group score[16] as follows; Grade 0 – fully active with no physical restrictions; Grade 1 – some physical restriction but able to carry out light work; Grade 2 – ambulatory and capable of self-care but unable to carry out any work activity, confined to bed or wheelchair less than 50% of waking hours; Grade 3 – capable of only limited self-care, confined to bed or wheelchair for more than 50% of waking hours; Grade 4 – completely disabled, unable to carry out any self-care, totally confined to bed or chair.

A decision on whether to treat a patient palliatively or with curative intent was made based on a combination of clinical, pathological and imaging criteria. Criteria for palliative management were age > 70 years, co-morbidities precluding major surgery, ECOG status >1, serum albumin < 25g/l, tumour length > 8 cm or advanced tumour stage.

Statistical analysis

Data were processed and analysed using Stata 13.0 (StataCorp, 2013). Continuous variables were summarised using mean and standard deviation or median and interquartile range if evidence of skewing or asymmetrical outliers.

Results

Demographics

One hundred and eight patients were entered into the database over the study period. Eight patients were excluded from analysis: two had adenocarcinoma and six had no histological diagnosis. There were 59 males and 41 females and the mean age was 61 years (SD = 12.8) The overall ASR (95%CI) was 25.2 per 100 000. It was 29.1 in males and 17.2 in females. All patients were African with 94% first language isiZulu. The majority of patients (70%) were referred from the three regional hospitals that fall within the drainage area of Greys hospital. The remainder of the referrals were equally distributed amongst the rural district hospitals and one patient was from outside area 2. The patient characteristics are summarised in Table 1.

Clinical characteristics

Clinical characteristics of the patient cohort are shown in Table 2. Of the 100 patients analysed, dysphagia was the primary presenting symptom in 97% of patients with 44% reporting grade 3 or 4 dysphagia. Sixty percent reported significant weight loss. BMI could be calculated in 94 patients. The median BMI was 20.0 (range 11–45) and 49% of patients had a low BMI at presentation. Furthermore, 19% were severely underweight (BMI < 16 kg/m^2). The majority of patients

Table 1: Cohort Characterisation	
Characteristic	**N = 100**
Mean age in years (range)	61 (32-93)
M:F	1.5:1
	59:41
Race	
African	100
Home language	
Zulu	94
English	4
Xhosa	2
Level of referral centre	
Regional	70
District	29
Outside drainage area	1

Table 2: Frequency of the clinical and biochemical assessment parameters

Assessment parameter	Number
Dysphagia score	**N = 100**
0	3
1	29
2	24
3	36
4	8
ECOG status	**N = 90**
0	4
1	38
2	27
3	18
4	3
Body Mass Index	**N = 94**
Severely underweight (<16kg/m²)	17
Underweight (16-18.4kg/ m²)	29
Normal (18.5-24.9kg/ m²)	34
Overweight (>/=25kg/m2)	14
Serum Albumin g/l	**N = 92**
< 30	40
30 – 35	25
>35	27

(70%) were hypoalbuminaemic (serum albumin < 35 g/l) at the time of presentation. The median serum albumin level was 30 g/l (range 13–42). Only four out of 90 patients had a normal ECOG performance status, while 50% of patients had a performance status poorer than ECOG 1.

Table 3: Criteria for palliative management	
Criterion for palliative management	**Number of patients**
Age >70 years	23
Prohibitive co-morbidities	5
Serum Albumin<25g/l	17
ECOG >/= 2	48
Tumour length > 8cm	37
Advanced tumour stage	4

Table 4: Frequency of indicators of late presentation	
Indicator	**Percentage of patients**
Dysphagia grade >/= 2	68
BMI </=18.5	53
Serum Albumin<35g/l	70
ECOG >/= 2	50
Degree of tumour differentiation – Moderate to severe	92

Pathology and treatment

The mean tumour length was 6.4 cm (SD = 3.5) and the majority (72%) were moderately differentiated with only 8% being well-differentiated. Ninety percent of patients were treated palliatively. Five percent were treated surgically and five percent declined treatment, could not be palliated or were lost to follow-up. Self-expanding metal stents (SEMS) were inserted in 82 of 90 patients selected for palliative treatment. The other forms of palliation used included chemoradiotherapy in two patients and serial oesophageal dilatation in six. Details of patients that fulfilled the criteria for palliative management are shown in Table 3. A number of patients had more than one indication for palliative management.

The factors that indicate a late presentation and their frequencies are shown in Table 4.

Discussion

Our study indicates that OSCC is a significant health care problem in KwaZulu-Natal. The fact that all of the 100 patients collected over a one-year period were African underscores the burden this disease puts on this particular population group. Our ASR of 25 is higher than the recorded incidence in South Africa,[17] indicating that the disease may be under-reported nationally. The mean age of 61 years is in keeping with reports in the published literature. Our male to female ratio of 1.5:1 also shows a similar male preponderance to other regions of Africa (1.6:1) but much lower than the 3:1 ratio reported from other regions of the world.[1,8,18]

We have identified a number of factors that are associated with late presentation and diagnosis at an advanced stage, which is a world-wide problem, but seems to be a particular problem in our patient population.[19,20,21] Dysphagia indicates a more advanced T-stage of oesophageal cancer.[21,22,23] The

Table 5

Series	Year	No	Mean Age	Gender M:F	OSCC	BMI <18.5	ECOG>1	DS >1	HG M&P	Albumin <3.5g/l	Palliative Treatment %	Stent	CDXT	Other
Africa														
Mannell[37]	1989	1926	56	3:1	100	NS	51	36	NS	NS	87	37c	57	6
Dandara[34]	2016	1868	60b	2:1	90	NS	33	50	NS	NS	80	27	34	15e
Loots[38]	2017	159	60	1:1	100	NS	48	63	NS	NS	NS	NS	NS	NS
Ferndale	2018	100	60	1.5:1	100	49	53	68	92	70	95	91	2	6
Tettey[39]	2012	152	58	4:1	79	NS	NS	NS	NS	NS	100	12c	NS	NS
Mchembe[40]	2013	328	47	2.2:1	96	NS	NS	95	68	NS	NS	NS	NS	NS
China														
Sun[41]	2013	502	58	3:1	100	15	9	NS	NS	NS	NS	NS	NS	NS
Ren[42]	2015	1176	68	3:1	100	24	NS	NS	68	NS	NS	NS	NS	NS
Song[43]	2017	202	58b	3:1	85	21	28	NS	77	19	NS	NS	NS	NS
Developed world														
Earlam[44]	1984	444	NS	NS	NS	NS	NS	NS	NS	NS	90	20e	14	6d
Oka[45]	1996	50	60	12:1	100	NS	NS	22	66	NS	NS	NS	NS	NS
Lahman[27]	2012	287	65	3:4	100	5	NS	NS	NS	NS	NS	NS	NS	NS
Okuno[46]	2017	131	62b	9:1	100	NS	1.5	NS	NS	69	NS	NS	NS	NS
Singla[47]	2018	226	61b	13:1	9	NS	6	NS	95	NS	NS	NS	NS	NS

HG = Histology Grade
a = <38g/L
d = palliative surgery
NS = Not specified

M&P = moderate and poorly differentiated
b = median
e = best supportive care

DS = Dysphagia Score
c = plastic

prevalence of dysphagia (97%) and advanced grade (44% with grade 3 or 4 dysphagia) was particularly striking. Secondly, a history of weight loss, low body mass index and low serum albumin, factors often used in combination to identify patients with malnutrition, were present in the majority of our patients.[24] A low BMI has been shown to have a negative impact on survival and may even increase the risk of developing OSCC.[25,26,27] These paramaters, alone or in combination, also impact on prognosis, and predict response to chemo-radiotherapy.[28,29,30] Thirdly, patients with an ECOG status 0 made up only 4% of the cohort, a proportion much lower than reported in the literature.[31] The last indicator of late presentation among our patients is the degree of differentiation on pathological assessment. The degree of differentiation has been shown to be a risk factor for poor prognosis at an advanced stage[32,33] and more than 80% of our patients had moderately to poorly differentiated tumours.

The abovementioned factors culminated in only 5% of patients in our series being offered potentially curative treatment, a figure much lower than reported by others.[6,34] In the context, it is reassuring that placement of self-expanding metal stent which is considered the standard of care in palliation of dysphagia was available and could be performed in 90% of patients who were palliated.[35,36] Table 5 highlights the paucity and variability of data points we have identified as indicators of late presentation in oesophageal cancer in other series.

The drivers of late presentation in our patient population need further investigation. Some patients seek help from traditional healers before presenting to hospital, with socio-economic factors given as the main reason given by the remainder.[7] Whereas patients factors are a major contributor to delay, the lack of knowledge among health care workers and lack of clear care pathways in the health care system probably also contribute to delay in diagnosis and treatment. These factors need to be quantified in order to devise strategies to address the problem.

Conclusion

Our data show a higher incidence of oesophageal cancer than expected and that patients with oesophageal cancer in our population have a poorer prognosis than patients with the same diagnosis elsewhere. Potential interventions to improve outcomes are population and health care worker education particularly around the recognition of dysphagia as an alarm symptom and the need for urgent endoscopic evaluation. This would include streamlining of referral patterns and monitoring times from presentation to diagnosis, assessment and treatment. Implementation would require a coordinated research agenda not simply addressing health systems research but also epidemiological and basic science approaches to better understand the diseases aetiopathogenesis with a view to the possible introduction of screening strategies.

The study was approved by the Biomedical Research Ethics Committee of University of KwaZulu-Natal (ref. no. BF270/15).

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