Clinicopathological review of ocular surface squamous neoplasia in Malawi

T Tiong,[1] S Borooah,[1] J Msosa,[2] W Dean,[3] C Smith,[1] E Kambewa,[3] C Kiire,[4] M Zondervan,[5] P Aspinall,[6] B Dhillon[1,6]

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[1]University of Edinburgh, Edinburgh, UK
[2]Department of Ophthalmology, Kamazu Central Hospital, Lilongwe, Malawi
[3]Department of Ophthalmology, Nkhoma hospital, Nkhoma, Malawi
[4]Oxford Eye Hospital, Oxford University Hospitals, Oxford, UK
[5]VISION 2020 links programme, London School of Hygiene & Tropical Medicine, London, UK
[6]Heriot-Watt University, Edinburgh, UK

Correspondence to
Dr Shyamanga Borooah, Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh, EH3 9HA, UK; shyamanga@aol.com

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ABSTRACT

Background Ocular surface squamous neoplasia (OSSN) is the most common cause of malignancy of the conjunctiva. Variable clinical presentation means that invasive malignant OSSN is often difficult to discriminate from other similarly presenting differential diagnoses which can be managed more conservatively.

Aims Identification of clinical factors associated with a histopathological diagnosis of conjunctival squamous cell carcinoma (SCC).

Methods Prospective consecutive case series of suspected OSSN cases presenting at two hospitals in Central Malawi over a 1 year period. A pro forma was completed assessing preidentified clinical variables. Suspected lesions underwent excisional biopsy followed by histopathological investigation.

Results Fifty-eight patients were recruited. Mean age was 35.8 (range 22–62). 51 cases of histopathologically confirmed OSSN were found. 30 (50%) patients were confirmed HIV seropositive which rose to 86.67% in invasive SCC. Larger size of tumour (p=0.008), male gender (p=0.025) and HIV seropositivity (p=0.010) were associated with invasive SCC pathology.

Conclusions A clinicopathological study of OSSN has not previously been performed in Malawi. The association of HIV with SCC corresponds to previous reports from sub-Saharan Africa. A new finding in our study is a relationship between larger tumour size and invasive lesions confirmed by histopathology. When integrated into a clinical decision-making model, tumour area provides a simple clinical measure for ophthalmic practitioners to use in order to differentiate higher risk OSSN from more benign pathology. The higher risk lesions can subsequently be treated with greater surgical care and undergo closer follow-up.

INTRODUCTION

Ocular surface squamous neoplasia (OSSN) covers a range of conjunctival epithelial diseases from mild, moderate and severe dysplasia, carcinoma intraepithelial neoplasia to invasive squamous cell carcinoma (SCC) which breaches the epithelial basement membrane. SCC is the most common malignancy of the conjunctiva.[1] Recent reports indicate that the prevalence of SCC continues to increase in sub-Saharan Africa. The majority of cases in Malawi relate to the two main risk factors, high ultraviolet (UV) exposure and HIV seropositivity.[2 3]

Diagnosis of SCC by examination alone is notoriously difficult and is correctly diagnosed in only 30% of cases even by experienced clinicians.[4] Conjunctival SCC can cause localised tissue morbidity and occasionally metastasises, which can rarely lead to mortality.[4] Clinical diagnosis of malignant OSSN is important due to the high recurrence rate reported at 16.6%, scarce pathology services and due to most suspected cases in sub-Saharan Africa being managed in local hospitals without further specialist referral.[5] Non-invasive OSSN can now be easily treated with an increasing range of treatments including topical 5-fluorouracil, topical mitomycin C and subconjunctival interferon-α2b.[6–8] However, the current standard treatment for SCC is complete excision with 2–3 mm margins and long term monitoring for recurrence.[4] This is also the current treatment for all suspected OSSNs in Malawi at present which may lead to unnecessary morbidity. Together these points highlight the need to find simple clinical features of OSSN which differentiate SCCs from more benign lesions.

METHOD

This study was designed as a prospective clinicopathological case series. Data was obtained from consecutive cases presenting to central Malawi ophthalmic hospitals over a 1 year period (June 2010–May 2011). The study was undertaken at the only two eye hospitals in the central region; Kamazu Central Hospital, a state funded teaching hospital in Lilongwe which serves the central region and has a population of 5 491 034[9] and Nkhoma Eye Hospital, a charity funded hospital 50 km away.

Full ethical approval for the study was obtained from the regional Kamazu Central Hospital ethics committee. Suspected OSSN cases were seen by ophthalmologists at the respective sites. A pro forma was completed (see online supplementary information) for each patient consisting of demographic data and a set of clinical questions, formulated by experienced clinicians, thought to be important for diagnosis. Clinical parameters included history, laterality and position of lesion, lesion size, corneal neo-vascularisation, pigmentation, keratinisation, recurrence and HIV status. For lesion size, the two largest dimensions measured by scale were taken and multiplied to calculate area.

All suspected lesions underwent excisional biopsy performed by either an ophthalmologist or a trained clinical officer. Specimens were fixed in 10% buffered formalin and transported to the Western General Hospital, Edinburgh, UK for histopathological examination in the department of Neuropathology (CS). The specimens were graded as mild, moderate or severe dysplasia, conjunctival intraepithelial neoplasia or SCC.

SPSS statistics V.17.0 was used for all non-regression based analyses. A correlated component logistic regression was run with M fold cross validation (COREXpress, Statistical innovations) to

assess which variables independently discriminated between SCC and other pathologies. This method stabilises problems with colinearity in regression and can model a regression despite a partial dataset.[10]

RESULTS

Histopathology samples were received from 58 cases of which 15 were men (26.9%) and 43 women (74.1%) with a mean age of 35.8 years (range 22–62years). Pro forma reports were completed for all the patients with eight patients not consenting to HIV testing. Figure 1 shows the distribution of the pathological diagnoses.

We assessed which clinical parameters were associated with SCC pathology. Our data showed a strong association between HIV and SCC (χ^2=6.719, p=0.010) (figure 2). The odds of HIV positive patients having an invasive lesion was almost nine times greater than in HIV negative patients. (OR=8.90). We also found a statistically significant association between male gender and SCC (χ^2=4.180, p=0.041). Eight patients did not consent to HIV testing. The data for the eight patients was removed prior to calculations which included HIV. The odds of a man having an invasive lesion was four times greater than in women when considering all sizes of tumour (OR=4.32). However, Mann-Whitney U test showed insufficient evidence (p=0.458) for an association between the age of patients and SCC. Additionally, larger tumour size was significantly associated with invasive pathology (Mann Whitney U test, p=0.008) (figure 3).

There was no significant association found between laterality, location, keratinisation, pigmentation, vascularisation and corneal invasion of lesion and SCC (table 1).

In order to assess how the clinical variables could be used diagnostically a decision tree analysis (SPSS Answer Tree module) was also created. These structure the problem into a decision tree with the best predictor for discriminating variables identified at each junction of the tree. The predictors were selected in a hierarchical order which optimises their role in decision making. The optimum clinical parameter for discriminating SCC from non-invasive OSSN was size greater than 20.5 mm^2 (χ^2=12.7, df=1, p<0.001). Gender then discriminated invasive pathology for tumours greater than 20.5 mm^2 at the next level of the tree (figure 4). For tumours smaller than or equal to 20.5 mm^2 the next level of the tree that best discriminated SCC from other lesions was HIV status.

In order to assess the independent relationship of all the variables with SCC, a correlated component logistic regression was run with M fold cross validation. To simplify the analysis

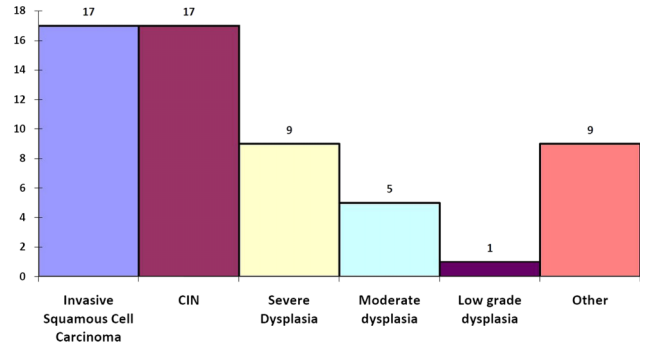

Figure 1 Bar chart showing the distribution of subtypes of between histopathological diagnoses. Access the article online to view this figure in colour.

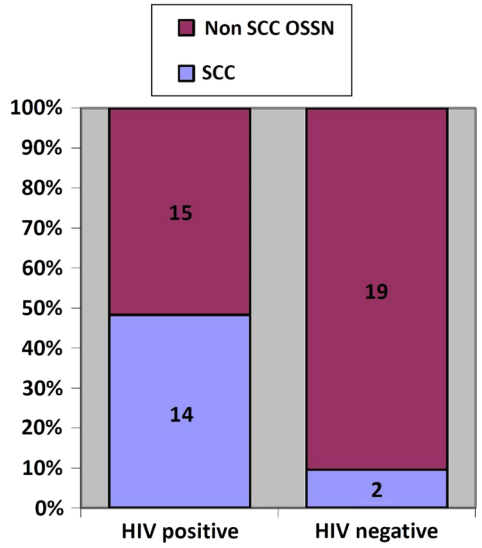

Figure 2 Proportion of patients with malignant and benign pathology divided by HIV status. SCC, squamous cell carcinoma; OSSN, ocular surface squamous neoplasia. Access the article online to view this figure in colour.

laterality and keratinisation were excluded following review of our preliminary data.

A three-parameter model using the top three variables was found to be most appropriate. These clinical parameters only included male gender, pigment and large size (see online supplementary information).

DISCUSSION

The aim of this study was to identify simple clinical parameters that could be used to differentiate histologically confirmed SCC from other differential diagnosis. Fifty-eight cases were enrolled in the study with 51 histopathologically confirmed cases of OSSN. Using the latest population figures of 5 491 034 in 2008 this is an estimated incidence of 9.2 cases per million per year for the central region. This rate is estimated assuming that all the cases that developed OSSN in the central region were enrolled in the study from the two eye hospitals of the region within 1 year. This rate is lower than estimates from Tanzania

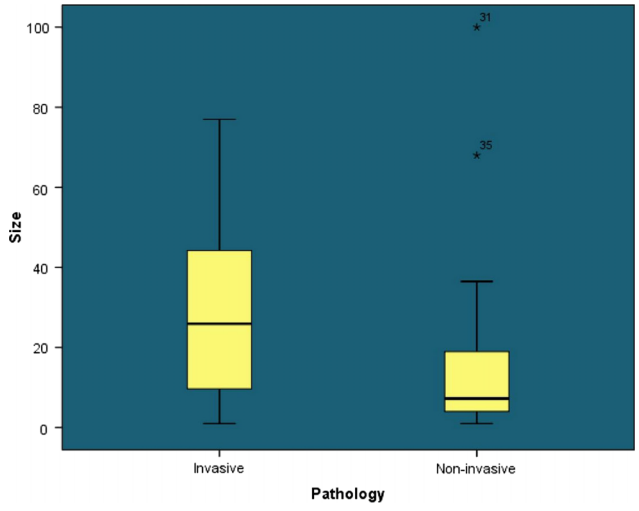

Figure 3 Box plot comparing the size distribution between squamous cell carcinoma (invasive) and other ocular surface squamous neoplasia diagnoses (non-invasive). Access the article online to view this figure in colour.

Table 1 Summary table of ORs of eight discrete variables, when comparing between squamous cell carcinoma (SCC) and non-invasive ocular surface squamous neoplasia (OSSN) and their respective CIs

Variable	OR	χ^2	95% CI		p Value
			Lower	Upper	
Gender (male/female)	4.317	4.180	1.234	15.107	0.041
HIV status (positive/negative)	8.867	6.719	1.739	45.206	0.010
Laterality (right/left)	3.606	2.433	0.891	14.600	0.119
Location of lesion (nasal/temporal)	1.208	Fisher's exact test used	0.340	4.289	0.755
Keratinisation (keratinised/non-keratinised)	3.333	Fisher's exact test used	0.993	11.195	0.071
Pigmentation (pigmented/non-pigmented)	0.343	Fisher's exact test used	0.067	1.743	0.237
Vessels in cornea (present/absent)	2.467	0.413	0.145	42.050	0.509
Corneal invasion (present/absent)	1.150	0.058	0.367	3.609	1.000

(22 per million)[3] and Uganda (21 per million per year) although there was no histopathological confirmation in these estimates which may have meant other diagnoses may have been included in these figures. Reviewing all cases of OSSN, more women were enrolled in the study (74.1%). This is similar to other recent studies in sub-Saharan Africa.[5] However, when looking at those with SCC, male gender was associated with SCC and this was also found to be an independently associated variable through regression analysis. We cannot explain this finding and it is not seen in other studies from the region.[3 11] However, the catchment area for our study included a large rural population. Male workers may have had high UV exposure levels which is known to be a risk factor for OSSN.[12]

Kaimbo Wa Kaimbo *et al*[13] suggested that in patients who were HIV positive, the disease occurred at a younger age than in patients with immunocompetence. When comparing our data, we did not find any significant association between HIV status and the age at which patients present. The current UN prevalence estimate of HIV in Malawi is 11% (10–12.1%) for adults aged 15–49 years from 2009.[14] In this study, patients with HIV seropositivity were eight times more likely to have SCC than no patients with HIV. Previous studies have noted an even greater OR up to 13.1.[2] During regression modelling, HIV was not found to be a significantly independent factor for SCC.

Perhaps the most interesting finding from our data was that lesion size was associated with SCC. The regression analysis revealed that size was also independently associated with SCC. By looking at the data in a diagnostic tree an area of greater than 20.5 mm^2 was found to be significant for SCC. For lesions equal to or smaller than 20.5 mm^2 other factors such as HIV status became relevant. Other recent studies have also found that larger size was associated with malignancy.[5] This may be a useful finding for guideline development as it provides a simple 'in the field' parameter that could easily be measured using a portable scale. Alternatively, a slit lamp beam could be used in the context of an outpatient clinic. Similar guidance has recently been given by the American joint committee on cancer for cutaneous SCC which provides evidence that tumours greater than 2 cm are more likely to be aggressive.[15]

There were several limitations to the study. Although a detailed training was given, potential cases were seen by a range of clinicians and clinical officers providing the possibility of missed cases. Second, the case numbers were small meaning that some relevant factors did not achieve statistical significance. A larger study is being planned to address the numbers and to look more specifically into the size findings.

In summary, this study characterises clinical features of invasive SCC to inform clinicians when making a decision in cases

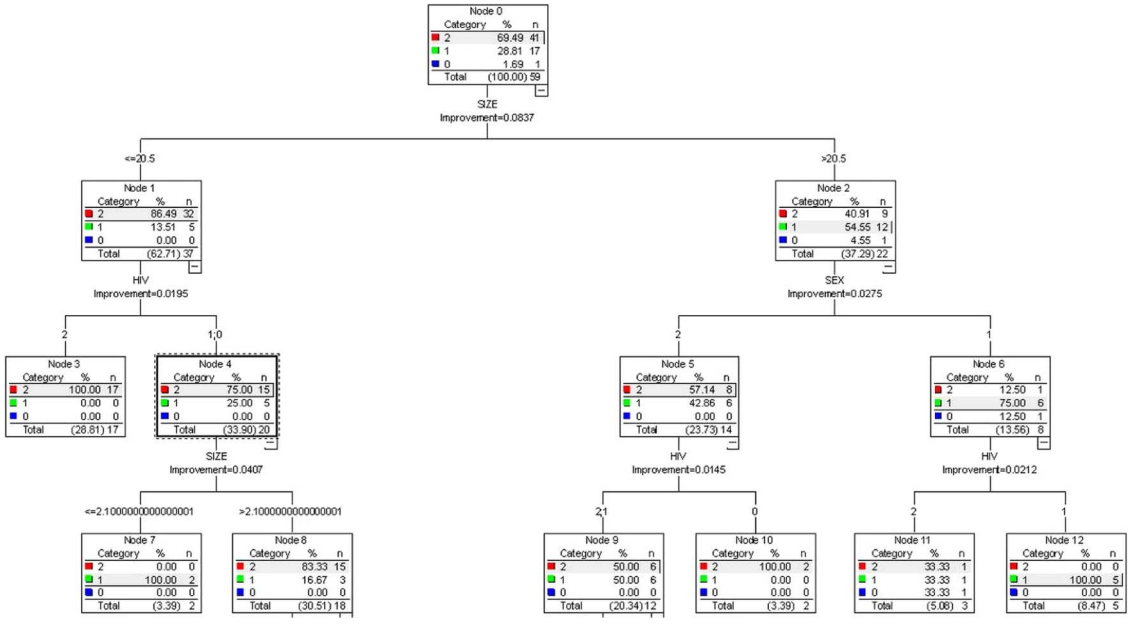

Figure 4 Clinical decision tree incorporating relevant clinical parameters identified by hierarchical ordering. Access the article online to view this figure in colour.

of suspected OSSN and provides the first perspective from Malawi. The study revealed that lesion size, gender and HIV status were most significantly associated with histopathologically confirmed invasive SCC. Of these clinical features the specific area of the lesion is a novel clinical indicator which could be usefully used by ophthalmic healthcare providers to identify higher risk lesions which potentially require more careful management and follow-up.

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Contributors TT, SB are joint first authors carrying out the writing. PA performed the statistical analyses. EK, WD, JM carried out the data collection. CS performed the histological analyses. MZ, BD proposed the study and edited the document.

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