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The clinicopathologic spectrum of anal cancer in KwaZulu-Natal Province, South Africa
Analysis of a provincial database

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ABSTRACT

Background: The occurrence of the considered rare anal cancer has not been documented in the South African context.
Patients and methods: Analysis of data extracted from a prospectively collected KwaZulu-Natal anal cancer database for the period 2000–2014. Data analysed included demographics, clinical picture, pathology, treatment and outcome. The study outcome measures were clinicopathologic spectrum, treatment and outcome.
Results: The study population comprised 244 patients of mean age 50.1 (SD 14.0) years. The age at presentation was lowest for Black African patients compared to Whites and Indians ($p < 0.001$) and lower for HIV positive vs HIV negative patients ($p < 0.001$). Histology was squamous carcinoma in 208 patients (margin 152, canal 56), adenocarcinoma in 34 (all anal canal), neuroendocrine tumour (1) and melanoma (1). Mean age for squamous carcinoma was 48.8 (SD 14.1) years compared to 58.7 years (SD ±11.1) for adenocarcinoma. Metastatic disease occurred in 22 patients (9%). Patients received definitive (139), palliative (53) and no (52) oncological therapy. Thirty patients (12%) underwent resection, seven of whom had positive margins. Seventy-six patients (31%) have been confirmed dead. The 5-year survival rate was 33.4% (95% CI: 23.4–44.6%). There was a highly significantly worse prognosis for adenocarcinoma compared to squamous cell carcinoma ($p = 0.038$). No significant difference was found in survival prospects based on race and tumour location.
Conclusion: Squamous carcinoma was more common and presented at a young age. Black African patients and HIV positive patients were younger. Adenocarcinoma was associated with poorer prognosis. Race and tumour location had no influence on survival.
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1. Introduction

Neoplasms of the anus are infrequent [1,2], making up 1–5% of gastrointestinal neoplasms [3–7]. They are classified into anal canal and anal margin tumours [1]. Anal squamous carcinoma is the most common followed by anal adenocarcinoma. The risk factors include human papilloma virus (HPV), smoking, immunosuppression with lower CD4 counts, Herpes Simplex-2 virus and ano-receptive intercourse [1,8–11]. HPV, especially subtypes 16 and 18, with their affinity for the genital epithelium is the main aetiological factor [1,8–17], which causes anal intraepithelial neoplasia and condyloma acuminata, both of which are precursor lesions for anal squamous carcinoma [1,8,10,11,17–19]. Anal canal adenocarcinoma arises from stratified columnar epithelium lining the anal glands [19,20]. Risk factors include chronic fistulae, inflammatory bowel disease, radiation for non-intestinal cancer, and anal intercourse [20]. Anal canal adenocarcinoma can be subclassified into (i) typical colorectal-type adenocarcinoma (CRTA) that occurs proximal to and within the anal transitional zone, and (ii) anal canal adenocarcinoma arising in anal canal mucosa and anorectal fistulae [5]. Little data on anal carcinoma have emanated from South Africa [21,22]. We have analysed data from an on-going anal cancer database for the KwaZulu-Natal (KZN) Province of South Africa.

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2. Methods

2.1. Setting

The study setting was the Colorectal Unit at the Inkosi Albert Luthuli Central Hospital (IALCH). After histological categorisation all patients with anal cancer are referred to the Multidisciplinary Clinic at IALCH which further stages the patients and makes management recommendations. Treatment delivery logistics are individualised. Follow-up is at the dedicated colorectal oncology clinics situated at IALCH, Addington Hospital and Grey's Hospitals. The standard curative treatment for anal carcinoma in our centre, regardless of histopathology, is definitive chemo-radiation. Indications for surgical excision are small tumours ($\leq$2 cm), larger tumours are given chemo-radiation and metastatic disease treated with chemotherapy. The standard protocol utilises external beam radiotherapy to the pelvis to a dose of 45 Gray followed by a tumour boost to 59.4 Gray in 1.8 Gray fractions. An electron boost to the inguinal area [23,24] is indicated for histology/cytology proven inguinal node disease. Concurrent chemotherapy used is weekly intravenous Cisplatin and 5-fluorouracil orally or intravenously. The threshold for concurrent chemotherapy is a CD4 $\geq$ 200 in HIV positive patients. A diverting colostomy is performed for obstructive bowel symptoms and for prevention of stool contamination.

2.2. Study design

This was an analysis of an on-going anal cancer database which is in the Colorectal Unit of the Department of Surgery, University of KwaZulu-Natal. The dataset analysis included demographic characteristics, clinical presentation, histopathological findings, tumour location and staging, treatment and follow-up. We use the WHO criteria which define anal margin tumours as arising from the skin outside the anal verge and tumours proximal to this landmark are considered anal canal tumours [6,25–27].

2.3. Patients

The data were extracted from the database covering the period 2000–2014. Patients who were referred as anal adenocarcinoma but in whom we could not exclude the possibility of low rectal carcinoma were excluded from the study. Population groups were defined as African, Indian, Coloured and White according to the criteria used by the South African Government. For the purposes of this paper the term "Black African" will be used for the benefit of international readers who may not be familiar with the South African context. In South Africa, "Coloured" is an ethnic label that refers to people of mixed ethnic origin who possess ancestry from Europe, Asia and various Khoisan and indigenous African tribes of Southern Africa. Complete clinical response was defined as disappearance of all target lesions on clinical examination. Complete pathological response was defined as absence of residual tumour or viable tumour cells on histopathological appraisal; intermediate or partial response was defined as an improvement in stage; and poor responders were defined as patients with no change or with persistent lymphadenopathy or metastasis. Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (R057/04).

2.4. Statistical analysis

Data were processed and analysed using Stata 13.0 [StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP]. The *t*-test was employed to identify significant mean differences for continuous variables by dichotomous classifications. The one way analysis of variance (ANOVA) was used to compare mean age at presentation across ethnic groups. Pairwise comparisons (between groups) were also performed and adjusted using a Bonferroni correction. The dates of death were identified where possible for patients in this cohort via the Department of Home Affairs. Kaplan–Meier survival curves were constructed and stratified on key characteristics such as ethnicity, tumour location (canal vs margin) and tumour type (adenocarcinoma vs squamous). Survival functions were compared using the log rank test to ascertain if significant differences existed by sub-group. A *p*-value of $<$0.05 was deemed statistically significant. Patients who were in poor general condition but whose status data could not be ascertained were presumed dead for the purposes of the study but were not coded as such during the statistical analysis.

3. Results

There were 244 patients comprising Africans (183), Indian (35), Coloured (10) and White (16) (Fig. 1). Patient profile is shown in Table 1. The mean age was 50.1 (SD 14.1) years. The peak age was lowest for Black Africans were significantly younger at presentation compared to Indians and Whites respectively by 15.4 and 15.0 years respectively (both $p < 0.001$) but only marginally significantly younger than Coloured by 6.8 years ($p = 0.097$). There was a female preponderance of 2:1 for squamous carcinoma and male preponderance of 2:1 for adenocarcinoma. There was no significant difference in age at presentation when comparing Coloured and Indians to Whites. Squamous carcinoma occurred in 208 patients (85%) of mean age 48.8 (SD 14.1). Thirty-four patients (14%) of mean age 58.7 (SD 11.1) years had adenocarcinoma. When comparing age at presentation among the adenocarcinoma group only, Black Africans did not present at a significantly younger mean age, i.e. 59.6 vs 62.4 years in the other ethnic groups combined (*p*-value = 0.300). This age gap was however significantly larger for squamous cell carcinoma group only with a mean age of 44.8 years among Black Africans compared to 60.3 years in the other ethnic groups combined (*p*-value $<$ 0.001). Of 119 patients tested for HIV status 91 patients (mean age 40.1 years [SD 8.6]) tested positive and 28 patients (mean age 53.6 years [SD 10.3]) tested negative. This mean age difference was statistically significant (*p*-value $<$ 0.001).

Of the 163 patients (67%) that could be staged, the majority were stage II and III (Table 2). Twenty two patients (9%) presented with metastatic disease, the target organs being lungs (10), liver (10), peritoneum (2), bone (1) and pleura (1). Histopathological evidence of HPV or condyloma acuminata was documented in only nine and six patients respectively. Anal margin tumours were more common than anal canal tumours in the whole cohort and in the squamous carcinoma cohort, but all adenocarcinomas arose from the anal canal.

Table 3 shows management. Thirty three patients were eligible for surgery, one refused and two did not return after accepting surgery. Of the 30 eligible patients (12%), three underwent resection *ab initio* and the rest received excision after chemo-radiation (Table 3). Seven patients had one or more positive margins (R-1 resection) following wide local excision. There was no tumour at re-resection in one patient. The other six patients were managed with definitive chemo-radiation with resultant complete pathological response in 5 patients and one patient died during subsequent chemo-radiation from advanced HIV disease and complications of chemo-radiation. The rest of the patients had R-0 resections. Of the patients who received chemo-radiation, there was complete clinical response in 34 (14%) patients (including 16 patients with complete pathological response). The reasons for failure to receive treatment in 52 patients are shown in Table 4.

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