Invasive cervical cancer and human immunodeficiency virus (HIV) infection at Tygerberg Academic Hospital in the period 2003-2007: Demographics and characteristics

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Background: Despite the prevalence of HIV infection in women with pre-invasive and invasive cervical diseases managed at the Gynaecologic Oncology unit of Tygerberg Hospital, there is a lack of local data on the effect HIV/AIDS has on invasive cervical cancer cases managed at this large tertiary institution. Cervical cancer is the most common gynaecological malignancy at Tygerberg Hospital.
Objectives: To establish the following in the local cervical cancer population: (1) HIV prevalence; (2) demographics and clinical characteristics (i.e. stage, histology) in HIV seronegative and seropositive women.
Methods: A retrospective, descriptive study. Study population: all cases of HIV/AIDS-affected women diagnosed with invasive cervical cancer and managed at the combined gynaecological oncology clinic in Tygerberg Hospital (TBH) compared with HIV/AIDS-unaffected women with cervical cancer 2003–2007; with a follow-up period ending 31 December 2009.
Results: In the period 2003–2007, 913 cases of invasive cervical cancer were seen at Tygerberg Academic Hospital (TBH). A total of 838 subjects were HIV seronegative and 75 were HIV seropositive. HIV seropositive subjects were 10 years younger compared with those who were HIV seronegative. The majority of patients in both cohorts never had cervical cytology documented prior to invasive cancer diagnosis. Most women presented with FIGO stages III–IV disease.
Conclusion: HIV-affected women present 10 years younger with cervical cancer compared with their HIV-unaffected counterparts. Effective screening is still lacking in this population. The majority of women present with advanced cervical cancer.

Keywords: Age, AIDS, Cervical Cancer, FIGO clinical stage, Histology, HIV negative, HIV positive, Tumour

Introduction

Since its recognition in the early 1980s, the HIV/AIDS pandemic has affected millions of individuals. It is estimated that 25 million people have died from HIV/AIDS so far. About two-thirds[1] of all HIV/AIDS cases occur in sub-Saharan Africa, with 22 million cases and an estimated 1.9 million new infections in 2008 alone.[1] In 2008 an estimated two million people died of HIV/AIDS. Women constitute 59% of all people living with HIV.[1]

Cervical cancer is the most common gynaecological malignancy in the developing world.[2] It is the leading cause of cancer mortality in sub-Saharan Africa because the majority of patients are diagnosed with advanced stage disease. High-risk human papilloma virus (HPV) infection is now well recognised as the most important cause of cervical intraepithelial lesion with the potential for malignant transformation and progression to invasive cervical cancer.[2]

Sexual behaviour is a recognised risk factor for HIV and HPV infection acquisition and there is evidence suggesting that HIV infection increases the risk of HPV acquisition and vice versa.[2] HIV infection with its subsequent immunosuppression favours persistent and recurrent HPV infection.[3] HPV infection may enhance HPV DNA integration into host-cell DNA with subsequent oncogenesis[4] leading ultimately to invasive cervical cancer.

As women constitute at least 50% of the HIV/AIDS-affected population, and HIV/AIDS affects the natural history of HPV infection, invasive cervical cancer incidence could peak in populations of high HIV/AIDS prevalence.

Though human immunodeficiency virus (HIV) infection is prevalent in women with pre-invasive and invasive cervical diseases managed at the Gynaecologic Oncology unit of Tygerberg Academic Hospital, there is a lack of local data on the effect HIV/AIDS has on the large patient population diagnosed with invasive cervical cancer at our institution.

This study therefore aimed to establish the following in the local cervical cancer population:

- HIV prevalence demographics (age, gravidity, parity, smoking history) at presentation in HIV-negative and HIV-positive women;
- cervical cancer characteristics (i.e. stage, histology) in HIV-negative and HIV-positive women;
- assessment of the outcome with regard to treatment complications, success and disease-free and ultimate survival.

Methods

This is a retrospective and descriptive study including all cases of HIV/AIDS-affected women diagnosed with invasive cervical cancer and managed at the gynaecologic oncology unit in Tygerberg Academic Hospital (TAH) compared with HIV/AIDS-unaffected women with cervical cancer in the period 2003–2007. The follow-up period ended on 31 December 2009.

Table 1: Demographics

Demographics	HIV negative	HIV positive
Age range (mean)	21–89 (52.2)	22–73 (42.9)
Gravidity range (average)	0–19 (4.5)	0–11 (4.4)
Parity range (average)	0–19 (4.5)	0–11 (4.3)
Married*	309	10

*Data not available for all.

Table 2: Cervical cytology

Cytology	HIV negative (%)	HIV positive (%)
No	514 (62.9%)	39 (53.4%)
Normal	9 (1.1%)	1 (1.4%)
ASCUS	9 (1.1%)	0
AGUS	6 (0.7%)	1 (1.4%)
LSIL	3 (0.4%)	0
HSIL	116 (14.2%)	15 (20.5%)
HSIL cannot be excluded	1 (0.1%)	0
Cancer	158 (19.4%)	17 (23.3%)
Total	816	73

Table 3: Colposcopy

Colposcopy	HIV negative (%)	HIV positive (%)
Not done	724 (90.1%)	56 (74.6%)
Normal	2 (0.2%)	0
Abnormal	78 (9.7%)	19 (25.3%)

Table 4: Tumour size

Tumour size (mm)	HIV negative	HIV positive
Average	51.2	60.6
Standard deviation	22.2	24.8
Median	50	65
Minimum	2.85	0.85
Maximum	100	100

Table 5: FIGO clinical stage

FIGO stage	HIV negative (%)	HIV positive (%)
Ia1	14 (1.7%)	3 (4%)
Ia2	3 (0.4%)	0
Ib1	56 (6.7%)	1 (1.3%)
Ib2	17 (2%)	0
IIa	6 (0.7%)	0
IIb	79 (9.4%)	4 (5.3%)
IIIa	1 (0.1%)	0
IIIb	465 (55.6%)	52 (69.3%)
Iva	98 (11.7%)	8 (10.7%)
IVb	85 (10.1%)	7 (9.3%)
Special category	13 (1.6%)	0
Total	837	75

Statistical analysis was carried out using SPSS® version 15 (SPSS Inc, Chicago, IL, USA)). The number and percentages of categorical data as well as the mean and standard deviation (SD) of continuous data were calculated. Comparison between mean values of continuous variables was calculated using Student's t-test while the chi-square was used for categorical data. Where an expected cell value was less than 5, Fisher's exact test was used. Statistical significance was set at a p-value less than 0.05.

The study was approved by the Ethics Committee of Stellenbosch University (No: N10/08/283) and the administration of Tygerberg Academic Hospital.

Results

Between 1 January 2003 and 31 December 2007, 913 patients with new diagnosis of cervical cancer were staged at the gynaecological oncology unit at TAH. A total of 838 patients (91.8%) were human immunodeficiency virus (HIV) seronegative and 75 patients (8.2%) were HIV seropositive. Seventeen of the seropositive women had CD4 counts less than 200.

In this paper, the following results will be considered:

- demographics: age, marital status and RPR test result;
- cervical cancer screening and diagnosis: cytology, colposcopy, LLETZ, cone biopsy and punch biopsy;
- cervical type, FIGO clinical stage and metastatic sites;
- HIV infection incidence.

Demographics
The average age at diagnosis among HIV seronegative women was 52.2 years (21–89). Among HIV seropositive patients, the average age at diagnosis was 42.9 years (22–73).

Table 1 displays selected demographics.

Screening and diagnosis
Nearly 63% of HIV seronegative patients had no cervical cytology done. Amongst HIV seropositive patients, 53.4% had no prior cytology. For details of cervical cytological screening in both groups, see Tables 2 and 3.

Cancer characteristics
The most common histological type was squamous cell carcinoma in 86.7% of HIV seronegative and 89.3% of HIV seropositive patients. Adenocarcinoma was found in 7.7% of HIV seronegative and 5.3% of HIV seropositive patients, or adeno-squamous carcinoma in 2.4% of HIV seronegative and 1.3% of HIV seropositive patients. There were seven (0.8%) neuroendocrine tumours in HIV seropositive compared with one (1.3%) in HIV seropositive patients. All other histological types were combined as other, which constituted 2.4% of HIV seronegative and 2.7% of HIV seropositive patients.

On clinical examination tumour size was available for 45.7% of HIV seronegative and 48% of HIV seropositive subjects. The maximum tumour sizes were similar in both groups (100 mm) (see Table 4 for full details).

Records regarding histological tumour differentiation were available for 49.64% of HIV seronegative and 45.33% of HIV seropositive patients. The most common was moderate differentiation (54.3% of the HIV seronegative compared with 55.9% of the HIV seropositive), followed by poor differentiation (42.1% of the HIV seronegative compared with 44.1% of the HIV
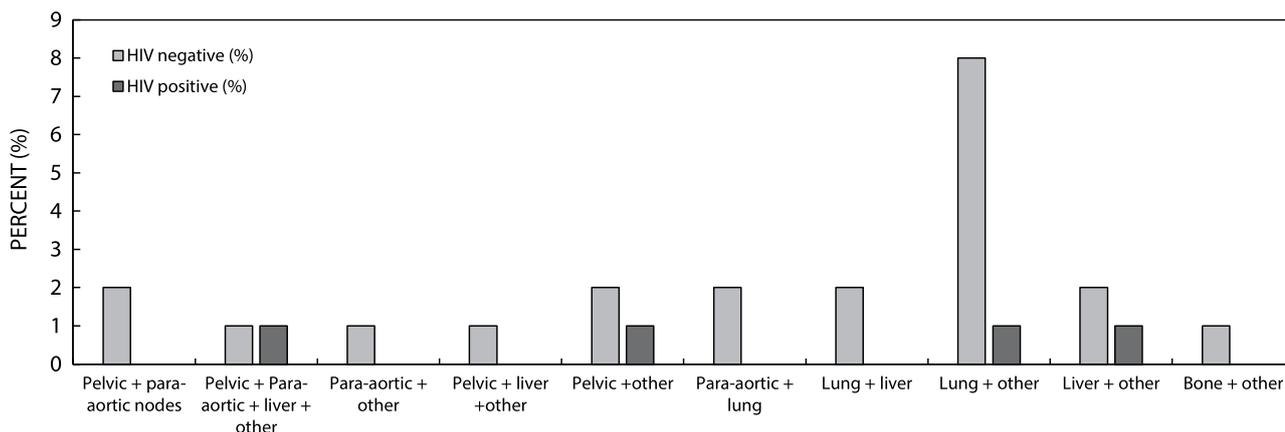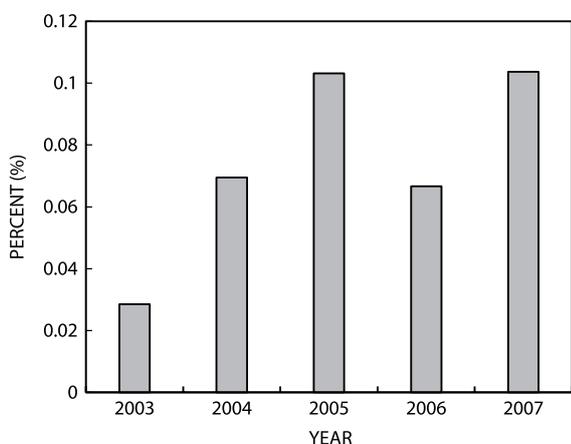
Figure 1: Sites of metastasis.

Figure 2: Yearly HIV incidence.

seropositive). Well-differentiated tumours constituted 3.6% of HIV seronegative patients' cancers with none in the HIV seropositive group.

Records concerning parametrial invasion at diagnosis were available for 96.53% of HIV seronegative and 97.33% of HIV seropositive subjects. In all, 100 (12.3%) HIV seronegative had no parametrial involvement compared with 4 (5.5%) HIV seropositive patients, unilateral involvement (10.9% of the HIV seronegative contrasted with 6.8% of the HIV seropositive), bilateral involvement (76.8% of the HIV seronegative compared with 87.7% of the HIV seropositive).

A total of 912 patients had recorded FIGO clinical stage. The most common was stage IIIB (55.6% of HIV seronegative compared with 69.3% of HIV seropositive patients), followed by stage IVA (11.7% and 10.7% respectively). FIGO stages III and IV combined
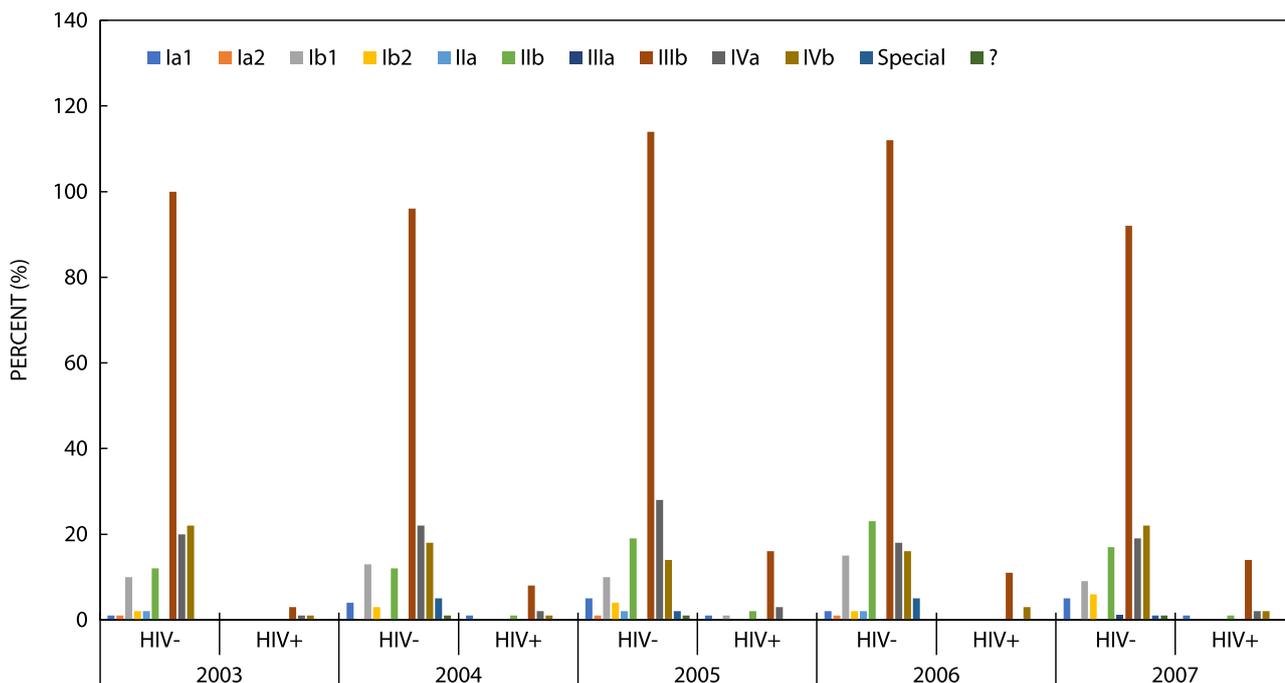

Figure 3: FIGO clinical stages.

represented 77% of HIV seronegative versus 89% of HIV seropositive patients. The difference between the two groups was significant ($p = 0.009$). See Table 5 for full details of FIGO stage.

Records were available for 99.16% of HIV seronegative and 96% of HIV seropositive women with regard to metastatic disease at diagnosis. No distant metastasis at diagnosis was reported in the majority of patients in both groups (73.5% of the HIV negative and 73.6% of the HIV positive). The most common sites of metastasis were lymph nodes, where inguinal nodes were involved in 3.81% of HIV seronegative and 5.33% of HIV seropositive patients. (For multifocal metastases, refer to Figure 1.)

Incidence of HIV infection

The overall incidence of HIV infection was 8.2%. There was, however, significant variation between years. The incidence of HIV infection in this cancer population rose sharply from 2.9% in 2003 to 7.5% in 2004, reaching 11.5% in 2005 and 11.6% in 2007. While all HIV cases in 2003 concerned only advanced stages (IIIb–IVb) of cervical cancer, in subsequent years earlier stage cancers also were seen in the HIV seropositive population, which may indicate that the targeted screening policy for HIV-positive women started to identify some cases earlier. (See Figures 2 and 3 for detail.)

Discussion

This study population, similar to the rest of South Africa, is profoundly affected by the pandemic of human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) on one hand and invasive cervical cancer on the other hand. It is with the hope of understanding the impact of both tragedies on the local population at Tygerberg Academic Hospital that the study was undertaken.

This paper deals only with the demographics, cervical cancer screening, diagnosis, characteristics and HIV infection incidence.

In this study HIV seropositive patients were 11 years younger compared with HIV seronegative ones, confirming what is already known from the literature.[5,6] The mean parity in the index study is comparable to that reported by Lomalisa et al.[5]

Though it is reported in the literature that HIV infection is related to risky sexual behaviors,[7] this study did not find a significant difference between HIV seropositive and HIV seronegative patients with regard to RPR test results.

Implementation and uptake of cervical cancer screening is a major problem in most developing countries and South Africa is no exception in that regard. Practical and effective screening programmes are lacking.[8] The national South African guideline for cervical cytology states that women should have cervical cytology at ages 30, 40, and 50.[9] The inadequate reach of the policy is demonstrated in this study by the fact that the majority in both cohorts had no previous history of cervical cytology prior to cancer diagnosis.

Many younger women under age 30 were diagnosed with invasive cervical cancer in both cohorts (minimum age 21 in the HIV seronegative and 22 in the HIV seropositive). This may indicate that the age at first screening may be too late in our population. Because of poor screening programmes, the majority of our population had never had colposcopic examination prior

to cancer diagnosis. However, one can infer from these data that more patients in the HIV seropositive cohort had cervical cytology and colposcopic examination prior to cancer diagnosis compared with the HIV seronegative cohort, though the difference was not statistically significant. The reason could be that our provincial guideline recommends cervical cytology at the diagnosis of HIV infection with more frequent repeats than for HIV seronegative women.[10]

The most common diagnostic test was biopsy. This simply underlines again that the majority of cervical cancers in this population are diagnosed at a late stage when the tumour becomes macroscopically visible. Squamous cell carcinoma was the most common cell type in both cohorts, followed by adenocarcinoma and adenosquamous carcinoma. This is comparable to the findings of Lomalisa et al.[5] The prevalence of neuroendocrine tumours was minimal in both cohorts. HIV infection therefore does not seem to have any influence on cell type of cervical cancer.

HIV infection did not seem to impact on lymph vascular space invasion by cervical cancer cells as similar percentages in both cohorts presented with lymph vascular invasion. Accordingly, the same proportion in both groups had positive lymph nodes. The majority of patients in both groups had parametrial involvement. From the data, inference can be made that HIV infection tends to be associated with parametrial invasion (especially bilateral). The study by Lomalisa et al.[5] seems to support a higher rate of parametrial invasion and reported extension to pelvis side wall in 50.7% of HIV-negative subjects and in 63.3% of HIV-positive ones (where 38.3% of the HIV positive had bilateral parametrial extension).

The vast majority in both groups presented with advanced stage (FIGO stages III–IV) disease. Even though Lomalisa et al.[5] reported similar findings (stage III–IV disease in 55.4% of the HIV negative and 65% of the HIV positive), the proportion of advanced disease in the current study is higher than that reported by the Johannesburg group.[5] Thomas[11] stated in the New England Journal of Medicine that in developing countries more women present with locally advanced stages (FIGO stages III and IVA) when compared with developed countries, where most women present with early stage cancer. That cervical cancer is diagnosed late in our population is further reflected in the number of patients with metastatic disease (spread beyond the uterine cervix) at initial diagnosis.

HIV prevalence in this population is slightly higher than the 7.2% reported by the Johannesburg group[5] but is lower than the 21% reported by the Durban group.[6] According to South African Department of Health records, HIV prevalence among the antenatal population in 2005 was 39.1% for KwaZulu-Natal (KZN) Province and 15.7% for Western Cape Province.[12] In 2008, according to the Actuarial Society of South Africa (ASSA) 2003 AIDS and Demographic model, HIV prevalence (adults ages 20–64) was 9% in Western Cape compared with 28% for KZN.[13] Over the years there has been no improvement in the number of patients diagnosed with earlier disease (FIGO stages I–II). Apart from the HIV prevalence in the number of patients diagnosed during 2006, HIV prevalence had been rising sharply from 2003. The data suggest a typical early epidemic and rates of HIV infection in newly diagnosed cases of cervical cancer are expected to rise.

The conclusion can be drawn that the fight against cervical cancer and HIV infection in developing countries requires new policies, new talents and hard work. In developed countries the majority of cervical cancers are diagnosed at an early stage.[11] In most parts of sub-Saharan Africa there is no effective screening programme, no radiotherapy services and no qualified medical personnel to deal with the complexities related to cancer diagnosis and treatment. In the same countries the HIV/AIDS pandemic is far from being overcome. It is estimated that 80% of cervical cancer patients[14] and two-thirds of HIV-infected people live in sub-Saharan Africa.[15]

Conclusion

This study confirmed that cervical cancer tends to present 10 years earlier in HIV-infected patients compared with HIV-negative patients. The incidence of HIV infection is increasing in the cervical cancer patient population. The majority of cervical cancer patients, independent of their HIV status, present with advanced FIGO stage disease due to a deficient screening programme.

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