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EFFECT OF HIV SEROLOGICAL STATUS ON OUTCOME IN PATIENTS WITH CANCER OF CERVIX TREATED WITH RADIOTHERAPY
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ABSTRACT

Objectives: **To investigate and compare the outcomes of invasive cervical cancer patients with known HIV serostatus treated with radiotherapy.**
Design: **A retrospective study.**
Setting: **Mulago Hospital Radiotherapy Department, Kampala, Uganda.**
Subjects: **Medical records of thirty six patients treated in our department between May and July 2000, whose serostatus and CD4 counts were known, was done after a four-year period to determine the outcomes and survival after radiotherapy.**
Results: **Of these, 29 (80.6%) were HIV seronegative and seven (19.4%) were HIV seropositive. All the seropositive patients had advanced disease (stage IIB and above) and only two (6.9%) among the seronegative patients had early disease (less than stage IIB) at presentation. The mean CD4 count was 289 (±122 SD) for the seropositive and 550 (± 237 SD) for the seronegative patients (p = 0.008). About 60% of all the patients received both external beam and intracavitary treatment. The one, two and three year survival probabilities (Kaplan-Meier) for the seropositive were 67%, 40% and 27% respectively while they were 89%, 62% and 51% for the seronegative patients. By the fourth year the survival probabilities had fallen to 0% for the seropositive while it was 46% for the seronegative patients.**
Conclusion: **Radiotherapy was effective in both sets of patients with comparable good objective response. The survival probabilities for the seropositive patients were significantly lower than for the seronegative patients at all periods with a P-value of 0.0001 by the fourth year.**

INTRODUCTION

Carcinoma of the cervix is the second most common cancer in females world-wide particularly in developing countries (1). Predisposing factors include human papilloma virus infection, immunodeficiency, early intercourse, multiple partners and smoking (2, 3). Radical radiotherapy is an effective modality for treating carcinoma of the cervix (2). Carcinoma of the cervix is the most common tumour among women in Uganda with an incidence of 41.7 per 100,000 in Kyadondo county (area around Kampala) in 1993-1997 (4). By 2000 the incidence of Human Immunodeficiency Virus (HIV) seropositivity in Uganda had reduced from a high value of over 20 % to a lower value of 8.3 % in the general adult population (5-7).

Invasive cervical cancer has been included as an AIDS defining illness since 1993 although the incidence is not increased significantly in HIV seropositive women. In contrast the precursor lesions, cervical intra-epithelial neoplasia (CIN) occurs more frequently in women with HIV (3, 8). The prolonged incubation between CIN and

invasive cervical cancer may account for the low incidence of invasive cervical cancer in HIV seropositive women whose life expectancy in many parts of the world will be shorter than this (9).

In patients who are HIV seronegative, radiotherapy has been proven to be effective in all stages of cervical cancer (1-5). In most centres HIV seropositive women with invasive cervical cancer are treated using the same protocols as immunocompetent women (10). This treatment is given despite the enhanced mucosal reactions which have been reported in AIDS patients receiving radiotherapy in head and neck cancers and Kaposi's sarcoma. The increased radiosensitivity has been attributed to inherent cellular radiosensitivity and glutathione deficiency. Recently increased reactions and poor patient tolerance has been reported in cervical cancers (11-13). However a long term study comparing outcomes in HIV seronegative and seropositive patients has not been reported in our region. We did a long term survival study comparing HIV seropositive and HIV seronegative patients with invasive cervical cancer treated in our institution. The patients were treated during the same time period and using the same treatment protocol.

MATERIALS AND METHODS

This was a retrospective study of 38 patients with proven cancer of the cervix with known HIV serostatus and CD4 counts who were treated in our department between May and July 2000. A review of their medical records was done in July 2004, a period of four years since they were treated. Two patients were excluded due to inadequate data. The following data were collected from their medical records:

i) HIV serostatus
ii) Age of the patients at presentation
iii) International Federation of Gynaecologists and Obstetricians (FIGO) staging
iv) CD4 counts at presentation
v) External Beam Radiotherapy (EBRT)
vi) Intracavitary treatment (ICT)
vii) Outcome on follow-up regarding tumour size, vaginal (PV) bleeding, PV discharge, pain control and complications
viii) Whether they developed metastases during follow-up
ix) Time in months when they got lost or died

Tumour response was graded as complete response (CR) when there was no residual tumour, partial response (PR) where there was a small residual tumour (less than 2 cm diameter), no change where there was no demonstrable tumour response and progressive disease where the tumour became larger. The radiation therapy oncology group (RTOG) scoring system was used for grading the complications of radiation therapy.

Treatment policy: All the patients were planned to receive both EBRT and ICT. External beam irradiation was administered using a cobalt-60 beam by two equally weighted opposed AP/PA pelvic fields, with the patient in supine position. All fields were treated daily for five days a week. The fields covered the primary tumour, internal and external iliac nodes and the lower common iliac nodes to the level of L4 –L5 inter-space. The lower limit was the inferior border of the obturator foramen and laterally the field extended 1.5-2.0 cm beyond the bony margin of the pelvis at its widest point. Standard dosages of 50-60 Grays (Gy) in 25-30 fractions over five weeks were administered. Brachytherapy treatment was given about one month after EBRT giving 20-30 Gy to point A by a single medium dose rate (2.75 Gy/hr) caesium-137 ICT insertion. Bladder and rectal doses were kept to a minimum by carefully performing vaginal packing with a view of maximising the distance between the sources and the posterior bladder and anterior rectal walls. For seropositive patients 4/7 (57%) and for seronegative patients 18/29 (62%) received ICT. The rest of the patients did not receive ICT because they were either too weak, or lost to follow-up. None of the patients received chemotherapy. Most patients received painkillers, antibiotics and antidiurectics depending on their condition. A few patients were also on anti-retroviral treatment (ARV's).

Statistical analysis: The survival probabilities for the seropositive and seronegative patients were worked out using the Kaplan-Meier method of estimating the survival. A statistical analysis using Epi-Info Version 6.0 for the patients' characteristics, outcomes and survival of the seropositive and seronegative patients was done. A P-value of < 0.05 was considered to denote statistical significance.

RESULTS

Seropositive patients were 7/36 (19.4%) while the seronegative ones were 29/36 (80.6%). Figure 1 shows the HIV serostatus in different age groups. The mean age of the seropositive patients was 40.7 years with a range of 28-49 years while the one for seronegative was 51.9 years, ranging from 29-78 years. All the seropositive patients were below 50 years of age. The peak age group for both seropositive and seronegative patients was 40-49 years. The difference in age at presentation between the seropositive and seronegative patients was just statistically significant with a P-value of 0.05. This age difference may be related to the fact that HIV mainly affects the younger individual who tends to be more sexually active.

Figure 2 shows the FIGO staging of the patients. Most of our patients presented with advanced disease. For seronegative patients 27/29 (93.1%) presented with stage IIB and above. All the seropositive patients presented with advanced disease of stage IIB and above. There was no statistically significant difference in stage at presentation between the seropositive and seronegative patients (p = 0.47).

Figure 1

HIV serostatus in different age groups (p = 0.05)

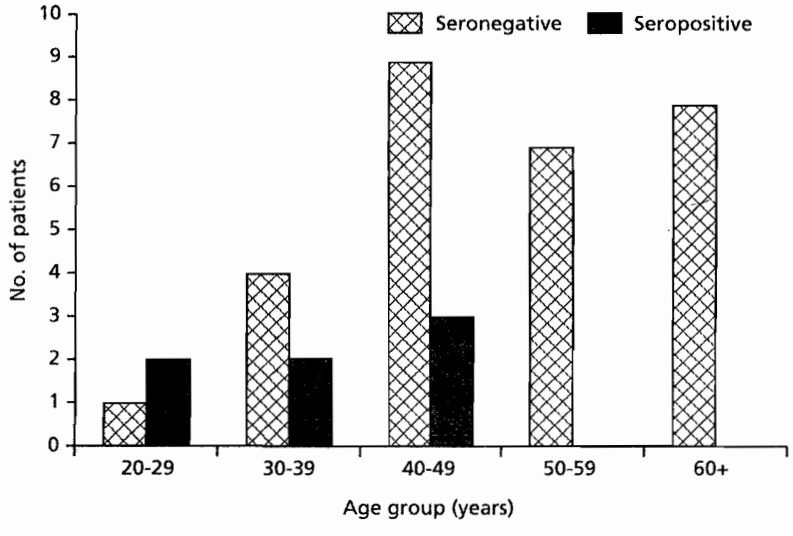


Figure 2

FIGO staging of the patients at presentation (p = 0.47)

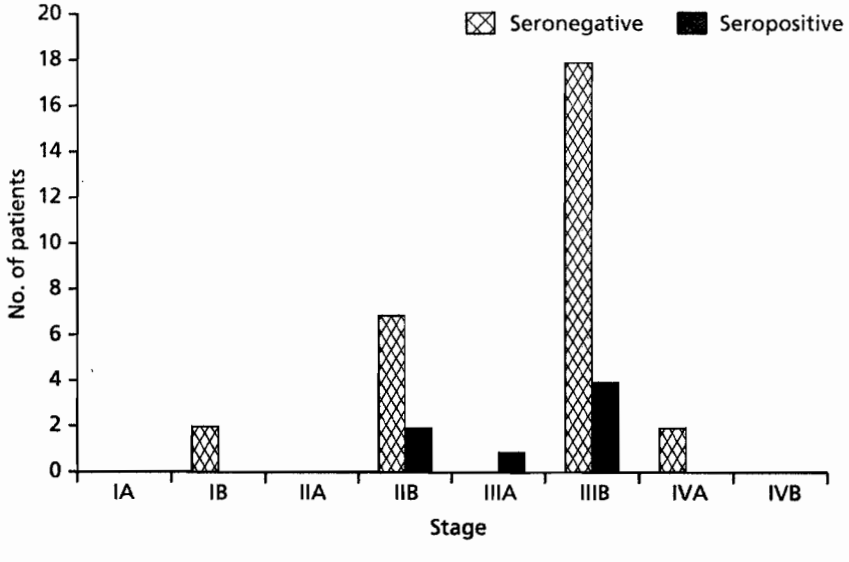


Table 1

CD4 counts at presentation

CD4 Counts (cells per ml)	Seropositive (n = 7) No. (%)	Seronegative (n = 29) No. (%)
Below 100	0	0
100 - 200	2 (29)	0
200 - 500	5 (71)	11 (37.9)
Above 500	0	18 (62.1)

The CD4 counts (indicating the degree of immunosuppression) at presentation were analysed. Table 1 shows the CD4 counts at presentation.

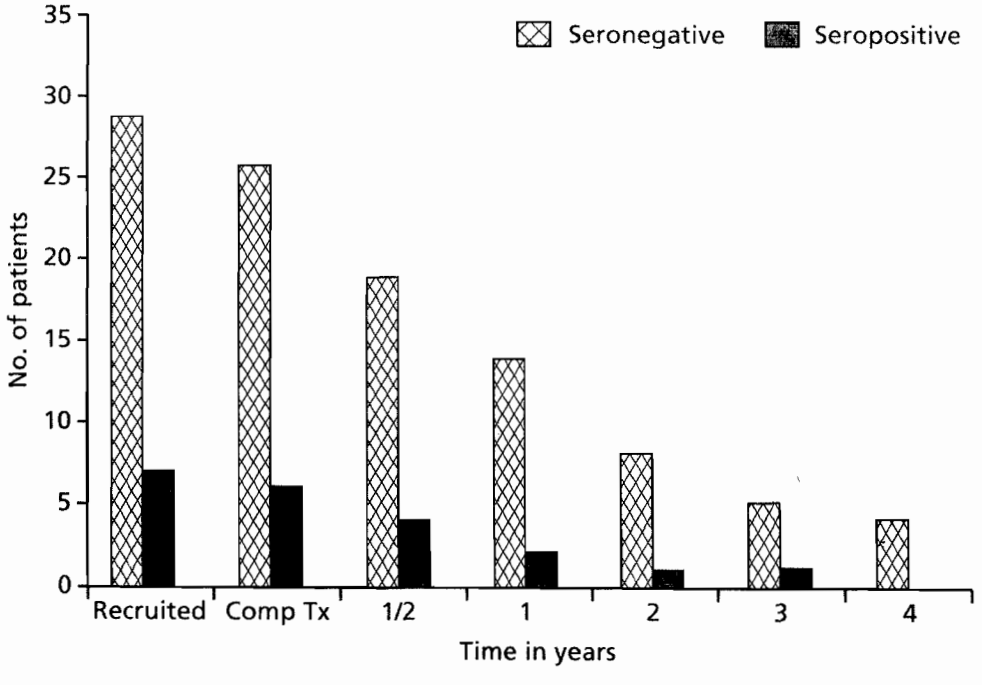
Overall the mean CD4 count was 501 (± 242 SD) cells / mm^3. However the mean CD4 cell count was significantly lower in the seropositive patients than in the seronegative ones being 289 (±122 SD) cells / mm^3 vs. 550 (±237 SD) cells / mm^3 ($p = 0.008$). All the seropositive patients had CD4 counts below 500 cells / mm^3. Only two (30%) of the patients who were seropositive had moderate immunosuppression with CD4 counts of 100-200 cells / mm^3. There was no patient with a count below 100 cells / mm^3. About 38% in the seronegative group had a reduction in their CD4 counts (200-500) which may be a sign that cancers cause some degree of immunosuppression. Only four patients had a CD4 count done at the end of their treatment. All of them were seronegative and they showed a percentage reduction in their pre-treatment values ranging from 1.4% to a high of 42.7%. This indicates that the treatment itself caused some degree of immunosuppression.

Of the seropositive patients 1/7 (14.3%) and the seronegative 4/29 (13.8%) developed metastatic disease while on follow-up. The rest of the patients had only local disease and its complications.

Figure 3 shows the actual number of patients recruited and seen at follow-up at different times. There is a gradual decrease in the number of patients turning up for follow-up for both the seronegative and seropositive patients. Figure 4 shows the follow-up pattern for early compared to late disease for seronegative patients. The number of patients with earlier disease (stage IIB and below) coming for follow-up was twice as much as those patients with advanced disease for the seronegative patients and this was statistically significant ($p = 0.0009$). This was a reflection of their survival chances.

Figure 3

Actual number of patients recruited and seen at follow-up at different times



Comp Tx = completed EBRT

Figure 4

Follow-up pattern for early compared to late disease for seronegative patients (p = 0.0009)

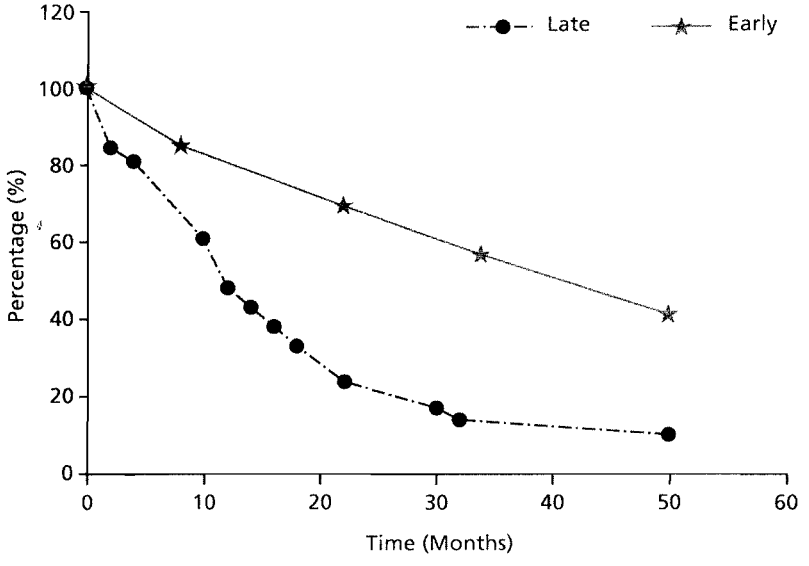


Figure 5

Overall survival probability (Kaplan-Meier) in patients with cancer of cervix who are seronegative and seropositive (Overall p-value = 0.000001)

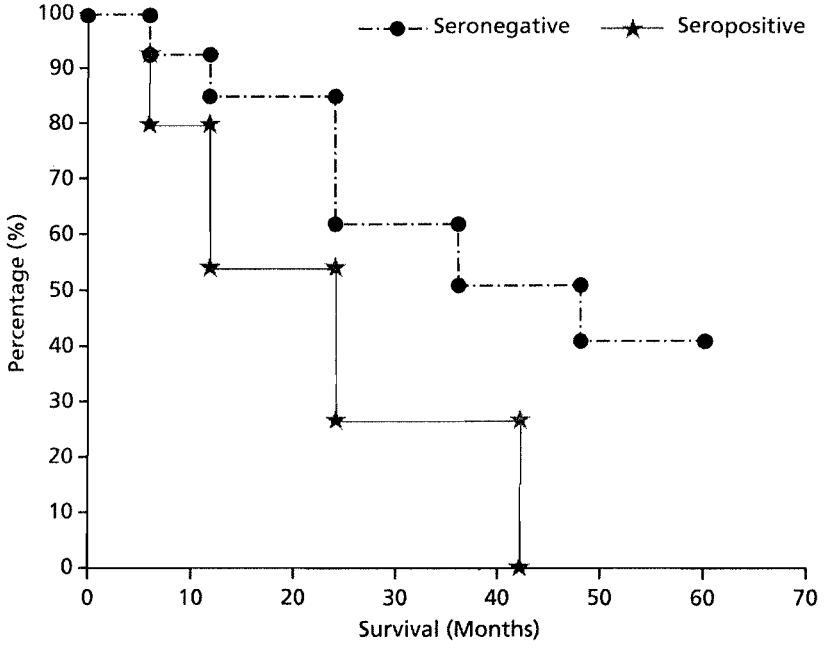


Table 2 summarises the outcome of seronegative cervical cancer patients after radiotherapy regarding tumour control, PV bleeding, PV discharge, pain and complication of the treatment. The responses were shown as percentages of the total number of people on follow-up at that particular time. At six months, there was a complete response (CR) of the tumour of 37% and partial response (PR) of 42%. Control of bleeding had an objective response of 100% while that of discharge was 95% and of pain was 85%. At one year one patient had a severe complication of persistent bleeding per rectum. By two years 89% of the seronegative patients had either mild or no complications while 11% had moderate

Table 2

Summary of outcomes for the seronegative patients (shown as percentages of the total number of people on follow-up at that particular time)

	1/2 - year	1-year	2-years	3-years	4-years
Tumour response					
Complete response	37	43	78	80	100
Partial response	42	15	22	20	0
No change	11	21	0	0	0
Progressive disease	10	21	0	0	0
Bleeding control					
Complete response	84	85	100	100	100
Partial response	16	8	0	0	0
No change	0	7	0	0	0
Progressive symptom	0	0	0	0	0
Discharge control					
Complete response	53	57	90	100	100
Partial response	42	22	10	0	0
No change	5	21	0	0	0
Progressive symptom	0	0	0	0	0
Pain control					
No pain	27	43	50	40	50
Mild pain	58	43	38	60	50
Moderate pain	5	14	12	0	0
Severe pain	10	0	0	0	0
RT complications					
No complications	53	50	56	100	100
Mild complications	42	29	33	0	0
Moderate complications	5	14	11	0	0
Severe complications	0	7	0	0	0

complications. Complications included dysuria, tenesmus, diarrhoea, labial oedema, skin hardening and were characterised as mild or moderate depending on the RTOG scoring system. By four years all the survivors had no evidence of disease with complete tumour response and no bleeding or discharge.

For the seropositive patients, there was complete tumour control in 75% and 25% were partial responders at six months. The objective response was 100%, 75%, and 50%, regarding bleeding, discharge and pain respectively. One patient developed a severe complication of a vesico-vaginal fistula. The rest had mild or no complications at six months. By the end of the second year one of the two seropositive patients who were still on follow-up had minimal local tumour but with good control of PV bleeding and discharge. The second patient who was on ARV's had good local control but died of other causes in the fourth year. There was no statistically significant difference in tumour control between the seropositive and the seronegative patients with a p-value of 0.53.

Figure 5 shows the overall survival probability (Kaplan-Meier) in patients with cervical cancer who are seronegative and seropositive. The one, two and three year survival probabilities (Kaplan-Meier) for the seropositive were 67%, 40% and 27% respectively while they were 89%, 62% and 51% for the seronegative patients. By the end of the fourth year the survival probabilities had fallen to 0% for the seropositive while it was 46% for the seronegative

patients. These differences between the seropositive and the seronegative patients were statistically significant with p-values of 0.009, 0.002, 0.0005 and 0.0001 at one, two, three and four years respectively.

DISCUSSION

From our results, the HIV seropositivity rate of 19.4% in cervical cancer patients was much higher than in the adult Ugandan population which was only 8.3% in the year 2000 (6,7). The reason for this is not clear to us and we suggest more investigation on the subject. However we think that it is due to the long period between the infection with HPV and HIV and eventual development of invasive cervical cancer. Our results associate cervical cancer as an AIDS defining illness, and this was in agreement with other investigators (9,15). Maiman *et al* (14), in their study in New York City (USA) also reported a seropositivity rate of 19% among patients with cervical cancer, which rate is quite similar to ours.

The results also demonstrated that both seropositive and seronegative patients had advanced cervical cancer with almost all of them presenting with stage IIB disease and above. Stage of the disease at presentation was one of the most prominent factors regarding survival. There was however a comparable good objective response in both seropositive and seronegative patients for similar FIGO stages at presentation. Radiotherapy was thus effective in both sets of patients with a good relief of symptoms in all patients treated. The response of seropositive patients was comparable to another study in India where radiotherapy was found effective in this set of patients (11).

The Kaplan-Meier survival probabilities for the seropositive patients were worse than for the seronegative patients at all periods as shown in Figure 5 with the curves separating at six months. From our results, HIV infection has a link on survival, with seropositive patients falling off at a faster rate than the seronegative patients. This was in agreement with another report by Maiman, *et al* (14). On the hand, it was however not possible to establish the cause of death in our seropositive patients in this study and it is likely that they were dying from other AIDS related illnesses.

Our four year survival rate for cervical cancer is generally low compared with data from developed countries (1), but this is greatly influenced by the late presentation. In our department we were also not using chemo-radiation due to financial restraints. It is however known that the addition of chemotherapy with cisplatin to treatment with external-beam and intracavitary radiation significantly improves the rates of survival and progression-free survival among women with locally advanced cervical cancer - 78% vs. 53% (16,17). Our survival rates may also have been negatively influenced by our relatively long waiting time between EBRT and brachytherapy. Ideally this treatment should be completed within 42 days (18, 19). However our three-year survival rates (51% for the seronegative patients) are comparable to reports from other developing countries like Zimbabwe (44.9%), India (57.5%), China (45.0%) and Thailand (41.3%) as reported by Vegas *et al* (20) and Wabinga *et al* (4).

In conclusion, survival and treatment outcomes are both dependent on the stage at presentation which therefore highlights the importance of cervical cancer screening programme in our country. There is also a higher incidence of cervical cancer in Uganda necessitating the integration of gynaecological care into medical services with a special emphasis on its prevention, early diagnosis and effective treatment for both seronegative and seropositive women (21). Radiotherapy was effective in both sets of patients with comparable good objective response and should be used in both sets of people. In a retrospective analysis such as this, it is not possible to exclude other unknown prognostic factors that may have been associated with survival. A carefully designed prospective study will be necessary to monitor treatment outcomes using chemoradiation and ARV treatment.

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