^{18}F-FDG-PET/CT imaging of uterine cervical cancer recurrence in women with and without HIV infection

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ABSTRACT:

Background: To compare the rate, time and, pattern of recurrence of cervical cancer between patients with and without HIV infection and to determine factors predicting cervical cancer recurrence in patients evaluated by ^{18}F-FDG-PET/CT.

Methods: We reviewed the ^{18}F-FDG-PET/CT images of patients with histologically proven cervical carcinoma who were presenting with suspected recurrence. We extracted epidemiologic data, previous treatment, histologic subtype, HIV status, viral load and CD4 counts from the electronic laboratory database and the referral form for the ^{18}F-FDG-PET/CT study.

Results: We studied 303 women including 112 HIV-infected patients. FIGO stage III disease was present in 131 patients. Of 198 patients with recurrence, 74 were HIV-infected while 124 were not (p=0.849). HIV infected patients were younger (41.99 ± 9.30 years) compared to HIV-uninfected (50.19 ± 11.09), p<0.001. Local recurrence was present in 125 patients while 100 patients had a distant recurrence. Recurrence occurred at a single site in 88 patients and two or more sites in 110 patients. No significant difference in the recurrent patterns between HIV-infected and uninfected patients. Median time to recurrence was 10.50 months (Range: 6.00-156.00) among HIV-infected versus 12.00 months (IQR:7.00–312.00) among the uninfected, p=0.065. FIGO stage III (p=0.042) and the presence of histological sub-types other than SCC (p=0.005) were significant predictors of recurrence. HIV infection by itself was not significant in predicting recurrence (p=0.843).

Conclusions: HIV infection has no significant impact on the rate, time or pattern of recurrence in women with suspected cervical carcinoma recurrence. Advanced disease and histological variant other than SCC are predictive of recurrence.

Keywords: ^{18}F-FDG-PET/CT, Carcinoma of the cervix, Squamous cell carcinoma, Recurrence, HIV infection

Introduction

Despite increasing availability of effective preventive measures, carcinoma of the cervix remains a significant cause of morbidity and mortality in women globally.[1-3] Carcinoma of the cervix has a strong association with infection with human papillomavirus (HPV), a common sexually transmitted oncogenic virus that predisposes to the development of squamous cell carcinoma (SCC) in many organs of the body. SCC of the cervix is one of the most common HPV-associated malignancies.[1-3] There is a high prevalence of infection with high-risk strains of HPV among human immunodeficiency virus (HIV)-infected patients. Besides, HIV-infected patients are less likely to clear this virus when they are infected by it compared with HIV-uninfected patients.[4] There is, therefore, a higher prevalence of high-grade intraepithelial lesion, the precursor lesion of SCC of the cervix, among HIV-infected patients,[4] and consequently, invasive SCC of the cervix.[5]

Treatment of carcinoma of the cervix includes surgery, radiotherapy, and chemotherapy in different combinations. About a third of patients who receive adequate treatment will experience disease recurrence.[6,7] Recurrence may be heralded by the onset of new symptoms which are confirmed by clinical and histological evaluation. Symptoms of recurrence often prove difficult to distinguish from therapy-related complications. Imaging, therefore, plays a vital role not only in the detection of recurrent disease but also in the evaluation of its extent. Pre-therapy evaluation of the extent of recurrent disease is crucial in selecting effective therapy.

The clinical utility of Fluorine-18 fluorodeoxyglucose positron emission tomography integrated computed tomography (^{18}F-FDG-PET/CT) for initial staging, radiotherapy planning, treatment response assessment and for prognostication in carcinoma of the cervix has been shown in recent studies.[8-11] ~~A~~ Few studies with modest study populations have shown its utility in the evaluation of recurrent carcinoma of the cervix uteri.[11-14] Data are scarce on the utility of ^{18}F-FDG-PET/CT to evaluate if any differences exist in the rate, time and pattern of treatment failure between HIV-infected and uninfected patients treated with curative intent for invasive carcinoma of the cervix. This

differentiation is essential to determine if both groups of patients should be treated similarly or not. The aim of this study was, therefore, to evaluate the diagnostic ability of ^{18}F-FDG-PET/CT for determining recurrence of cervical carcinoma in women treated with curative intent. We also aimed to determine the differences in the rate, time and pattern of recurrence of cervical carcinoma between HIV-infected and HIV-uninfected women who were treated for invasive cervical carcinoma.

Patients and Methods

Patients

This is a retrospective study of consecutive patients with histologically proven and previously treated carcinoma of the cervix referred by the treating oncologists on account of clinical concern of recurrence of carcinoma of the cervix. These patients were referred to the Department of Nuclear Medicine at Steve Biko hospital/University of Pretoria for ^{18}F-FDG-PET/CT between January 2014 and June 2018. Each patient signed a written informed consent to have an ^{18}F-FDG-PET/CT scan done, and for anonymous publication of their disease-related information. We reviewed the medical records of patients. The basic epidemiological parameters, HIV-status, histological sub-type of the tumor, the FIGO stage of the disease at diagnosis, type of treatment each patient underwent, the time from treatment to onset of symptoms suggestive of recurrence and current or previous history of tuberculosis were extracted into an excel spreadsheet from the medical records. In patients with HIV infection, we documented the CD 4 count, viral load and the duration of HIV infection. We excluded patients who remained symptomatic or became symptomatic within six months following treatment administered with curative intent. Also, patients with vesicovaginal fistula were excluded as radioactive urine in the cervix/vaginal cuff may preclude adequate assessment of local recurrence on PET images. We also excluded patients with technically sub-optimal image quality and those without documented HIV status. We confirmed recurrence by histopathological evaluation of biopsy specimen or correlative morphologic imaging with MRI. The diagnosis of recurrence was confirmed if histologic/cytological examination of tissue obtained at biopsy or cells obtained at fine-needle aspiration procedure was positive for malignancy. Patients with lesions showing intense ^{18}F-FDG uptake and MRI features suggestive of malignancy were assessed to have disease recurrence and proceeded to salvage therapy as indicated.

The Human Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria approved this study (Reference number: 223/2018).

^{18}F-FDG-PET/CT Imaging

We performed imaging according to published guidelines.[15] All patients had a minimum of six hours of fasting with a fasting blood sugar of less than 11 mmol/L. We adapted the injected activity of ^{18}F-FDG to patients' weight using the formula: [(body weight÷10)+1]x37 MBq. Patients were kept warm in a dimly-lighted room with low ambient noise during an uptake period of 60 minutes. Patients underwent ^{18}F-FDG-PET/CT imaging on a Biograph 40 Truepoint hybrid PET/CT scanner (Siemens Medical Solution, Illinois, USA). Gastrografin (Bayers, Isando, South Africa) was used for oral contrast, 30mls diluted in one liter of water administered over one hour before the commencement of imaging. Where no contraindications existed (such as iodine allergy or renal failure), we performed CT scan with intravenous contrast using 100ml Ominopaque 350 (GE Healthcare, Wisconsin, USA) with a scan delay time of 80 seconds. CT scan parameters were adjusted for patients' weight (120KeV, 40-150mAs), 5mm sectional width and a pitch of 0.8. Image acquisition was from mid-thigh to vertex in a caudocranial direction. We acquired PET imaging in 3D mode at 3 minutes per bed position. When indicated such as when urinary bladder activity obscures the adequate assessment of loco-regional recurrence, additional pelvic imaging was done following bladder emptying. We performed image reconstruction using ordered subset expectation maximization iterative reconstruction (4 iterations, 8 subsets) with a Gaussian filter applied at full-width at half-maximum of 5.0mm.

Image interpretation

Two nuclear physicians with a decade of experience interpreting ^{18}F-FDG-PET/CT scans performed image interpretation. The interpretation was made independently with disagreements resolved by consensus. The nuclear physician used qualitative interpretation (visual analysis) to determine if recurrence was present or not. The site of recurrence was documented as either, local (cervix or vaginal cuff with/without invasion into adjacent visceral), nodal (pelvic or extra-pelvic nodes), bone, or others (soft tissue visceral including peritoneum and anterior abdominal wall).

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) when they are normally distributed or as median (interquartile range, IQR) when they are skew. Categorical data are presented as proportions (percentages). We used the Chi-square test to compare categorical data, and the Mann Whitney U test and independent samples T-test for

continuous variables. We used multiple regression analysis to evaluate for the predictors of recurrence. The statistical significance was set at a *p*-value of less than 0.05. We performed statistical analysis using IBM SPSS Statistics 21.0 (IBM Corp, Armonk, New York USA).

Results

A total of 425 ^{18}F-FDG-PET/CT scans were acquired to determine recurrence of cervical carcinoma in 303 women, mean age 47.18 ± 11.18. The modal disease stage at the time of treatment was IIIB (n=126). SCC was the most common histological variant seen in 88.12%. Most patients were previously treated with either a combination of chemotherapy and radiotherapy (n=137) or radiotherapy alone (n=92). Out of 303 patients, 112 were HIV-infected while 191 patients were HIV negative. All the HIV infected patients were on stable combination antiretroviral therapy (cART) at the time of imaging with a median CD4 count of 434.00 cells/μL. There was a presence of HIV viremia in 19 patients with a median HIV viral load of 578.00 copies/mL. Viral load was below detectable limits (<40 copies per mL) in 93 HIV-infected patients. Twenty-nine patients had been previously treated for tuberculosis. No patient had an active tuberculous infection at the time of evaluation for recurrent cervical cancer. The detailed clinical and epidemiological characteristics of the study population are shown in table 1.

Recurrence

We confirmed recurrence in 198 patients (65.34%) with a median time to recurrence of 12 months. Cervical carcinoma recurred at one site in 88 patients, two sites in 71 patients and more than two sites in 39 patients. Distant metastatic recurrence was seen in 100 patients. The lymph nodes were the most frequent site of recurrence seen in 147 patients followed by local recurrence demonstrated in 125 patients. Other sites of recurrence as demonstrated on ^{18}F-FDG PET/CT included liver (n=23), bones (n=29), and lungs (n=31). ^{18}F-FDG PET/CT showed unusual sites of distant recurrence in the pleural (n=2), adrenal (n=3), and spleen (n=4). Among 125 patients with local recurrence, 44 of them had isolated local recurrence without any distant site of disease recurrence. Figure 1 shows a breakdown of distant metastatic recurrence seen in 100 patients.

Table 1 Demographic and clinical characteristics of the study population

Variable	Frequency	Percent
Age (years)		
Mean ± SD	47.18 ± 11.18	
Range	25 – 90	
FIGO stage		
Stage IA	7	2.3
Stage IB	48	15.8
Stage IIA	14	4.6
Stage IIB	78	25.7
Stage IIIA	5	1.7
Stage IIIB	126	41.6
Missing	25	8.1
Histological subtype		
Adenocarcinoma	17	5.6
Adenosquamous	5	1.7
Neuroendocrine	1	0.3
Squamous cell carcinoma	267	88.1
Missing	13	4.3
Previous treatment		
Chemoradiotherapy	137	45.2
Radiotherapy alone	92	30.4
Surgery & chemotherapy	56	18.5
Surgery & radiotherapy	17	5.6
Surgery & chemoradiotherapy	1	0.3
HIV		
Yes	112	37.0
No	191	63.0
Duration of HIV infection (months)		
Median (Inter-quartile range)	72.00 (36.00 – 100.50)	
CD 4 count (cells/µL)		
Median (Inter-quartile range)	434.00 (242.00 – 617.00)	
Viral load (copies/mL)		
Detectable	19	17.0
Not detectable	93	83.0
Median (Inter-quartile range)	578.00 (63.00 – 8009.00)	
Previous tuberculous infection		
Yes	29	9.6
No	274	90.4

FIGO: International Federation of Gynecology and Obstetrics.

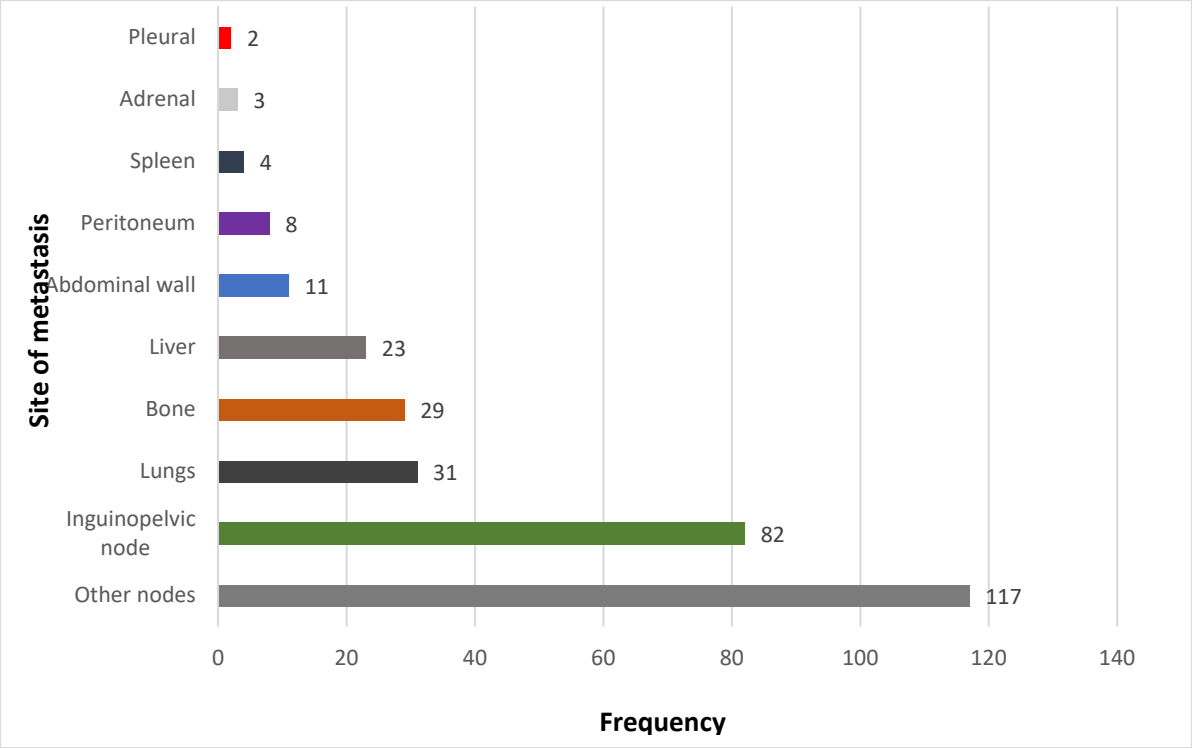

Figure 1 A detailed breakdown of the sites of extra-cervical recurrence seen in 100 patients 42 of whom had multiple sites of involvement.

Comparison between HIV-infected and HIV-uninfected patients

The HIV-infected patients were younger at the time of diagnosis of cervical cancer compared with the HIV-uninfected patients (41.99 ± 9.30 versus 50.19 ± 11.09, $p<0.001$). We found a significant difference in the FIGO stage of the disease between HIV-infected and HIV-uninfected patients, for example, 58.65% of the HIV-infected patients were treated for stage III disease compared with 40.22% among the HIV-uninfected patients ($p=0.009$). No significant difference in the histological sub-types of cervical carcinoma between the two groups. Similarly, the two groups were not significantly different regarding the initial treatment given, and the time to recurrence. ^{18}F-FDG PET/CT showed the incidence of recurrence of cervical carcinoma among HIV-infected women was not significantly different from its incidence among HIV-uninfected women. Similarly, on 18F-FDG PET/CT showed similar pattern of recurrence in the difference sites evaluated between HIV-infected and HIV-uninfected women ($p>0.05$). Table 2 shows the details of comparison of ^{18}F-FDG PET/CT imaging findings in HIV-infected and HIV-uninfected women. Figures 2 and 3 show representative images of an HIV-infected and HIV-uninfected patients with disease recurrence respectively.

Table 2 Comparison between HIV-infected and HIV-uninfected women

Variable	HIV		χ^2	*p* value
	Yes n (%)	**No** n (%)		
Age				
Mean ± SD	41.99 ± 9.30	50.19 ± 11.09	-6.559^t	**<0.001***
FIGO stage				
Stage I	18 (17.3)	37 (21.3)	9.321	**0.009***
Stage II	25 (24.0)	67 (38.5)		
Stage III	61 (58.7)	70 (40.2)		
Histology				
Squamous cell carcinoma	104 (94.5)	163 (90.6)	1.488	0.222
Others	6 (5.5)	17 (9.4)		
Previous therapy				
Radiotherapy alone	32 (28.6)	60 (31.4)	6.100^Y	0.192
Chemotherapy and Surgery	15 (13.4)	41 (21.5)		
Chemotherapy and Radiotherapy	61 (54.5)	76 (39.8)		
Surgery and Radiotherapy	4 (3.6)	13 (6.8)		
Chemotherapy, Surgery, and Radiotherapy	0 (0.0)	1 (0.5)		
Recurrence				
Yes	74 (66.1)	124 (64.9)	0.041	0.839
No	38 (33.9)	67 (35.1)		
Site of recurrence (n = 203) $^+$				
Nodes	54 (72.0)	93 (72.7)	0.110	0.991
Local	44 (58.7)	81 (63.3)		
Bone	11 (14.7)	18 (14.1)		
Others sites	21 (28.0)	37 (28.9)		
Time to recurrence (Months)				
Median (Range)	10.50(6.00–156.00)	12.00(7.00–312.00)	3773.000	0.065

χ^2: Chi-square; t: Independent Samples T-test; Y: Yates corrected Chi-square; *: *p*-value <0.05; +: presence of multiple sites of recurrence; FIGO: International Federation of Gynecology and Obstetrics.

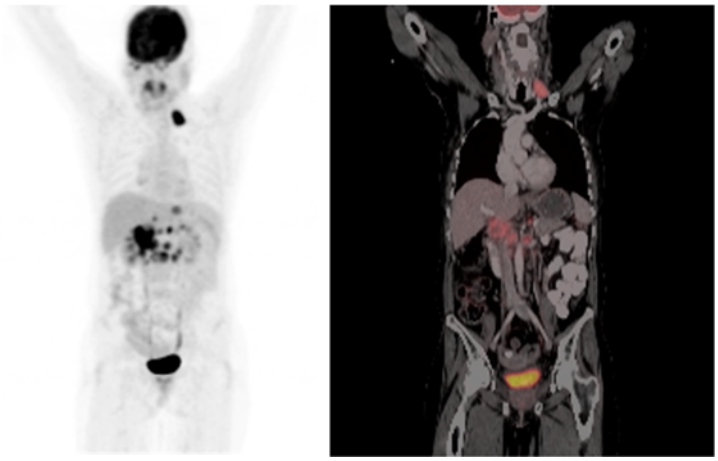

Figure 2 A 50-year-old HIV-infected female on cART, treated for FIGO stage IIIB carcinoma of the cervix with chemoradiotherapy six years earlier. She presented to the treating oncologist with complaints of bleeding per vagina, low abdominal pain, and an enlarged left supraclavicular node. She was treated for pulmonary tuberculosis three years earlier. ^{18}F-FDG-PET/CT obtained to evaluate for recurrence shows nodal metastases in the left supraclavicular, portal hepatitis, coeliac, and para-aortic regions as well as a solitary liver metastasis. No local recurrence is demonstrable.

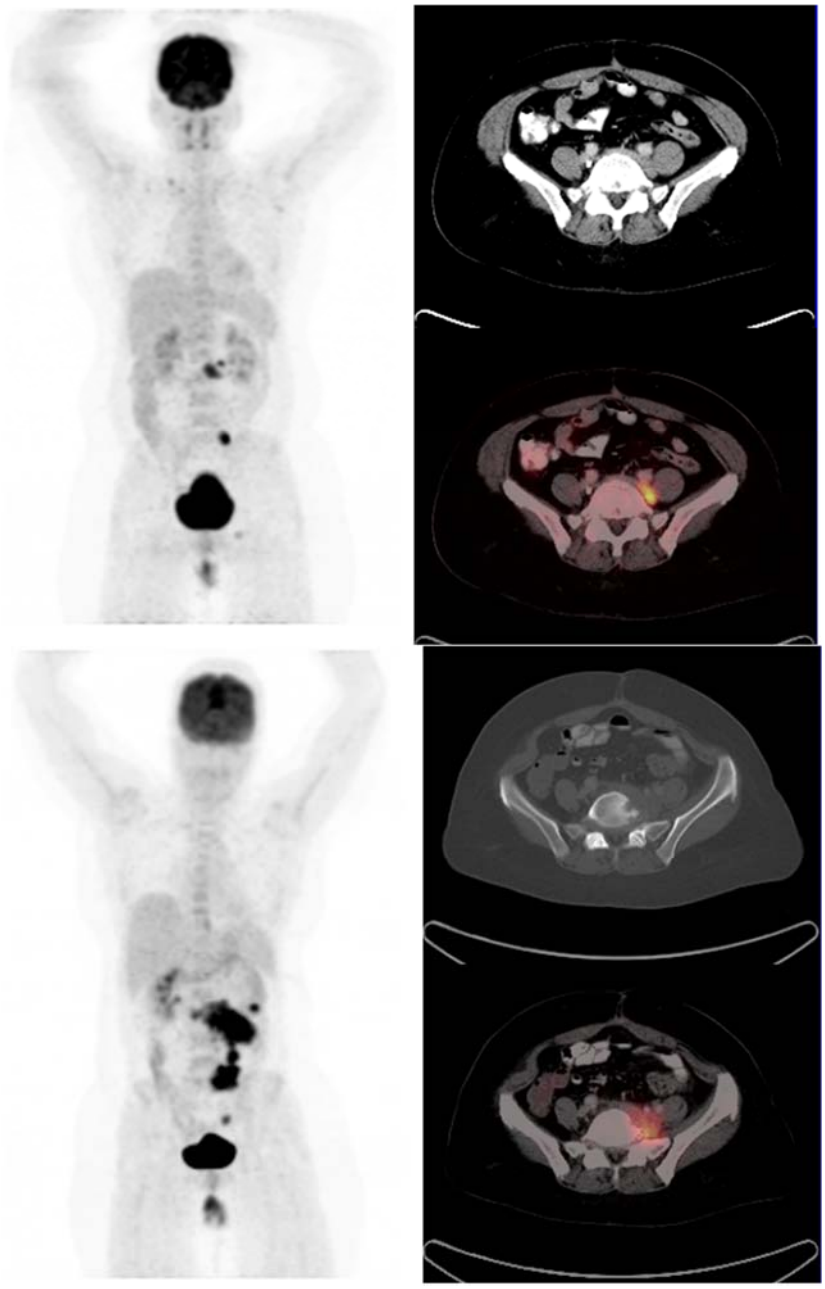

Figure 3 A 38-year-old HIV-uninfected female who previously had total abdominal hysterectomy plus lymph node dissection for a FIGO stage IB carcinoma of the cervix. ^{18}F-FDG-PET/CT obtained on account of clinical concern for recurrence show metastatic left para-aortic and iliac nodes (top row). No treatment was given following the initial PET/CT scan. A repeat ^{18}F-FDG-PET/CT scan obtained 11 months later show increased in size and ^{18}F-FDG avidity of the previously reported metastatic nodes with invasion into the adjacent L5 vertebra (bottom row). New metastases sites are seen in the anterior abdominal wall and pelvic node.

Factors predictive of recurrence

We found twice the odds of recurrence in patients with stage III disease compared with stage I and II (p=0.042).

Similarly, patients with tumors of histological sub-types other than SCC had higher propensity to recur (p=0.005).

Other variables such as age, HIV status, and previous treatment received were not significant predictors of disease recurrence (table 3). In a multivariate regression analysis, FIGO stage III disease, as well as histological sub-types other than SCC, remained significant predictors of disease recurrence (table 3).

Table 3 Factors predictive of disease recurrence

	Recurrence					Multivariate analysis		
	Yes	No	OR (95% CI)	χ^2	*p* value	B	*p*-value	OR (95% CI)
Variable	**n (%)**	**n (%)**						
Age								
Mean ± SD	47.03 ± 11.85	47.36 ± 9.87		-0.241 t	0.810			
FIGO stage								
Stage I and II REF	31 (56.4)	24 (43.6)						
Stage II	55 (59.8)	37 (40.2)	1.151 (0.585 – 2.264)	0.166	0.684	1.217	0.058	3.378 (0.958 – 11.913)
Stage III	94 (71.8)	37 (28.2)	1.967 (1.022 – 3.786)	4.164	**0.042***	1.966	**0.004***	7.142 (1.895 – 26.921)
Histology								
Squamous cell carcinoma	166 (62.2)	101 (37.8)	0.157 (0.036 – 0.682)	7.847	**0.005***	1.921	**0.016***	6.830 (1.440 – 32.385)
Others	21 (91.3)	2 (8.7)						
HIV infection								
Yes	74 (66.1)	38 (33.9)	1.052 (0.644 – 1.720)	0.041	0.839			
No	124 (64.9)	67 (35.1)						
Previous therapy								
Radiotherapy alone REF	69 (71.7)	26 (28.3)						
Chemotherapy and Surgery	35 (62.5)	21 (37.5)	0.628 (0.311 – 1.270)	1.6887	0.194	0.876	0.196	2.402 (0.636 – 9.062)
Chemotherapy and Radiotherapy	82 (59.9)	55 (40.1)	0.562 (0.319 – 0.989)	4.031	**0.045***	-0.334	0.281	0.716 (0.390 – 1.315)
Surgery and Radiotherapy	14 (82.4)	3 (17.6)	1.759 (0.467 – 6.623)	0.294	0.588	1.152	0.203	3.163 (0.536 – 18.648)
Chemotherapy, Surgery and Radiotherapy	1 (100.0)	0 (0.0)		0.000	1.000			

χ^2: Chi square; *: *p* value <0.05; FIGO: International Federation of Gynecology and Obstetrics.
B: Coefficient of logistic regression; OR: Odds ratio; 95% CI: 95% Confidence Interval;
REF: Reference category

In a subgroup analysis to determine the factors predictive of recurrence among HIV-infected women, only the CD4 count was significant in predicting recurrence, p=0.024. Other factors such as the age of patients, the FIGO stage of disease, histological sub-type, previous therapy administered, viral load, and duration of HIV infection were not significant predictors of disease recurrence. Table 4 shows the details of factors evaluated for their ability to predict recurrence among HIV-infected women.

Table 4 Factors predictive of disease recurrence among HIV-infected patients

Variable	Recurrence: Yes n (%)	Recurrence: No n (%)	OR (95% CI)	χ^2	*p* value
Age					
Mean ± SD	40.93 ± 8.93	44.03 ± 9.79		-1.676[t]	0.097
FIGO stage					
Stage I [REF]	12 (66.7)	6 (33.3)			
Stage II	12 (48.0)	13 (52.0)	0.462 (0.132 – 1.620)	1.479	0.224
Stage III	44 (72.1)	17 (27.9)	1.294 (0.419 – 4.001)	0.201	0.654
Histology					
Squamous cell carcinoma	67 (64.4)	37 (35.6)	0.362 (0.041 – 3.217)	0.256[Y]	0.619
Others	5 (83.3)	1 (16.7)			
Previous therapy					
Radiotherapy alone [REF]	21 (65.6)	11 (34.4)			
Chemotherapy and Surgery	12 (80.0)	3 (20.0)	2.095 (0.486 – 9.026)	0.439 [Y]	0.508
Chemotherapy and Radiotherapy	37 (60.7)	24 (39.3)	0.808 (0.331 – 1.971)	0.221	0.638
Surgery and Radiotherapy	4 (100.0)	0 (0.0)			
CD4 count					
Median (Inter-quartile range)	357.50 (219.50 – 556.25)	529.00 (314.00 – 755.00)		787.000[U]	**0.025***
Viral load					
Median (Inter-quartile range)	768.00 (58.25 – 15423.50)	203.00 (92.00 – 4296.50)		30.500 [U]	0.677
Duration of HIV infection					
Median (Inter-quartile range)	78.00 (45.00 – 108.00)	60.00 (36.00 – 84.00)		449.500 [U]	0.203

χ^2: Chi square; U: Mann Whitney U test; *: *p* value <0.05; FIGO: International Federation of Gynecology and Obstetrics. REF: Reference category

Discussion

Our study found no difference in rate, time and pattern of recurrence between HIV-infected and uninfected population, however, we found the CD4 count to be a predictor of recurrent disease among HIV-infected women. We also found the stage and histological type to be predictors of recurrence in all patients with recurrent cervical cancer.

Our findings suggest that the treatment modification may not be necessary for the management of cervical cancer in HIV-infected patients. Our study confirms the utility of ^{18}F-FDG-PET/CT to detect recurrence in patients previously treated for carcinoma of the cervix presenting to the oncologist with symptoms suggestive of recurrence. ^{18}F-FDG PET/CT is a useful imaging modality for staging and re-staging of cervical carcinoma. The European Society for Medical Oncology (ESMO), in its clinical practice guidelines, recommended the inclusion of ^{18}F-FDG PET/CT for initial staging of locally advanced carcinoma of the cervix.[16] Periodic ^{18}F-FDG PET/CT is recommended during follow-up to detect disease recurrence.[16] In our cohort of 303 women with cervical carcinoma, 162 of whom had ^{18}F-

FDG PET/CT for pre-treatment staging of their disease, we demonstrate that ^{18}F-FDG-PET/CT was useful in both HIV-infected and uninfected patients. We confirmed recurrence in about two-thirds (67.00%) of these patients. This high rate of recurrence is related to the population we studied. We included patients with a clinical suspicion of recurrence in this study. Our study population included 247 patients (81.51% of study population) who had been treated with pelvic radiotherapy either alone or in combination surgery or chemotherapy. Radiotherapy is a vital treatment option for patients with bulky disease not curable by surgery alone.[17-19] Pelvic radiotherapy, however, is associated with gastrointestinal and genitourinary side effects which may be difficult to distinguish or even indistinguishable from the symptoms of local recurrence.[17,18] This, therefore, makes imaging essential in the evaluation of recurrence of carcinoma of the cervix uteri in women presenting with new symptoms following treatment.

Accurate evaluation of the presence of recurrence, the site, and the extent of such recurrence is necessary to plan salvage therapy. In our patient population, we found isolated local recurrence in 44 patients while 81 patients had local with distant metastatic recurrence. Of 198 patients with recurrence, 88 patients had a single site of recurrence while 110 patients had two or more sites of recurrence. Patients in whom recurrence is localized to the pelvis may benefit from pelvic exenteration surgery, an effective treatment which may be curative but with high morbidity and mortality.[20,21] Cetina et al. evaluated recurrent or persistent cervical cancer post-treatment, and like in our study, found the lymph nodes as the most frequent sites of persistent/recurrent disease.[22] The lymph nodes are sites of early disease recurrence, often seen within the first 24 months of treatment while visceral metastases often occur at a later time.[23]

We compared the rate, time and pattern of recurrence between HIV-infected and HIV-uninfected women and found no significant difference between both groups. The HIV-infected patients were however significantly younger at the time of diagnosis. The rate of recurrence was expectedly associated with the FIGO stage in both groups. While HIV-infected patients were treated for more advanced-stage disease, this did not translate into a higher rate of recurrence in them. Cervical cancer recurrence increases with the duration of surveillance.[23] This may suggest that the younger HIV-infected patients may live longer to experience recurrence compared with the older HIV-uninfected patients. This is not true in reality; while the life expectancy of the HIV-infected patients is increasing due to the availability

of antiretroviral therapy, it is yet to catch-up with that of HIV-uninfected patients particularly in the developing countries. HIV-associated malignancies and other non-communicable diseases remain significant contributors to HIV-associated mortalities for which ^{18}F-FDG PET/CT role in their evaluation is evolving.[24,25]

On analysis of factors predictive of recurrence, we found the FIGO stage of the disease and the histological subtype of the tumor to be significant predictors of recurrence. Patients with FIGO stage III as well as the presence of histological variant other than SCC were at a higher risk of recurrence. Others have also found that advanced disease has a higher rate of recurrence.[23,26] Presence of HIV infection itself is not a significant predictor of disease recurrence. Patients who have low CD4 count despite being on cARV are however more likely to recur compared with those with higher CD4 count. There is a scarcity of studies evaluating the impact of HIV infection on recurrence of cervical carcinoma. In our previous pilot study of 119 women with cervical carcinoma recurrence, including 40 HIV-infected patients, we reported a lower CD4 count in the study population.[27] This was a result of the inclusion of 15 patients who were not yet on cART at the time of evaluation for recurrence. In this current study, all patients included were on a stable cART treatment for their HIV infection. The differences in the study population may account for other differences between findings in this study and our previous pilot study. For example, we previously reported a shorter time to recurrence among HIV-infected patients compared with HIV-uninfected women. This current study with a larger patient population has now shown that in patients with HIV infection who are on regular anti-retroviral therapy, HIV plays no significant role in the time, rate or pattern of recurrence of carcinoma of the cervix uteri.

The strength of this study lies in its large study population including 112 HIV-infected women. We also comprehensively evaluated the impact of HIV infection on disease recurrence among women with cervical carcinoma. The study, however, suffers from some limitations including its retrospective design. A prospectively designed study may be necessary to confirm our findings. Patient with disease recurrence tends to have a shorter overall survival compared with those without.[23] We, however, did not present data on the implications of our findings on patients' survival. Also, in patients with multiple sites of recurrence, it was neither practical nor ethical to biopsy each lesion for histological confirmation. This is especially important due to the inclusion of HIV-infected patients since ^{18}F-FDG uptake is known to occur in HIV-associated reactive lymphadenopathy and in infective

foci.[27,28] This may be misinterpreted as sites metastases on ^{18}F-FDG PET/CT. We and others have previously described ^{18}F-FDG uptake in reactive lymphadenopathy due to HIV infection. The level of uptake, as well as the distribution of these nodes, is strongly linked to the duration of the HIV infection, the CD4 count and the viral load.[29-32] In these patients, we based our assessment of recurrence on a typical pattern of ^{18}F-FDG uptake, correlative MRI imaging or interval change on follow-up ^{18}F-FDG-PET/CT. Furthermore, all the HIV-infected patients included in this study were on regular use of cART and majority of them had undetectable HIV viremia at the time of imaging.

Conclusions

^{18}F-FDG-PET/CT is a useful modality for the diagnosis of recurrent disease in women with clinical symptoms suggestive of recurrent carcinoma of the cervix uteri. It can determine the site and the extent of recurrence which are prerequisites for salvage treatment planning. Advanced disease and histological variant other than squamous cell carcinoma are predictive of recurrent disease. HIV-infected women are diagnosed with a more advanced disease and at a younger age compared with HIV-uninfected patients. HIV infection does not impact on the time to recurrence, the rate of recurrence or pattern of recurrence of cervical carcinoma. A low CD4 count is predictive of recurrence among HIV-infected women with previously treated for cervical cancer.

Notes

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References

1. de Martel C, Plummer M, Vignat J, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141:664-670.

2. Shack L, Lau HY, Huang L, Doll C, Hao D. Trends in the incidence of human papillomavirus-related noncervical and cervical cancers in Alberta, Canada: a population-based study. CMAJ OPEN. 2014. DOI:10.9778/cmajo.20140005.
3. Razzaghi H, Saraiya M, Thompson TD, et al. Five-year relative survival for human papillomavirus-associated cancer sites. Cancer. 2018;124:203-211.
4. Orlando G, Bianchi S, Fasolo MM, et al. Cervical human papillomavirus genotypes in HIV-infected women: a cross-sectional analysis of the VALHIDATE study. J Prev Med Hyg. 2017;58:E259-E265.
5. Mudini W, Palefsky JM, Hale MJ, et al. Human papillomavirus genotypes in invasive cervical carcinoma in HIV seropositive and seronegative women in Zimbabwe. J Acquir Immune Defic Syndr. 2018;79:e1-e6.
6. Takekuma M, Kasamatsu Y, Kado N, et al. Adjuvant chemotherapy versus concurrent chemoradiotherapy for high-risk cervical cancer after radical hysterectomy and systematic lymphadenectomy. Int J Clin Oncol. 2016;21:741-747.
7. Matsuo K, Shimada M, Aoki Y, et al. Comparison of adjuvant therapy node-positive clinical stage IB-IIB cervical cancer: systemic chemotherapy versus pelvic irradiation. Int J Cancer. 2017;141:1042-1051.
8. Liu FY, Lai CH, Yang LY, et al. Utility of ^{18}F-FDG PET/CT in patients with advanced squamous cell carcinoma of the cervix receiving concurrent chemoradiotherapy: a parallel study of a prospective randomized trial. Eur J Nucl Med Mol Imaging. 2016;43:1812-1823.
9. Decazes P, Thureau S, Dubray B, Vera P. How to use PET/CT in the evaluation of response to radiothereapy. Q J Nucl Med Mol Imaging. 2018;62:152-64.
10. Adam AJ, Arkies H, Hinnen K, Stalpers LJ, van Waesberghe JH, Stoker J, et al. 18F-FDG-PET/CT guided external beam radiotherapy volumes in inoperable uterine cervical cancer. Q J Nucl Med Mol Imaging. 2018;62:420-8.
11. Liu FY, Su TP, Wang CC, et al. Roles of posttherapy ^{18}F-FDG PET/CT in patients with advanced squamous cell carcinoma of the uterine cervix receiving concurrent chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2018;45:1197-1204.
12. Bjurberg M, Brun E. Clinical impact of 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG)-positron emission tomography (PET) on treatment choice in recurrent cancer of the cervix uteri. Int J Gynecol Cancer. 2013;23:1642-1646.

13. Burger IA, Vargas HA, Donati OF, et al. The value of ^{18}F-FDG PET/CT in recurrent gynecologic malignancies prior to pelvic exenteration. Gynecol Oncol. 2013;129:586-592.
14. Brar H, May T, Tau N, et al. Detection of extra-regional tumour recurrence with ^{18}F-FDG-PET/CT in patients with recurrent gynecological malignancies being considered for radical salvage surgery. Clin Radiol. 2017;72:302-306.
15. Boellaard R, Delgado-Bolton R, Oyen WJG, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328-354.
16. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Supplement 4):iv72-iv83.
17. Shrivastava S, Mahantshetty U, Engineer R, et al. Cisplatin chemoradiotherapy vs. radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: A randomized clinical trial. JAMA Oncol. 2018;4:506-513.
18. Thakur P, Seam R, Gupta M, et al. Prospective randomized study comparing concomitant chemoradiotherapy using weekly cisplatin & paclitaxel versus weekly cisplatin in locally advanced carcinoma cervix. Ann Transl Med. 2016;4:48. Doi:10.3978/j.2305-5839.2015.11.19.
19. Kokka F, Bryant A, Brockbank E, et al. Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer. Cochrane Database Syst Rev. 2015;4:CD010260. Doi:10.1002/14651858.CD010260.pub2.
20. Rema P, Mathew AP, Suchetha S, et al. Salvage surgery for cervical cancer recurrences. Indian J Surg Oncol. 2017;8(2):146-9.
21. Graves S, Seagle BL, Strohl AE, et al. Survival after pelvic exenteration for cervical cancer: A national cancer database study. Int J Gynecol Cancer. 2017;27:390-395.
22. Cetina L, Serrano A, Cantú-de-León D, et al. F-18-FDG-PET/CT in the evaluation of patients with suspected recurrent or persistent locally advanced cervical carcinoma. Rev Invest Clin. 2011;63:227-235.
23. Sakurai H, Mitsuhashi N, Takahashi M, et al. Analysis of recurrence of squamous cell carcinoma of the uterine cervix after definitive radiation therapy alone: patterns of recurrence, latent period, and prognosis. Int J Radiat Oncol Biol Phys. 2001;50:1136-1144.

24. Lawal IO, Nyakale NE, Harry LM, et al. The role of F-18 FDG PET/CT in evaluating the impact of HIV infection on tumor burden and therapy outcome in patients with Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2017;44:2025-2033.
25. Lawal IO, Ankrah AO, Popoola GO, et al. Arterial inflammation in young patients with human immunodeficiency virus infection: A cross-sectional study using F-18 FDG PET/CT. J Nucl Cardiol. Epub ahead of print on February 07, 2018. Doi: 10.1007/s12350-018-1207-x.
26. Ryu SY, Kim MH, Choi SC, et al. Detection of early recurrence with ^{18}F-FDG PET in patients with cervical cancer. J Nucl Med. 2003;44:347-352.
27. Ololade K, Mokgoro NP, Lawal IO, et al. A comparison of 18F-FDG PET/CT findings in HIV positive compared to HIV negative patients with recurrent cervical cancer. Hell J Nucl Med. 2017;20 Suppl:71-79.
28. Glaudemans AW, Prandini N, Di Girolamo M, Argento G, Lauri C, Lazzeri E, et al. Hybrid imaging of muscxuloskeletal infections. Q J Nucl Med Mol Imaging. 2018;62:3-13.
29. Catalano O, Maccioni F, Lauri C, Auletta S, Dierckx R, Signore A. Hybrid imaging in Crohn's disease: from SPECT/CT to PET/MR and the new image interpretation criteria. Q J Nucl Med Mol Imaging. 2018;62:40-55.
30. Iyengar S, Chin B, Margolick JB, et al. Anatomical loci of HIV-associated immune activation and association with viremia. Lancet. 2003;362:945-950.
31. Lucignani G, Orunesu E, Cesari M, et al. FDG-PET imaging in HIV-infected subjects: relation with therapy and immunovirological variables. Eur J Nucl Med Mol Imaging. 2009;36:640-647.
32. Sathekge M, Maes A, Kgomo M, et al. Fluorodeoxyglucose uptake by lymph nodes of HIV patients is inversely related to CD4 cell count. Nucl Med Commun. 2010;31:137-140.