Original Article

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HIV status does not have an impact on positron emission tomography-computed tomography (PET-CT) findings or radiotherapy treatment recommendations in patients with locally advanced cervical cancer

Hannah Simonds,[1,2] Matthys Hendrik Botha,[2,3] Annare Ellmann,[2,4] James Warwick,[2,4] Alex Doruyter,[5] Alfred I Neugut,[6,7] Haynes Van Der Merwe,[2,3] Judith S Jacobson[6]

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For numbered affiliations see end of article.

Correspondence to
Dr Hannah Simonds, Radiation Oncology, Stellenbosch University, Stellenbosch, Western Cape 7505, South Africa; hsimonds@sun.ac.za

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Highlights

- More than 80% of patients had pelvic nodal involvement, and more than 40% had uptake in common iliac and/or para-aortic nodes.
- Overall, 84.5% were upstaged after PET-CT scan and it was not associated with HIV status.
- HIV status did not have an impact on PET-CT findings or oncology treatment decisions.

ABSTRACT

Introduction Positron emission tomography-computed tomography (PET-CT) imaging is commonly used to identify nodal involvement in locally advanced cervical carcinoma, but its appropriateness for that purpose among HIV-positive patients has rarely been studied. We analyzed PET-CT findings and subsequent treatment prescribed in patients with locally advanced cervical carcinoma in Cape Town, South Africa.

Methods We identified a cohort of consecutive cervical carcinoma patients International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IIIB at our cancer center who underwent a planning 18-fluorodeoxyglucose (^{18}FDG) PET-CT scan from January 2015 through December 2018. Demographics, PET-CT findings, and subsequent treatment prescribed were recorded. Patients were selected for PET-CT only if they had no signs of distant disease on staging chest X-ray or abdominal ultrasound; were deemed suitable for radical chemoradiation by the multidisciplinary team; and had normal renal function. HIV-positive patients ideally had to have been established on continuous antiviral therapy for more than 3 months and to have a CD4 cell count above 150 cells/µL. Small cell and neuroendocrine carcinoma cases were excluded from the study. Differences in demographic and clinical measures between HIV-positive and HIV-negative patients were evaluated by means of t-tests for continuous variables and χ^2 tests for categorical variables.

Results Over a 4 year period, 278 patients—192 HIV-negative (69.1%) and 86 HIV-positive (30.9%)—met the inclusion criteria. HIV-positive patients had a median CD4 count of 475 cells/µL (IQR 307–612 cells/µL). More than 80% of patients had pelvic nodal involvement, and more than 40% had uptake in common iliac and/or para-aortic nodes. Nodal involvement was not associated with HIV status. Fifty-four patients (19.4%) had at least one site of distant metastatic disease. Overall, 235 patients (84.5%) were upstaged following PET-CT staging scan. Upstaging was not associated with HIV status (HIV-negative 83.9% vs HIV-positive 87.2%; p=0.47). Ten patients who did not return for radiotherapy were excluded from the analysis. Following their PET-CT scan, treatment intent changed for 124 patients (46.3%): 53.6% of HIV-positive patients and 42.9% of HIV-negative patients (p=0.11).

Conclusion We found no differences between HIV-positive or HIV-negative patients in nodal involvement or occult metastases, and PET-CT imaging did not lead to, or justify, treatment differences between the two groups. Future studies will evaluate survival and correlation of upstaging with outcome.

INTRODUCTION

Cervical carcinoma is one of the most frequently diagnosed malignancies in women throughout sub-Saharan Africa. In South Africa, its age-standardized incidence rate is >40 per 100 000 women; in 2018, more than 12 000 women were diagnosed with invasive cervical cancer.[1 2] In addition, cervical carcinoma is associated with HIV, and in South Africa HIV prevalence is 26.3% among women aged 15–49 years.[3] Various imaging modalities (eg, chest X-ray, abdominal ultrasound) are used to determine the extent of disease in cancer patients. In higher-income countries, newer technologies, such as magnetic resonance imaging and positron emission tomography-computed tomography (PET-CT) scanning, are often used for this purpose. The latter has proved to be highly effective in identifying poor prognostic features of cervical carcinoma, such as positive pelvic lymph nodes, and in accurately defining targeted treatment by radiation.[4 5] The addition of PET-CT to the staging algorithm has changed treatment intent and enhanced the accuracy of radiotherapy planning.

PET-CT is now increasingly available in middle-income countries, including South Africa. A small study found that PET-CT led to conversion to palliative regimens or the addition of extended field irradiation for involved para-aortic nodes in more than 35% of patients.[6]

The 2018 update to the International Federation of Gynecology and Obstetrics (FIGO) staging of cervical cancer has highlighted the need for accurate imaging of nodal involvement.[7] Patients with evidence of nodal disease must be upstaged to IIIC1r for pelvic or IIIC2r for para-aortic nodal disease. HIV-positive patients who undergo PET-CT imaging may have fluorine-18 fluorodeoxyglucose (^{18}FDG)-avid benign pathology, such as reactive lymphadenopathy or co-existent tuberculosis. This limitation in specificity may lead to some uncertainty in interpretation of abnormal findings and thus raises questions about the suitability of ^{18}FDG PET-CT staging for HIV-infected patients with cervical carcinoma. We therefore conducted a study of the contribution of PET-CT to staging and stratification for treatment in HIV-negative and HIV-positive women in a large cohort of patients with cervical cancer. Our hypothesis was that nodal involvement, as determined on PET-CT, would be more prevalent in HIV-positive than in HIV-negative patients due to a greater proportion of false positives in the former group; and that PET-CT findings among HIV-positive patients would lead to inappropriate changes in radiotherapy fields or treatment intent.

METHODS

This retrospective/prospective cohort study was undertaken at Tygerberg Academic Hospital, in Cape Town, South Africa. Study participants were consecutive HIV-positive and HIV-negative patients diagnosed with locally advanced cervical carcinoma (FIGO stage IIB-IIIB) who underwent a staging PET-CT scan from January 2015 through December 2018. Ethical approval was obtained from the University of Stellenbosch Human Research Ethics Committee (S17/01/016). For the retrospective cohort (January 2015 through February 2017) patients were identified through the Nuclear Medicine booking system. For the prospective cohort (March 2017 through December 2018), patients were consented at their new-patient visit to Radiation Oncology and referred to Nuclear Medicine as per routine clinical practice.

For the 12 gynecology oncology patients scheduled per week for radiotherapy, only 3–5 PET-CT planning scan appointments were available. Patients were selected for PET-CT only if they had advanced stage IIB, IIIA or IIIB disease with no signs of distant disease on staging chest X-ray or abdominal ultrasound; were deemed suitable for radical chemoradiation by the multi-disciplinary team; and had normal renal function. HIV-positive patients ideally had to have been established on continuous antiviral therapy for more than 3 months and to have a CD4 cell count above 150 cell/µL. Small cell and neuroendocrine carcinoma cases were excluded from the study.

Patients fasted for at least 4 hours before administration of the radiopharmaceutical. The PET-CT scans were performed using a Phillips Gemini Big Bore time-of-flight 16-slice PET/CT camera (Philips Medical Systems, Best, The Netherlands) with a flat couch top suitable for radiotherapy planning. The systems were calibrated according to the European Association of Nuclear Medicine Research Ltd standards. Patients were imaged from base of skull to mid-thigh in the supine position with a low-dose CT and PET scan. A second, contrast-enhanced planning CT scan from the pelvic area up to T10 was exported to the radiation oncology planning system for volume delineation. The PET and low-dose CT images were evaluated and reported jointly by an experienced team that included a nuclear medicine physician and a radiologist. Lymph nodes were interpreted as inflammatory when located in nodal basins not draining the primary tumor (directly or indirectly), and when the nodes appeared symmetrical in distribution and were sub-centimeter with only mild uptake. Lymph nodes were interpreted as malignant when enlarged and demonstrating moderate or intense uptake well above the degree of uptake in presumed inflammatory nodes. Avidity in nodes similar to the primary lesion was reported as malignant. Complex cases were discussed with the radiation oncologist when clarification was needed. Equivocal or ill-defined lesions on the PET-CT were highlighted as suspicious, and further investigations were left to the clinician's discretion (capacity to biopsy suspicious lesions was limited because of long surgical and diagnostic radiology waiting lists).

Table 1 Patient demographics and clinical characteristics by HIV status

	HIV-positive	HIV-negative	Whole cohort	P value
	86 (30.9%)	192 (69.1%)	278	
Age (median)	41 years (26–67 years) SD 8.75	50 years (26–79 years) SD 11.77	47 years (26–79 years)	**0.00***
Histology†				0.65
Squamous cell	81 (96.4%)	178 (92.7%)	259 (93.8%)	
Other	3 (3.6%)	14 (6.3%)	17 (6.2%)	
FIGO stage				0.46
IIB	15 (17.4%)	29 (15.1%)	44 (15.8%)	
IIIA	0	3 (1.6%)	3 (1.1%)	
IIIB	71 (82.6%)	160 (83.3%)	231 (83.1%)	

*P<0.05 considered significant.
†Complete data for 84 out of 86 HIV-positive patients.
FIGO, International Federation of Gynecology and Obstetrics.

Original data, including demographic and clinical characteristics, were extracted from the patients' folders. Reports and images were retrieved from the Nuclear Medicine database (Hermes Medical Solutions, Stockholm, Sweden). Radiotherapy data were retrieved from the MOSAIQ patient management system. PET-CT reports were coded for involved pelvic nodes, common iliac nodes, para-aortic nodes, distant nodal disease, and metastases to lung, liver, bone, and other sites. Equivocal or unrelated clinical findings were noted. Following introduction of the revised FIGO 2018 staging system, patients were allocated to stage IIB, IIIA, IIIB, IIIC1r, IIIC2r, or IVB based on clinical examination and the PET-CT findings.

All locally advanced cervical carcinomas deemed fit for treatment received 46–50.4 Gy in 23–28 fractions external beam radiotherapy (EBRT) to primary disease, parametria, upper vagina, and pelvic node groups up to and including the common iliac nodes. Forty-five Gray (45 Gy) in 25 fractions to a para-aortic node field extending to the renal hilum was prescribed for involved para-aortic node or upper common iliac nodes at the clinician's discretion. Prophylactic para-aortic node radiotherapy was not performed for positive nodes if all were below the common iliac vessels. EBRT was delivered concurrently with cisplatin 40 mg/m^2 up to five cycles, if renal function allowed, and was followed by high dose-rate brachytherapy 22–25 Gy in 4–5 fractions. During the period of this cohort, intensity-modulated radiotherapy to boost involved nodes was not in use; EBRT was delivered using 3D conformal techniques. Patients unsuited for radical radiotherapy were prescribed hypofractionated EBRT 40.05 Gy in 15 fractions with or without brachytherapy. Palliative patients received 10 Gy in a single fraction, repeated monthly to three fractions in selected cases, and/or palliative chemotherapy. Additional factors considered before starting treatment included deterioration in performance status and new-onset renal dysfunction.

Differences in demographic and clinical measures between HIV-positive and HIV-negative patients were evaluated by means of t-tests for continuous variables and χ^2 tests for categorical variables. All tests were two-sided, and values of $p \leq 0.05$ were considered significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistics software program (version 25.0; SPSS, Inc, Chicago, IL).

RESULTS

In the 4 year study period, 1093 patients with cervical carcinoma, including all radical, adjuvant, and palliative patients registered on MOSAIQ, were referred for radiation therapy. Of these patients, 278 met the inclusion criteria and were included in the final analysis (Table 1). The study included 192 HIV-negative patients (69.1%) and 86 HIV-positive patients (30.9%) (Table 1). The median age was 47 years (range 26–79). The HIV-positive patients were significantly younger than the HIV-negative patients ($p<0.001$) with a median CD4 count of 475 cells/µL (IQR 307–612 cells/µL). Viral load was available for 79 of 86 patients with a median of 0 copies/mL (IQR 0–100 copies/mL); 91.1% (n=72) had <1000 copies/mL as per WHO guidelines for viral suppression.[8] Most patients had squamous cell carcinomas and were clinically staged FIGO IIIB before their PET-CT imaging.

PET-CT findings

More than 80% of patients had pelvic nodal involvement, and more than 40% had uptake in common iliac and/or para-aortic nodes (Table 2). Nodal involvement was not associated with HIV status. Fifty-four patients had at least one site of distant metastatic disease, including lung (n=34), nodes (n=30), bone (n=7), liver (n=3), and sacral nerve (n=3) (Figure 1). Overall, 235 patients (84.5%) were upstaged to FIGO (2018) IIIC1r (37.4%), IIIC2r (27.7%) or IVB (19.4%) after PET-CT staging scan (Table 3). Upstaging was not associated with HIV status (HIV-negative 83.9% vs HIV-positive 87.2%; p=0.47). More than two-thirds of the patients also had benign or unrelated pathology (n=191; 68.7%), mainly post-inflammatory lung nodules. Other findings included active respiratory infections, bone marrow hyperplasia secondary to anemia, and undiagnosed breast cancer. These findings were unrelated to HIV status (HIV-negative 67% vs HIV-positive 73.3%; p=0.27). HIV-related lymphadenopathy was identified in 20 patients.

Treatment intent after PET-CT

Among the 268 patients who returned for treatment after the PET-CT planning scan, the intent of treatment changed from radical chemoradiation to hypofractionated EBRT in 27 (10.1%) patients, and to palliative EBRT in 32 (11.9%) (Table 4). Radical radiation was altered to include extended field para-aortic node EBRT in 65 cases

Table 2 PET-CT findings by HIV status

	HIV-positive N=86	HIV-negative N=192	All N=278	P value
Positive nodes (any)	75 (87.2%)	159 (82.8%)	234 (84.2%)	0.35
Pelvic	73 (84.9%)	150 (78.1%)	223 (80.2%)	
Common iliac	45 (52.3%)	85 (44.3%)	130 (46.8%)	
Para-aortic	38 (44.2%)	74 (38.5%)	112 (40.3%)	
Distant	12 (14%)	18 (9.4%)	30 (10.8%)	
Lung	12 (14%)	22 (11.5%)	34 (12.2%)	0.56
Liver	0	3 (1.6%)	3 (1.1%)	0.24
Bone	1 (1.2%)	6 (3.1%)	7 (2.5%)	0.33
Other	1 (1.2%)	2 (1.0%)	3 (1.1%)	0.93

CT, computed tomography; PET, positron emission tomography.

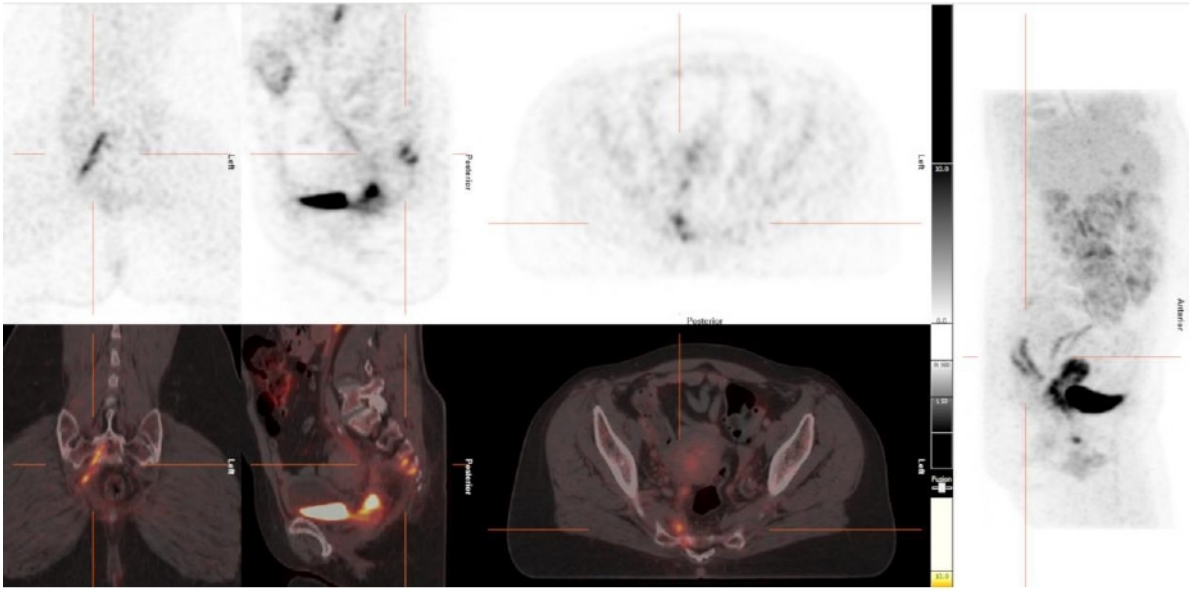

Figure 1 PET-CT images of a 63-year-old woman, initial stage IIIB squamous cell carcinoma of the cervix, HIV negative. Imaging findings included nodal uptake, lung metastases, and infiltration of the right sacral nerve. The patient received palliative pelvic radiotherapy and was started on palliative chemotherapy. CT, computed tomography; PET, positron emission tomography.

(24.3%). Following the PET-CT, overall treatment intent changed in 124 patients (46.3%), 53.6% in HIV-positive patients and 42.9% in the HIV-negative patients (p=0.11) (online supplementary figure 1). Of the 104 patients upstaged to IIIC1r, 95 (91.3%) proceeded to standard fractionation radiotherapy. Of the 77 patients upstaged to IIIC2r, 67 (87.0%) underwent EBRT. Para-aortic nodal extended-field radiotherapy was prescribed to 31.1% (n=65) of cases, including 75% (n=48) of the IIIC2r patients and 11.8% (n=11) of the IIIC1r patients, all of whom had common iliac nodal uptake on PET-CT. None of the patients staged IIB, IIIA or IIIB on PET-CT received extended field EBRT. Of the 54 patients upstaged to IVB disease, 13 were still prescribed radical EBRT (including six who received extended-field EBRT) after multi-disciplinary review of the images by the oncologist and nuclear medicine team.

DISCUSSION

Most of the 278 patients in our study had nodal disease, and nearly half had a change in treatment after PET-CT. Integrating PET-CT into the staging algorithm upstaged 85% of patients overall, including 65.1% upstaged to the current FIGO 2018 groups of IIIC1r or IIIC2r following findings of pelvic and/or para-aortic nodal involvement. The remaining 20% were diagnosed with distant metastatic disease, which in some cases was isolated (oligometastatic). The HIV-positive patients included in this cohort were immune-competent, with a high median CD4 count, and more than 90% were virally suppressed. Baseline clinical stage (before PET-CT) was not associated with HIV status. HIV status was not associated with differing PET-CT findings for either nodal disease or distant metastases.

Table 3 Final FIGO stage (2018) by HIV status

	HIV-positive N=86	HIV-negative N=192	All N=278	P value
IIB	2 (2.3%)	7 (3.6%)	9 (3.2%)	0.34
IIIA	0	2 (1.0%)	2 (0.7%)	
IIIB	10 (11.6%)	22 (11.5%)	32 (11.5%)	
IIIC1r	28 (32.6%)	76 (39.6%)	104 (37.4%)	
IIIC2r	25 (29.1%)	52 (27.1%)	77 (27.7%)	
IVB	21 (24.4%)	33 (17.2%)	54 (19.4%)	

FIGO, International Federation of Gynecology and Obstetrics.

In a recent study in South Africa, Id et al found that 36.4% of 126 patients with cervical carcinoma (including 74 with HIV and 88 with stage IIb or IIIB disease) had positive nodal involvement on PET-CT.[9] Stage was not associated with HIV status. In our cohort, more patients had positive nodes, most probably due to more advanced disease. Because the HIV-positive patients included in our cohort were immune-competent, our findings may not be generalizable to patients with a high HIV viral load.[10] Other recent studies have found no difference in stage distribution between HIV-negative and HIV-positive patients with malignancy. Mhlanga et al compared HIV-positive lymphoma patients to a control group without malignancy and found that the best way of distinguishing them was through asymmetry and quantitative measures of intensity of ^{18}FDG uptake (higher scores in malignant nodes)—methods similar to those used in our institution.[11] In a South African retrospective cohort of patients with Hodgkin's lymphoma, Lawal et al found no significant difference between those with and those without HIV in PET-CT findings and metabolic indicators.[12]

The accuracy of PET-CT in detecting nodal metastases in patients with locally advanced disease is difficult to determine with absolute certainty; in most clinical settings, such nodes are unlikely to be sampled to confirm involvement. The prevalence of pelvic and/or para-aortic node positivity on PET-CT was higher among our patients (both HIV-positive and HIV-negative) than has been reported in international data on HIV-negative populations. In the

Table 4 Treatment intent by HIV status

	HIV-positive N=84	HIV-negative N=184	All N=268*	P value
Standard fractionation EBRT	39 (46.4%)	105 (57.1%)	144 (53.7%)	0.11
Extended field EBRT	24 (28.6%)	41 (22.3%)	65 (24.3%)	
Hypofractionated EBRT	12 (14.3%)	15 (8.2%)	27 (10.1%)	
Palliative EBRT	9 (10.7%)	23 (12.5%)	32 (11.9%)	

*Exclusion of 10 patients who did not return for treatment.
EBRT, external beam radiotherapy.

recent EMBRACE trial, of more than 1000 cervical cancer patients, 52% had positive nodes on imaging.[13] That study included patients with earlier-stage disease and thus lower risk of nodal metastases. Similarly, a large PET-CT study undertaken by Kidd et al found positive nodal uptake in 58% of squamous cell carcinomas, a smaller proportion than in our cohort.[14] In a second study by Kidd et al, only 32% of patients with stage IIIB disease had positive nodes.[15] Our study population was a selected high-risk group in that most had stage III disease, most likely due to more delayed access to healthcare than is common in more developed countries.

The main purpose of integrating PET-CT into the staging algorithm in our cohort was to identify patients who needed a change in the planned radiation fields or in treatment intent. Nearly half of our patients were allocated to palliative treatment, hypofractionated radiotherapy, or extended field radiotherapy. In our previous cohort study, PET-CT findings imparted a 40% change in treatment intent.[6] In the future, in our institution, affected nodal areas may receive intensity-modulated radiotherapy boosts; if so, the value and importance of including PET-CT in our staging algorithms will increase. A randomized Canadian trial comparing imaging with CT to that with PET-CT was performed to determine whether PET-CT would find more distant disease than CT, and whether or not patients would receive more extensive EBRT due to increased detection of para-aortic nodes.[16] The two groups proved not to differ in terms of distant disease, but only eight out of 171 patients had such disease. More patients in the PET-CT group than in the CT group received extended field EBRT; some of the patients did not have positive para-aortic nodes and were treated off protocol.

The limitations of our study include the factors that influenced patient selection in the first 2 years of the cohort. In those years, we formed the cohort as a selected population of advanced disease patients who were deemed suitable for radical treatment and referred from the multi-disciplinary clinic. That sample is not representative of the entire cohort of cervical cancer patients at our institution. Due to limited surgical and diagnostic radiology resources, we were unable to biopsy equivocal pelvic or para-aortic nodes. The differential diagnoses of nodal uptake in this population would include HIV-reactive adenopathy, and infectious processes, including local tumor infection and tuberculosis. Diagnosis relies on pattern recognition; our nuclear medicine physicians have extensive experience in reporting PET-CT findings in patients with tuberculosis, an endemic disease in the hospital's catchment area. A number of patients had evidence of post-inflammatory lung lesions that may have represented metastatic disease in a small number of patients. Although the differences in age of our two study groups was significant, the evidence for an age effect (in the reported age ranges of our samples) on the prevalence of either metastases or reactive lymphadenopathy is lacking, and we did not consider it to be a limitation.

The strengths of our study include its sample size; our cohort of 278 patients, of whom 84 were HIV-positive, is one of the largest in which HIV status and PET-CT findings have been described in any malignancy. Furthermore, consecutive patients were included; all patients referred in the study time period were evaluated. A multi-disciplinary team consisting of gynecological oncologists, a clinical oncologist, radiologists, and nuclear medicine physicians contributed to the treatment decisions and clinical care in our setting. Imaging findings were discussed when needed and a collective decision was made on interpreting equivocal findings. A single oncology team was responsible for all final treatment decisions providing consistent management for this patient cohort.

CONCLUSION

We found no differences between HIV-positive and HIV-negative patients in nodal involvement or occult metastases, and PET-CT did not lead to, or justify, treatment differences between the groups. We will continue to follow this cohort for survival outcomes, and correlation of upstaging with outcome.

Author affiliations
[1]Radiation Oncology, Stellenbosch University, Stellenbosch, South Africa
[2]Tygerberg Hospital, Cape Town, South Africa
[3]Gynaecological Oncology, Stellenbosch University, Stellenbosch, South Africa
[4]Nuclear Medicine, Stellenbosch University, Stellenbosch, South Africa
[5]Node for Infection Imaging, Central Analytical Facilities, Stellenbosch University, Stellenbosch, South Africa
[6]Epidemiology, Columbia University Mailman School of Public Health, New York, New York, USA
[7]Herbert Irving Comprehensive Cancer Centre, NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, New York, USA

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