Use of a Sentinel Lymph Node Biopsy Algorithm in a South African Population of Patients With Cervical Cancer and High Prevalence of Human Immunodeficiency Virus Infection

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Objectives: Cervical cancer is common in resource-poor settings with high prevalence of tuberculosis, pelvic inflammatory disease, and human immunodeficiency virus (HIV) infection. There are no data regarding the sentinel lymph node (SLN) algorithm in these high-risk cancer populations. Our objectives were to establish the sensitivity, specificity, positive predictive value, and negative predictive value of the SLN algorithm in cervical cancer and to compare the detection rate of indocyanine green (ICG) versus blue dye versus technetium Tc 99m nanocolloid (^{99m}Tc).
Methods: This prospective study was conducted at the University of Pretoria. ^{99m}Tc-nanocolloid tracer, ICG dye, and methylene blue (MB) were used to detect SLNs. Pathological ultrastaging was performed on hematoxylin-eosin–negative nodes.
Results: Results of 72 women were analyzed. The mean age was 47.2 years, 5.5% had a history of tuberculosis, 18.1% had pelvic inflammatory disease, and 65.3% were HIV positive. The SLN detection rate was 65.3%. Detection rate of MB was 56.9%; ^{99m}Tc, 69.4%; ICG, 87.5%; and the combination of MB and ^{99m}Tc, 91.7%. Pelvic nodal metastases occurred in 26.4%. The sensitivity, specificity, negative predictive value, and positive predictive value of SLN biopsy were 85.7%, 100%, 100%, and 98.33%, respectively. The false-negative rate was 14.3%, and it was 0% if the algorithm was applied.
Conclusions: The SLN algorithm is a feasible option for use in cervical cancer women with a high prevalence of HIV infection. The detection rate is generally lower, but in select subgroups of women, it was comparable to that reported elsewhere. This is the first report of the use of SLN biopsy in a substantial group of HIV-infected women.

Key Words: Cervical cancer, HIV infection, Sentinel lymph node biopsy algorithm, SLN

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Cervical cancer is the second most common cancer in South African women, with an estimated incidence of 31.5 per 100,000 women.[1] Although the International Federation of Gynecology and Obstetrics (FIGO) classification system of cervical cancer does not include pelvic lymph node status, it is well recognized and accepted that lymph node metastasis is an important risk factor for recurrence and death in patients with cervical cancer.[2,3] Oncologic information of the lymph nodes is important for the planning of optimal treatment and adjuvant treatment strategies in patients with early-stage disease. For the purpose of this study, early-stage cervical cancer was defined as disease diagnosed and clinically staged as FIGO stage I to IIA.

Surgical treatment of early-stage cervical cancer consists of radical hysterectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy. In approximately 80% of women, lymphadenectomy will be unnecessary. A sentinel lymph node biopsy (SLNB) algorithm has been proposed as a reasonable alternative to full lymphadenectomy in these patients.

The reported pooled detection rate of sentinel lymph nodes (SLNs) in cervical cancer is 89%, and the reported pooled sensitivity rate is 90%.[4] Sentinel lymph node biopsy procedures appear to be more accurate with smaller tumors and in patients with bilaterally detected SLNs.[5–8]

Cormier et al[9] proposed an SLN algorithm to overcome the high false-negative rate (FNR) of SLNBs. This algorithm includes a side-specific evaluation and recommends lymphadenectomy on the side(s) where no SLNs are detected, as well as the removal of clinically enlarged lymph nodes. This strategy resulted in a sensitivity of 100% and negative predictive value (NPV) of 100%. A review of 46 studies with 4130 patients concluded that in patients with tumors smaller than 40 mm and no preoperative or intraoperative suspicious nodes with bilateral negative SLNs after ultrastaging the FNR was 0.08%.[10]

Prospective data with regard to SLN procedures in women with cervical cancer are sparse. Niikura et al[11] reported on the outcomes of 35 women with FIGO stage IA1 to IIA1 disease, of whom pelvic lymphadenectomy was omitted in 23 women who had negative bilateral SLNs. There were no recurrences among the women who underwent SLNB; furthermore, the incidence of lymphedema was 8.7% in those who underwent SLNB compared with 42% in those who underwent systematic pelvic lymphadenectomy.

There are no reported data on the ability of SLNB to predict pelvic lymph node status in a population of women with early-stage cervical cancer and high prevalence of human immunodeficiency virus (HIV) infection. South Africa has the highest HIV infection rate in the world, as well as high rates of related conditions such as pelvic inflammatory disease (PID), tuberculosis (TB), and human papillomavirus infection. In 2012, an estimated 12.2% of the South African population was infected with HIV (14.4% of women and 9.9% of men).[12] In 2015, more than 1 million South Africans were newly enrolled for HIV care, of whom 11.7%, or nearly 128,000 people, were designated as TB cases.[13] The prevalence of high-risk human papillomavirus among the general female South African population is as high as 54.3%.[14] How these infections affect the lymphatic channels and the lymph nodes in this population is unknown; however, it is evident that South African women face unique health care challenges, and data from well-developed countries need to be verified before they can be applied in the clinical practices of this region.

This study aimed to investigate the sensitivity, specificity, NPV, and positive predictive value (PPV) of SLNB in South African women. The study also compares the use of SLNB in HIV-positive versus HIV-negative patients and investigates factors influencing detection rates.

Materials and Methods

As part of this prospective study, which was conducted at the academic hospitals of the Gynaecological Oncology Unit of the Department of Obstetrics and Gynaecology, University of Pretoria, from April 2015 to February 2017, women diagnosed with early-stage cervical cancer (FIGO stage IA to IIA) and scheduled for primary surgical treatment were recruited for enrollment. Their surgical treatment consisted of laparoscopic or open radical hysterectomy and pelvic lymphadenectomy. In our setting, patients with locally advanced stage disease (IB2 to IIA2) are offered radical surgery, as a significant number of these patients will benefit from surgery alone, and many patients from rural areas experience difficulty in completing radiation therapy.

Sentinel lymph node detection was achieved using technetium Tc 99m nanocolloid tracer (^{99m}Tc), indocyanine green (ICG) dye, and/or methylene blue (MB) dye. ^{99m}Tc was injected into the cervix of some of the women scheduled for surgery 1 day before the procedure, and MB (2 mL at the 3- and 9-o'clock positions, respectively) was injected preoperatively after the induction of general anesthesia. In some women, ICG was also used. After the identification and removal of all SLNs, total pelvic lymph node dissection was performed in addition to the appropriate type of hysterectomy with or without bilateral salpingo-oophorectomy. Para-aortic lymphadenectomy was performed at the discretion of the treating gynecologic oncologist.

The SLN and the remainder of the pelvic lymph nodes were sent separately for histological examination. Each SLN was bisected into two halves. One half was managed as a frozen section, whereas the other half was processed and stained using hematoxylin-eosin, as per normal routine. If the SLN was found to be negative for metastases, the node then underwent ultrastaging with further sectioning and immunohistochemical staining.

Calculations

The detection rate was calculated as the number of patients with at least 1 detected pelvic SLN divided by the total number of patients who underwent SLN mapping. Diagnostic performance was calculated for hemipelvises with at least 1 SLN harvested. Exact 95% confidence intervals (CIs) for the proportions were calculated, and subgroup analyses were performed using a 2-sided χ^2 test or Fisher exact test ($\alpha = 0.05$).

Ethical Considerations

The Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria, granted ethics approval for the study (434/2014).

Results

Of 78 women enrolled on the study, 72 were evaluable for analysis. Six patients were excluded because of death after recruitment but before surgery (n = 1), missing hospital files (n = 1), or upstaged disease (n = 4). Of the patients who were upstaged, 1 patient was diagnosed with lung metastases on fluorodeoxyglucose positron emission tomography/computed tomography scanning, 2 patients were upstaged to FIGO stage IIB, and 1 patient to FIGO stage IIIB disease during examination under anesthesia immediately prior to undergoing surgery. The mean age of the patients was 47.2 years (range, 32–77 years). Other patient demographic data as well as the histological data are listed in Table 1.

Thirteen women (18.1%) had undergone previous surgery. Four patients (5.5%) had a history of TB, of whom 3 (4.2%) had pulmonary TB and 1 (1.4%) had abdominal TB. Thirteen patients (18.1%) were previously diagnosed with PID. Four women (5.6%) had FIGO stage IA2, 48 women (66.7%) had FIGO stage IB1, 13 women (15.3%) had FIGO stage IB2, 4 women (5.6%) had FIGO stage IIA1, and 5 women (6.9%) had FIGO stage IIA2 cervical cancer.

Seventy-one patients (98.6%) underwent radical hysterectomy and pelvic lymphadenectomy procedures. Laparoscopic radical hysterectomy with pelvic lymphadenectomy was completed in 21 patients (29.2%). In another 9 patients (12.5%), the laparoscopic approach was started but converted to open radical hysterectomy, and 41 patients (56.9%) had planned open hysterectomy from the start.

HIV Status

Forty-seven women (65.3%) were HIV positive. Forty-three (91.5%) of these women were undergoing antiretroviral therapy, 28 of them (80.8%) for more than 6 months. The mean CD4 count in the HIV-positive women was 434.60 cells/μL (range, 43–950 cells/μL; SD, 222.13 cells/μL; SEM, 33.11 cells/μL; 95% CI, 367.86–501.34 cells/μL), and the mean viral load was 24,916.29 copies/μL (range, undetectable to 666,811 copies/μL; SD, 119,540.02 copies/μL; SEM, 21,470.02 copies/μL; 95% CI, 18,931.35–68,763.93 copies/μL). Human immunodeficiency virus–infected women were significantly younger and had lower body mass indices (BMIs). Furthermore, significantly fewer women in this group had tumors of 2 cm or greater compared with those who were HIV negative. There were no statistically significant differences in stage distribution between the 2 HIV groups.

Table 1. Demographic and histological data (n = 72)

Demographic Data

	Mean	SD	Range
Age, y	47.21	9.09	32–77
Parity	3.10	1.63	0–8
Gravidity	3.28	1.69	0–8
BMI, kg/m^2	27.51	5.41	18.37–43.03

Histological Data

Tumor Type	No. Patients (%)
Squamous cell carcinoma	62 (86.1)
Adenocarcinoma	6 (8.3)
Adenosquamous carcinoma	2 (2.8)
Clear cell carcinoma	1 (1.4)
Carcinosarcoma	1 (1.4)

SLN Detection

Sentinel lymph nodes were detected in 47 patients, yielding a detection rate of 65.3%. Bilateral SLN detection was achieved in 22 patients, yielding a bilateral detection rate of 30.5%. The histologically confirmed SLN count was 135 nodes, of which 62 were detected on the left side and 73 on the right side (mean count, 3.0 nodes; range, 1–9 nodes; SD, 1.92 nodes; SEM, 0.29 nodes; 95% CI, 2.42–3.77 nodes).

In 66 hemipelvises, there were 6 true-positive, 59 true-negative, and 1 false-negative SLNs. Per definition, false-positive SLNs do not exist.

The sensitivity, specificity, NPV, and PPV of SLNB in this patient population were 85.7%, 100%, 100%, and 98.33%, respectively. The FNR was 14.3%.

For the HIV-negative group, the sensitivity, specificity, NPV, and PPV of SLNB were 100%, 100%, 100%, and 100%, respectively, and the FNR was 0%. For the HIV-positive group, the respective values were 83.3%, 100%, 100%, and 97.62%, with an FNR of 8.3%.

Methods of SLN Detection

Methylene blue was administered to all 72 patients. Thirty-six patients (50%) also received intracervically administered ^{99m}Tc with lymphoscintigram examinations. Eight patients (11.1%) received ICG as well. Thirty-six patients (50%) received MB and ^{99m}Tc; 3 patients (4.2%) received MB and ICG, and 5 patients (6.9%) received MB, ^{99m}Tc, and ICG.

Sentinel lymph nodes were detected with MB alone in 41 patients (56.9%). In the 36 women who received MB and ^{99m}Tc, SLNs were detected by ^{99m}Tc in 25 patients (69.4%). Sentinel lymph nodes were detected with ICG in 7 (87.5%) of the 8 patients who received ICG. The combination of MB and ^{99m}Tc detected SLNs in 33 women (91.7%). The comparative detection rate data are listed in Table 2.

Nodal Status

Seventy-one patients (98.6%) underwent full systematic pelvic lymphadenectomy. One patient (1.4%) had morbidly adherent lymph node metastases that were deemed unsafe to remove, and these nodes were only biopsied. This patient did not undergo a hysterectomy.

Nineteen patients (26.4%) had pelvic lymph node metastases. Patients with nodal metastases had significantly larger tumors (mean diameter, 40.88 vs 23.26 mm; P = 0.0087) and were more likely to have tumors of 2 cm or

Table 2. Comparative detection rates between MB, ^{99m}Tc, and ICG

MB Only		^{99}Tc Only		MB + ^{99m}Tc		ICG Only		
Detection Rate, %	n	Detection Rate, %	n	Detection Rate, %	n	Detection Rate, %	n	*P*
56.9	72	69.4	36					0.2113
39.4	33			91.7	36			<0.0001
		69.4	36	91.7	36			0.0176
56.9	72					87.5	8	0.0959
		69.4	36			87.5	8	0.3042
				91.7	36	87.5	8	0.7114

greater (83.3% vs 40.7%; $P = 0.0019$) and grossly enlarged lymph nodes (66.7% vs 20.4%; $P = 0.0003$). The SLN detection rate in women without metastases was 72.2% compared with 44.4% in women with metastases ($P = 0.0332$).

Body Mass Index

The mean BMI of all patients was 27.51 kg/m^2. Twenty-seven women (37.5%) had a BMI of less than 25 kg/m^2, 45 (62.5%) had a BMI of 25 kg/m^2 or greater, and 23 (31.9%) had a BMI of 30 kg/m^2 or greater. The SLN detection rate was 77.7% in women with a normal BMI compared with 43.5% in those with a BMI of greater than 30 kg/m^2 ($P = 0.0140$).

FIGO Stage

The SLN detection rate was significantly better in women with FIGO stage IA2 to IB1 disease compared with women with locally advanced disease. The comparative data for the 2 groups are listed in Table 3.

History of TB and PID and the Presence of Pelvic Adhesions

Twenty-seven women (37.5%) had a history of TB and/or PID and/or the presence of adhesions at the time of surgery, compared with 45 women (62.5%) who did not. The

Table 3. Comparative data of early-stage disease versus locally advanced disease

	Stage IA–IB1 (n = 51)		Stage IB2–IIA2 (n = 21)		
	Mean	SD	Mean	SD	*P*
Age, y	48.82	9.51	43.29	6.69	0.0179
Parity	3.14	1.71	3.00	1.45	0.7435
Gravidity	3.32	1.74	3.19	1.60	0.7697
BMI, kg/m^2	27.42	5.29	27.73	5.82	0.8269
Tumor diameter, mm	14.85	12.61	53.75	20.08	<0.0001
Macro SLN count	2.11	1.31	2.00	0.71	0.8097
Histology SLN count	3.11	2.05	2.56	1.24	0.4475
Pelvic node count	24.37	9.01	27.10	11.90	0.3032
	n	%	n		
HIV positive	36	70.6	11	52.4	0.1431
Previous TB	4	7.8	0	0	0.1910
Previous PID	11	52.4	2	9.5	0.0008
Previous surgery	8	15.7	5	23.8	0.4200
Adhesions	12	23.5	4	19.1	0.6852
Enlarged nodes	10	19.6	10	47.6	0.0166
Tumor ≥2 cm	16	31.4	21	100	<0.0001
Nodal metastases	8	15.7	10	47.6	0.0048
SLN detection rate	36	74.5	9	42.9	0.0110
Bilateral SLN detection	16	31.4	6	28.6	0.8160
Intraoperative complications	6	11.8	1	4.8	0.3663
Postoperative complications	8	15.7	5	23.8	0.4200

SLN detection rate in the TB/PID/adhesion group was 63% compared with 66.7% in the comparative group ($P = 0.7512$).

Bilharzia and TB

One patient had bilharzia ova reported in her lymph nodes, and another patient had TB reported in her lymph nodes. The patient with TB in her nodes was found to have micrometastases in her SLN; her non-SLNs were negative for metastases.

The SLNB Algorithm

According to the algorithm, patients without mapping should undergo a full pelvic lymphadenectomy, and all enlarged or suspicious nodes should also be removed regardless of mapping. In this cohort, SLNB was associated with an FNR of 14.3%, as there was a false-negative SLNB in 1 patient. This patient had enlarged nodes on the side of lymph node metastases; if the algorithm were applied to this patient, there would have been no false-negative results, yielding an FNR of 0%.

Discussion

Although the rate of HIV infection in South Africa is relatively high, the rate among this group of women was even higher, which was unexpected considering the study and recruitment designs were not structured to accrue more HIV-infected than noninfected women. Previous data from our Gynaecological Oncology Unit have demonstrated an HIV infection rate of 26% among women with cervical cancer, and this rate has been consistent among all stages through several years.[15] Although there were no significant differences with regard to mean tumor diameter between the 2 groups, significantly more women in the HIV-negative group had tumors measuring 2 cm or greater, despite similar stage distributions. This might be attributable to more screening in HIV-infected women on antiretroviral treatment. Human immunodeficiency virus–infected women tended to have more previous episodes of TB infection, although because of the small number of patients, this difference did not reach statistical significance.

The almost similar proportions of HIV-positive and HIV-negative women with enlarged lymph nodes, as well as with nodal metastases, are somewhat unexpected, as one would have suspected higher rates of both in the HIV-infected group. The finding that there was no difference in the SLN detection rates between the 2 groups is an important finding, as there are no published data on the detection rate of SLNs in HIV-infected women.

Women with a BMI of 30 kg/m^2 or greater achieved a detection rate that was significantly lower than that of women with a BMI of less than 25 kg/m^2 (43.5% vs 37.5%; $P = 0.0140$). Body mass index is therefore a significant factor in the detection of SLNs. This finding is consistent with similar findings in the published literature.[16]

Enlarged Lymph Nodes

Almost 32% of women had clinically enlarged lymph nodes. Human immunodeficiency virus status did not show an effect on macroscopic nodal status, with almost identical rates among the 2 groups. This is an unexpected finding, as one would expect a higher proportion of women to present with clinically enlarged nodes in the HIV-infected group.

The macroscopic appearance of lymph nodes in women with cervical cancer is not a good predictor of the presence of pelvic nodal metastatic disease in these women, with 52% of women with macroscopic enlarged nodes having metastatic disease in these enlarged nodes. The sensitivity, specificity, PPV, and NPV of enlarged nodes were 83.3%, 32.1%, 44.1%, and 75%, respectively. Macroscopic assessment based on lymph node size alone is not accurate for clinical decision making in the treatment of women with cervical cancer.

The overall SLN detection rate of 65% in this study population is lower than the detection rates published in the international literature. The combination of MB and ^{99m}Tc had statistically significantly better detection rate compared with MB alone or ^{99m}Tc alone, whereas the detection rate with ICG was as good as the combination of MB and ^{99m}Tc. This is consistent with results of other studies in the international literature.[17] Indocyanine green performed better than MB alone, although the difference did not reach statistical significance. The sample size of ICG was very small. These detection patterns are consistent with the published literature.[18–25]

The SLN detection rate in women with no metastases was significantly higher than that of women with metastases (72.2% vs 44.4%, respectively). This too is consistent with the published literature.[18]

The better detection rate in node-negative women with early-stage cervical cancer is reassuring, as this might result in fewer unnecessary pelvic lymphadenectomy procedures in select patients if the SLNB algorithm is followed correctly.

Tumor size, as expected, was significantly associated with less nodal metastases. Sentinel lymph node detection was statistically significantly better in those with tumors of less than 2 cm in largest diameter compared with those with tumors of 2 cm or greater (77.1% vs 54%, respectively; $P = 0.0411$). The published literature also shows a correlation between tumor size and detection rate, with significantly better detection rates when the tumor size is less than 2 cm.[6] When 4 cm is used as a size cutoff, there is also a significant difference in detection rates.[26] The smaller the tumor, the better the detection rate of SLNs.[27]

The SLN detection rate was significantly higher in the group of patients with stage IA to IB1 disease compared with those with stage IB2 to IIA2 disease (74.5% vs 42.9%, respectively; $P = 0.0110$). This correlates with the findings of better detection in smaller tumors, as well as in women with no nodal metastases.

Conclusions

The SLN algorithm is a feasible option for use in South African women with early-stage cervical cancer and a high prevalence of HIV infection. The algorithm provides useful information on lymph node status that may carry adjuvant treatment implications. Although the detection rate is generally lower than that reported in the literature, in select subgroups of women the detection rate was comparable to that reported elsewhere.

The factors influencing SLN detection rates are pelvic lymph node status, tumor size, FIGO stage, and BMI. Women with smaller tumors, normal BMI, and lower stage of disease had statistically significantly better detection rates.

The procedure also has high sensitivity, and the FNR for this cohort of women when using the Memorial Sloan Kettering SLN algorithm was 0%.

There is still a lack of prospective data on the use of SLN procedures in women with early-stage cervical cancer, and it is unclear what the effect on disease-free and overall survival will be should this technique be implemented in routine care. At this stage, it would be reasonable to suggest the use of the SLN algorithm as part of the individualized care of select women.

The results reported here are the first with regard to SLNB in South African women with a high prevalence of HIV, TB, and PID. This is also the first report of the use of SLNB in a substantial group of HIV-infected women.

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