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ORIGINAL RESEARCH

Feasibility and safety of the sentinel lymph node procedure for early vulval cancer in a low-resource high HIV-prevalence setting: a pilot study

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Background: The Groningen International Study on Sentinel Nodes in Vulval cancer (GROINSS-V) showed that if a sentinel lymph node (SLN) is negative, the risk of groin relapse due to a false negative finding is less than 3%. The SLN procedure (SLNP) is the standard of care in the management of early vulval squamous cell carcinoma (SCC). We aimed to evaluate the feasibility and safety of the SLNP in a low-resource setting with a high prevalence of HIV and human papillomavirus (HPV)-associated vulval SCC.

Methods: Between August 2012 and August 2016, women with early vulval SCC managed at Groote Schuur Hospital (GSH), Cape Town, South Africa, who fit the criteria, were offered the SLNP. For quality control, full inguinofemoral lymphadenectomy (IFL) was also done in the first 10 patients.

Results: In our setting, 40% of women with vulval SCC are HIV-infected and there is a predominance of HPV-associated vulval SCC, consequently, only 10.4% (10/96) of women were suitable for the SLNP. Most patients have multifocal tumours and/or enlarged groin nodes. Women with HIV and SCC presented at a younger age than those who were HIV-negative and had more SLN, which were expensive to ultra-stage.

Conclusion: At GSH, multifocal vulval SCC arising in vulval high-grade intraepithelial lesion (VHSIL) in HIV-infected women is relatively common. The main resource issue was the ultrastaging cost. However, more significant limiting factors to safely performing the SLNP were the multifocality of the disease, as well as enlarged (mainly reactive) groin lymph nodes, which could not be distinguished from metastases preoperatively. As a result, relatively few of our patients are suitable for the SLNP, so maintenance of skills is a concern.

Keywords: vulval squamous cell carcinoma, inguinofemoral lymphadenectomy, sentinel lymph node procedure, human immunodeficiency virus, human papillomavirus

Introduction

Vulval SCC is usually described as a rare disease. It is one of the least common gynaecological malignancies, with an incidence of two to three per 100 000 women per year.[1] Previously, it was a condition that affected mainly older women, with a peak incidence in the sixth and seventh decades. The most usual precursor lesion in these women is thought to be differentiated vulval intraepithelial neoplasia (dVIN), often associated with vulval lichen sclerosus (LS).

Recently, the median age of occurrence of this disease has decreased worldwide, largely due to HPV.[2–4] This is particularly the case in South Africa, where there is a high prevalence of HIV infection, resulting in a high HPV prevalence. South Africa has the largest HIV epidemic in the world, with an estimated 4.8 million women living with HIV in 2022; a prevalence rate of 23.5%.[5]

Women with HIV are more likely to have persistent infection with multiple oncogenic strains of HPV and can present with HPV-related SCC of the vulva in their 20s. They often have multifocal pre-invasive and invasive diseases, and treatment results in severe psychosexual morbidity. The surgical treatment of vulval SCC has become less radical over the years, with the current gold standard being a radical wide local excision of the vulval primary and a SLNP or full IFL.[3,6] However, young patients with multifocal HPV-related diseases are often not suitable for less extensive surgery, and the reactive lymphadenopathy of HIV often precludes the SLNP.

We embarked on a pilot study to assess the feasibility of performing the SLNP for women with early vulval cancer at GSH in Cape Town, South Africa.

Aim

This study aimed to evaluate the feasibility and safety of the SLNP in a low-resource setting with a high HIV infection prevalence and an increasing incidence of HPV-associated vulval SCC.

Methods

Institutional Research Ethics approval to keep and maintain a database of women who underwent the SLNP was obtained (R004/2013).

Between August 2012 and August 2016, all women managed at GSH for early vulval carcinomas, who had indications for a SLNP

as per the GROINSS-V, were offered SLN biopsy as part of their treatment. Indications for a SLNP included:

1. unifocal vulval SCC;
2. tumours < 4 cm in size with > 1 mm depth of invasion;
3. no suspicious inguinofemoral lymph nodes clinically or on imaging; and
4. the ability to give informed consent.

The exclusion criteria were:

1. multifocal or multizonal areas of invasion;
2. tumours > 4 cm in size;
3. non-squamous histology;
4. clinically or radiologically suspicious inguinofemoral nodes; and
5. the inability to give informed consent.

Patients were admitted the day before surgery, informed consent was obtained, and EMLA (anaesthetic) cream was applied to the area around the vulval tumour. One hour later, they were transported to the Nuclear Medicine department, where they underwent four intradermal injections of Technetium-99m Nanocolloid around the tumour. Static planar and single-photon emission computerised tomography (SPECT-CT) imaging of the groins and pelvis was then performed for up to four hours. Sentinel nodes were identified on imaging, and skin markings were made over the site of the groin sentinel nodes.

The following day, patients were transported to the operating theatre. After anaesthesia, they were positioned in lithotomy, and four intradermal injections of methylene blue dye were injected around the tumour. They were then cleaned and catheterised. The location of the sentinel nodes was confirmed with a gamma probe and small incisions were made over the nodes, which were then dissected free and removed. The node with the highest radioactivity was labelled as the "first/primary" sentinel node, and if present, other radioactive and blue nodes were also removed. As recommended for quality control, full groin dissection was also done in the first 10 patients.[1] Radical wide local excision of the vulval primary was then performed.

Ultrastaging was performed on the sentinel nodes if they were negative for metastases on routine sectioning. Two sections of 300 microns were cut from the lymph node; one section was stained with haematoxylin and eosin (H&E), and one unstained slide was kept in reserve for potential immunohistochemical confirmation. Compared to routine staining, which only cuts one section of the lymph node, ultrastaging typically requires 10 levels to confirm a negative node (i.e. 10 × cost of the routine sections). Currently, the cost of H&E staining is approximately R 300 and that of immunostaining is approximately R 1 000 per slide. The approximate routine cost of a lymph node is therefore R 300, whereas a negative node that has been ultrastaged will cost approximately R 3 000 per block of sentinel node. The cost will be higher for a large node that has to be divided into multiple blocks or if multiple/bilateral sentinel nodes need to be ultrastaged. Immunohistochemical confirmation, although not routinely performed, may also be required particularly for micrometastases or isolated tumour cells.

Details regarding the preoperative investigations, intraoperative and postoperative management, and results were documented for these first 10 patients. These women have been followed up for at least five years, and mortality and morbidity data is available for this period.

Results

At GSH, 25% of women with vulval cancer between 2002 and 2012 were HIV infected, and this has increased to approximately 40% at present.[7] There has been a steady increase in the incidence of vulval SCC (16 patients in 2012, 22 in 2016).[8] Only 10.4% (10/96) of women were suitable for the SLNP during the period of this study. Most patients with vulval SCC had multifocal HPV-associated disease and/or suspicious enlarged groin nodes. Even if these nodes were reactive HIV nodes rather than metastatic, this still prevented their inclusion in this study.

Only three of our first 10 SLN patients were HIV-infected (30%) (Table I). These women had a mean age of 39 years, which was significantly younger than the mean age of the HIV-negative women (61.6 years). All the HIV-positive women had VHSIL as

Table I

Patient	Age at and Year of Diagnosis	Background Lesion	HIV Status	Number of Positive Sentinel Lymph Nodes	Number of Positive Non-sentinel Lymph Nodes	Status 5 Years Post-SLNP
1	66	Lichen Sclerosus (LS)	Negative	5/7	0/20	Died of disease at 8 months
2	76	Vulval HSIL (VHSIL)	Negative	0/6	0/13	Died at 52 months (cause of death unrelated to cancer)
3	66	LS	Negative	0/3	0/8	Died of disease at 19 months
4	37	VHSIL	Positive	0/6	0/6	Excision of vulval recurrence at 84 months
5	60	Differentiated VIN	Negative	0/3	0/8	Alive and well at 76 months
6	38	HPV	Positive	1/7	0/5	Alive and well at 69 months
7	63	VHSIL	Negative	0/2	0/10	Alive and well at 81 months
8	42	VHSIL	Positive	0/9	0/5	Alive and well at 77 months
9	53	VHSIL and LS	Negative	0/2	0/15	Alive and well at 75 months
10	47	LS	Negative	1/1	0/13	Alive and well at 70 months

their precursor lesions, whereas LS and dVIN was the precursor lesion in five of the seven (71%) HIV-negative women.

The HIV-positive women had a higher number of suspicious or enlarged nodes removed, but not higher node counts overall. One young woman had a micrometastasis in one of her sentinel nodes, which was diagnosed on ultrastaging, and two others had positive sentinel nodes, though no other nodal metastases on full IFL.

These women have now all had at least five years of follow-up (Table I). Two have died of disease, and one died of a cause unrelated to her cancer. One HIV-infected woman developed a second vulval SCC seven years after her initial diagnosis, which was excised. The other six patients are alive and free of cancer. There have been no groin recurrences.

Discussion

A SLN is the node that is the first site of lymphatic drainage from a primary tumour. It is identified by imaging (lymphoscintigraphy) and the potential usefulness of this procedure in the management of vulval SCC was recognised more than four decades ago.

Radical wide local excision of the vulval tumour and IFL is the gold standard of surgical staging and treatment of vulval SCC. Involvement of the groin nodes by the tumour is the most important prognostic factor in terms of survival.[9] IFL yields groin recurrence rates of 1–10%.[1]

However, in the early stage of the disease, only 25–35% of women will have lymph node metastases. This means that up to 75% of women will be subjected to the significant risks of a full groin lymphadenectomy with no resulting benefit.[1] Of them, 20–40% will suffer lymphocyst formation and wound breakdown, and 30–70% of them will have lymphoedema and recurrent erysipelas or cellulitis.[1]

Nonetheless, unrecognised groin node metastases have a 75% mortality rate.[1] A less invasive and morbid way of assessing patients for groin node spread, while still maintaining a low false negative rate, was sought. Ramon Cabanas was the pioneer of the SLN biopsy in 1977, based on his work treating carcinomas of the penis.[10] Several small studies using the SLNP for vulval cancer showed that it was very accurate in diagnosing lymph node metastases, with a negative predictive value of almost 100%.[1] These lead to two large multicentre trials: GROINSS-V and the GOG protocol 173.[1,11]

The GROINSS-V study was an observational study of 276 women with early-stage vulval SCC. It aimed to investigate the safety of omitting a full groin node dissection (GND) in patients with negative sentinel nodes and to do a morbidity comparison.[1] Indications for the SLNP in this study were:

- unifocal SCC confined to the vulva (T1 or T2);
- tumour < 4 cm in diameter – the SLNP has a decreased sensitivity and higher false positive rate in tumours > 4 cm, so full IFL should be performed for these tumours;[11]
- depth of stromal invasion > 1 mm – the low risk (< 1%) of lymph node metastases for tumours ≤ 1 mm depth of invasion has meant that surgical assessment of the groin nodes in these women is not necessary;[12] and
- clinically and radiologically (USS/CT/MRI) non-suspicious/negative groin nodes.

The protocol of the study was to do a radical excision of the vulval tumour with a sentinel node procedure using both a radioactive tracer and blue dye. If the SLN was negative (both on routine sectioning and ultrastaging), then no further treatment was offered. If the SLN was positive, a full GND was done and postoperative radiotherapy was offered.

Patients in the GROINSS-V study had a groin recurrence rate of 2.3% over a median follow-up time of 35 months. The false negative rate was 5.9% (4.6% for unifocal disease) and the false negative predictive value was 2.9%. They had much lower rates of surgical complications than women who had full GND: wound breakdown 11.7% versus 34%, cellulitis 4.5% versus 21.3%, recurrent erysipelas 0.4% versus 16.2%, and lymphoedema 1.9% versus 25.2%.[1]

The GOG 173 study looked at patients who had the SLNP and full GND. The false negative predictive value for SLN biopsy was 3.7%, and this was lower in women with tumours 2–3.9 cm than in women with tumours 4–6 cm in size (2.0% vs 7.4%).[11]

Following these studies, it was clear that women with tumours < 4 cm in maximal diameter have < 3% risk of groin recurrence if they undergo a SLNP, i.e. it is safe to omit a full IFL if the sentinel node(s) is/are negative.

If there are metastases in the ipsilateral sentinel nodes, the convention has been to perform full IFL on both sides with adjuvant (chemo)radiotherapy treatment. The GROINSS-VII study showed that women with sentinel node metastases ≤ 2 mm can be offered inguinofemoral radiotherapy without first having IFL.[13] A recent study by Van der Kolk et al.[14] investigated whether it is safe to omit a contralateral IFL in women with early vulval cancers who have metastases to the ipsilateral SLN, using the GROINSS-V dataset. They found that the rate of contralateral lymph node metastases in patients with unilateral SLN involvement who had a successful SLN biopsy is low, at 3.3%. Therefore, unilateral groin treatment by IFL or radiotherapy is safe. The risk of contralateral non-SLN metastases or recurrences was greater in women with tumours > 30 mm, though this was not statistically significant.[14]

It is increasingly recognised that HPV-independent and HPV-associated vulval SCC do not only have two different aetiologies, but that their behaviour in terms of recurrence risk, sensitivity to radiotherapy, and survival is also different.[15] As HPV-independent tumours tend to be unifocal, they are usually more suitable for a SLNP when they present early, unlike their multifocal HPV-associated counterparts.

Another possible indication for the SLNP is malignant melanoma of the vulva. Melanoma is the second most common cancer of the vulva, after SCC, and may represent up to 10% of vulval malignant lesions.[15] These tumours have a 50% recurrence rate and a poor prognosis, and there is no evidence that IFL improves survival.[15] The SLNP has been used in the surgical staging of

vulval melanoma, even though there are few options for effective adjuvant therapy.

With this pilot study, we believe we have shown that it is feasible to perform the SLNP in a low-resource setting. While most articles on this subject are from well-resourced environments, they also have a crucial difference in the origin of the SCC being treated. In the United Kingdom, Europe, North America, Australia, and New Zealand, most women who present with early SCC of the vulva have LS and/or dVIN, which tends to produce unifocal tumours. In Southern Africa, on the other hand, due to our high HIV prevalence, we see more multifocal tumours originating from extensive VHSIL, and though these women are often young and fit, the multifocality of their tumours renders them unsuitable for the SLNP. Also, women with HIV often have bulky reactive groin lymphadenopathy, which is difficult to distinguish from metastatic disease – another contra-indication to the SLNP. Added to this, due to poor access to healthcare in low-resource countries, women with vulval cancer often present late.

Conclusion

This article presented a SLNP pilot study in a low-resource high HIV-prevalence setting and discussed current indications for the SLNP. While HIV and HPV have ensured that vulval SCC is becoming more common, this does not necessarily translate into more patients with disease suitable for the SLNP. Therefore, concerns about the skill maintenance of the entire team (gynaecological oncologists, nuclear medicine specialists and pathologists) to keep their false negative rates low is justified. One team doing all these procedures in a cancer centre may be one way of maintaining both skills and safety, though having surgery at a hospital farther from home is a sacrifice and inconvenience for patients and their families.

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Conflict of interest

The authors declare no conflict of interest

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Ethical approval

Ethical approval was obtained from the University of Cape Town Institutional Research Ethics Committee to keep and maintain a database of women who underwent the SLNP (R004/2013).

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