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Pathological process has a crucial role in sentinel node biopsy for vulvar cancer☆

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HIGHLIGHTS

- In this interim report, sentinel node (SN) biopsy appears feasible and within expected safety parameters.
- Pathology protocol violations may be associated with missed SN metastases.
- Strict adherence to the SN pathology protocol minimizes risk of groin recurrence in women with negative SNs.

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ABSTRACT

Objectives. To report the interim findings of an audit of the outcomes of sentinel node (SN) biopsy performed as a replacement for groin node dissection in women with early stage vulvar cancer in routine clinical practice in Australia and New Zealand.

Methods. A prospective multi-center study in 8 participating centers. Eligible patients had squamous cell carcinomas clinically restricted to the vulva <4 cm in diameter. SN procedures and pathological assessment were to be performed in accordance with the methods published by the GROINSS-V collaboration [1].

Results. 130 women with apparent early stage vulvar cancer were enrolled. Seventeen women subsequently did not meet the eligibility criteria and were excluded. SNs were identified in 111/113 of the remaining women. Twenty-two women had positive nodes. Sixteen of these women had at least 12 months follow up and 7 (44%) had recurrent disease. Eighty-nine women had only negative nodes. Seventy-four of these women had at least 12 months follow up and 6 (8%) had recurrent disease (including 2 [2.7%] with recurrence in the groin). On subsequent review of the two women with negative SNs who had groin recurrences, it was found that the

☆ This trial was approved by the New Zealand Multi-region Ethics Committee (Ethics reference: MEC/10/07/063, has site local ethical approval, and clinical trial registration (UTN: U1111-1182-6358).

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recommended pathology protocol had not been followed. In both cases, SN metastases were identified following serial sectioning of the nodes.

Conclusions. SN biopsy is feasible in routine clinical practice. However, undetected metastases in a removed SN may be associated with groin recurrence. To ensure patient safety, strict adherence to the pathology protocol is an essential component in the utilization of the sentinel lymph node technique in vulvar cancer.

1. Introduction

Vulvar cancer is a relatively rare malignancy that affects ~56 women a year in NZ [2], ~300 women per year in Australia [3], and ~6000 women per year in the United States of America where the incidence is reported as 2.6/100,000 women per year (https://www.cdc.gov/cancer/knowledge/provider-education/vaginal-vulvar/epidemiology.htm) [4]. Until recent years, standard management for women with Vulvar squamous cell carcinoma (SCC) clinically restricted to the vulva with a depth of invasion >1 mm has been radical local excision and either ipsilateral or bilateral groin node dissection [5]. Groin node dissection is associated with significant morbidity including lymphocyst, cellulitis, wound breakdown and lymphedema [6]. Because ~70% of women with early stage disease will have negative nodes this morbidity is considered substantial [7,8]. The premise which underlies the sentinel node (SN) biopsy technique is that a negative SN biopsy excludes the presence of occult disease in other nodes within that groin, thus avoiding the need for radical treatment to the groin/s. Since the publication of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) study in 2008 [1] and the subsequent publication of GOG 173 (Phase III Study of Intraoperative Lymphatic Mapping in Patients With Invasive Squamous Cell Carcinoma of the Vulva) [7], SN biopsy is considered by many to be a safe alternative to groin dissection for women with early stage vulvar cancer. It is clearly associated with reduced morbidity and systematic reviews have identified the procedure to be both safe [1,7,9] and cost effective [10,11]. SN biopsy has been included in vulvar cancer treatment guidelines published by the National Comprehensive Cancer Network [12], the European Society of Gynaecological Oncology [13,14], and the Royal College of Obstetricians and Gynaecologists [15]. Many centers have developed experience in SN biopsy and now offer this procedure as an alternative to groin dissection for selected women.

Vulvar cancer is rare and even high volume gynecological oncology centers in New Zealand and Australia treat a small number of women with this disease. Of these women, only a proportion may be eligible for SN procedures. The SN procedure in vulvar cancer is a relatively new technique and the findings of the GROINSS-V study require confirmation in routine clinical practice. We hypothesized that the groin node failure rate in our study would be approximately 3% (equivalent to that in the GROINSS-V study), and that a groin recurrence rate of 5% or greater would be unacceptable [16]. The overall aim of this prospective multicenter observational study was to confirm the feasibility and safety of the SN procedure for vulvar cancer in participating gynecological oncology centers in New Zealand and Australia. We present the results of a planned interim analysis (Phase 1).

2. Methods

All Australian and New Zealand gynecological cancer centers already offering SN procedures as an alternative to formal groin dissection for women with vulvar cancer were invited to participate in this prospective audit (UTN U1111-1182-6358). The audit was approved by the New Zealand Multi-region Ethics Committee (Ethics reference: MEC/10/07/063). Operating surgeons were required to demonstrate prior experience in the procedure or to perform at least three SN procedures under the supervision of an investigating surgeon. Participating centers were required to show that they had the necessary equipment, expertise, and experience to undertake the radio-colloid scintigraphy and use of the intraoperative gamma probe. Investigators agreed to follow the designated protocol and obtain site local approval. After obtaining consent, participant case report forms were completed at enrolment, at the time of surgery, on receipt of the pathology report, at the 3 month follow up visit, and at subsequent annual follow up (for up to 3 years), and at detection of recurrence or other serious adverse event. All data were collated and stored centrally at the coordinating site.

The SN protocol was designed in accordance with the methods published by the GROINSS-V collaboration [1]. In addition, women who had previously undergone local excision of a vulvar carcinoma without groin dissection who were undergoing a second procedure to remove the SNs were included (secondary SN procedure) [17]. Preoperative imaging of the groins by ultrasound, CT or MRI was mandatory. The radio-colloid utilized varied between institutions, dependent on local availability, and these were accepted as equivalent following discussion between investigators and nuclear medicine departments. A pre-operative single-photon emission computerized tomography scan was considered a helpful addition to the SN imaging protocol where available.

The inclusion criteria were as follows: women with a histologically confirmed unifocal invasive squamous cell carcinoma of <4 cm in maximal dimension (not including in-situ component) with a depth of invasion at least 1 mm; the tumor not invading the urethra, anus or middle third of the vagina and no clinical evidence of groin node metastasis on palpation, imaging, or fine needle aspiration; no past medical history of squamous cell carcinoma, previous groin node dissection or major vulvar surgery; at least 18 years old. Where primary excision of the lesion had already occurred, prior reconstruction of the vulva using a flap was considered an exclusion criterion.

Phase 1 of the study (reported here) was a planned interim analysis to document the recurrence rate in the first 100 women with negative SNs. The node positivity rate was expected to be approximately 20%, thus the interim analysis was planned following the recruitment of ~130 women.

Phase 2 of the study (still underway and not reported here) is designed to document that the rate of recurrence in women with negative SNs is <5% within 95% confidence intervals. At least 280 women will be recruited.

3. Results

At the time of this report, 130 women were enrolled at 8 participating centers. Two women were excluded upon review due to a clinically positive node and one woman excluded due to multi-focal disease on initial biopsy. Following surgery, a further 14 women did not meet the eligibility criteria and were also excluded from analysis. See Fig. 1.

Demographic and clinical features for the 113 women remaining in the analysis are provided in Table 1. Vulvar excisions were undertaken for 109/113 women. Four women did not have a vulvar excision at the time of SN surgery to preserve function due to proximity of the lesion to the anus. A lesion size was therefore not recorded for these women, however, the clinical estimate of lesion size was between 2 and 3 cm. These women were treated with primary radiotherapy with or without

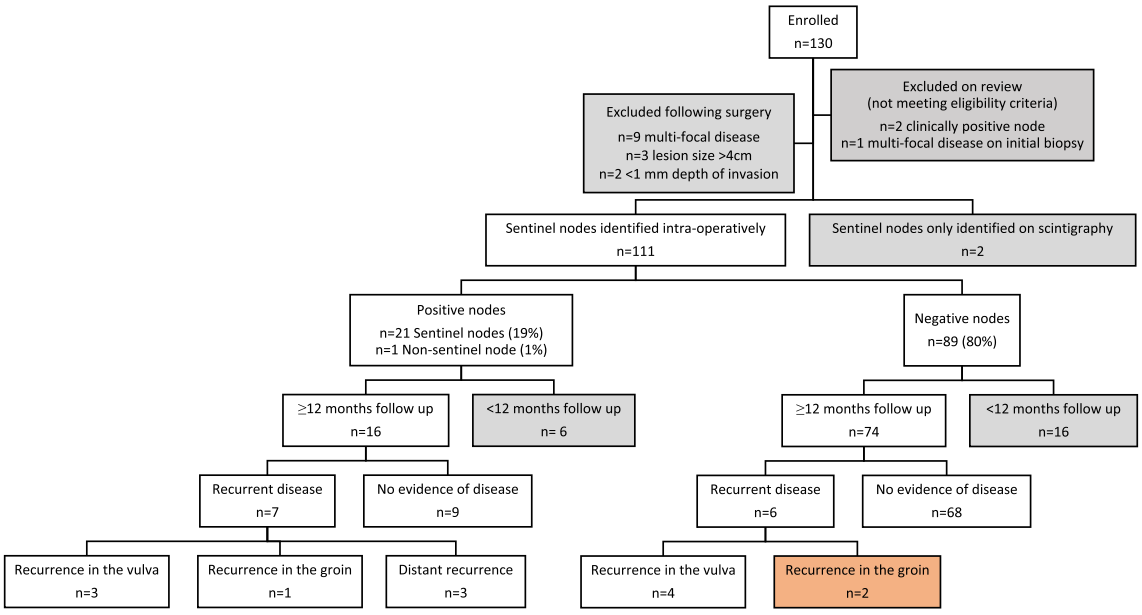

Fig. 1. Study flow chart.

chemotherapy. Tumor size was recorded for 105/109 women (with the remaining 4 women having only a small focus of disease).

Primary SN procedures were completed in 72 women and 41 underwent a secondary SN procedure.

SNs were identified intra-operatively in 111/113 women. In the remaining 2 women, a SN was identified on scintigraphy but could not be identified intra-operatively, thus SNs were not removed. A total of 278 SNs were removed. SNs were identified by scintigraphy (248), blue dye (212) and by the intra-operative gamma probe (262). Intra-operatively, 12 SNs were identified with only blue dye and 38 with only the probe.

Bilateral SNs were identified in 31/41 (76%) of women with midline lesions and 26/47 (55%) with lesions within 1 cm of, but not involving, the midline. Where a SN was removed, the mean number of SNs removed from each groin was 1.6 (range 1–4).

Of the SNs identified, 26 were positive in 21 (19%) women, one woman had negative SNs but a positive non-sentinel node, while the remaining 89 (80%) women had only negative nodes (see Fig. 1). The woman with negative SNs but a positive non-sentinel node, had a small focus of invasion in a 2 cm area of usual type VIN. She had two sentinel nodes identified in the ipsilateral groin and none in the contralateral groin. The two sentinel nodes were negative but had a non-sentinel node, which was macroscopically normal, removed on the ipsilateral side containing 2 small foci of tumor.

SNs were considered positive if they contained any tumor cells whether detected by haematoxylin and eosin stains (H&E) or immunohistochemistry. Most of the women with positive SNs (17/21) had one positive SN identified, however 3 women had 2 positive SNs and 1 woman had 3 positive SNs. Most of the women with positive SNs (19/21) had positive SNs in one groin but 2 had positive SNs in both left and right groins. Lymph node metastases were visible with H&E in 23/26 specimens and detected by immunohistochemistry alone in the remaining 3 specimens.

Sixteen of the 22 women with a positive SN or non-SN have had at least 12 months follow up. Of these 16 women, 7 (44%) have had recurrent disease and 5 (31%) have died of disease.

Seventy-four of the 89 women with negative nodes have had at least 12 months follow up. Of these 74 women, 6 (8%) have experienced recurrent disease including 3 (4%) who have died of disease. An additional woman died of other causes. Of those 6 women with recurrent disease, 3 women have had an isolated recurrence in the vulva and are all still alive at the time of publication. Another woman had a recurrence in the vulva and underwent a full groin dissection which revealed a microscopic positive node. This woman subsequently had a distant recurrence and died of her disease. Two other women presented with isolated groin recurrences:

The first was a 60-year-old woman with no significant past medical history who had a lateral left sided vulvar lesion 10 × 11 mm in size with 2.5 mm depth of invasion. Lymphatic space invasion was not present. No suspicious groin nodes were seen on CT scan. Radical local excision and a primary SN procedure were undertaken. A single SN on the left side was identified by scintigraphy, blue dye and the intraoperative probe. This was removed and reported as negative. The patient had an isolated left-sided groin recurrence at 12 months. Following review, it was determined that the SN pathology protocol had not been followed and the node had only been bisected and not cut to extinction and ultrastaged as specified by the protocol. When the node was re-examined as per protocol, a sub-capsular focus (0.06 mm) of 5 to 6 metastatic cells was identified on immunohistochemistry. The patient subsequently underwent surgical resection of the groin with adjuvant radiation and is alive and tumor free >3 years later.

The second patient was a 48-year-old woman with a history of diabetes and a 20 mm × 20 mm right sided lateral vulvar lesion. The depth of invasion was 4.5 mm and lymphatic invasion was present. No suspicious nodes were identified on CT. The patient underwent a radical local excision and primary SN procedure. A single right SN was identified by scintigraphy, blue dye and the intraoperative probe. The node was reported as negative. Eight months post-operatively, the patient

Table 1
Demographic and clinical features of study participants.

Demographic and clinical features	
Age ($n = 113$)	Median 64 years (range 28–93 years, IQR 53–78 years)
Localization of tumor ($n = 113$)	$n = 41$ (36%) midline lesion $n = 47$ (42%) ≤ 1 cm from the midline $n = 25$ (22%) >1 cm from the midline
Depth of invasion ($n = 109$)	Median 2.8 mm (range 1–15 mm, IQR 2.0–4.5 mm)
Tumor size ($n = 105$)	Median 1.7 cm (range 0.02–4.0 cm, IQR 1.0–2.5 cm)
Relevant co-morbidities ($n = 113$)	$n = 10$ (9%) diabetes $n = 9$ (8%) immunosuppression $n = 4$ (4%) lower limb swelling

Table 2
Demographic and clinical features of women with false negative sentinel nodes.

Case	Age at date of registration	Maximum dimension of lesion	How identified	Protocol violation	Maximum dimension of metastasis	Treatment	Outcome
Case 1	60 years	1.1 cm	Groin recurrence	Pathology	0.06 mm	On recurrence, groin dissection and radiation therapy	Alive with no evidence of disease at 36 months
Case 2	48 years	2.0 cm	Groin recurrence	Pathology	1.8 mm	On recurrence, groin dissection and radiation therapy	Died of disease
Case 3	59 years	0.6 cm	Positive non-sentinel node at initial surgery	None identified	1.0 mm	Radiation therapy	Alive with no evidence of disease at 36 months

developed recurrent disease in her right groin. Further investigation suggested the presence of lung metastases. On review of the histology, the SN had been serially sectioned but cut along, rather than perpendicular to, the longitudinal axis of the node, and the node only partially sectioned, rather than cutting to extinction as the protocol dictates. The remaining tissue was serially sectioned and a small discoid 1.8 mm × 0.3 mm sub-capsular micro-metastasis was identified on H&E stain. This woman subsequently died of disease.

The demographic and clinical features of the three women with false negative sentinel nodes are outlined in Table 2.

A review of the pathology of all women with negative SNs was subsequently undertaken. Protocol deviations were identified in 4 institutions. Subsequent re-sectioning of all nodal tissue (in accordance with the original protocol) in these women did not reveal any further missed metastases. Recruitment to the study was temporarily ceased, but recommenced following an institutional root cause analysis and adverse events committee review, review of protocols, processes, and further ethical review.

4. Discussion

This multicenter prospective audit was undertaken to ensure the safety of SN biopsy in the treatment of vulvar cancer, which is being offered to women in a large number of institutions internationally, including New Zealand and Australia. The low incidence of vulvar cancer and the low likelihood of failure of the technique does not allow for meaningful audit within single centers in Australia and New Zealand.

The SN technique relies on a number of important steps including patient selection, correct technique for tracer injection, identification of SNs by lymphoscintigraphy, correct surgical removal of SNs utilizing both blue dye and a hand held gamma probe, and pathological detection of microscopic nodal metastases.

There are numerous reports of false negative SNs, including in women with large vulvar lesions, multifocal disease and clinically enlarged nodes. These reports inform the inclusion/exclusion criteria for the current audit. We note in this study one woman had a positive non-SN removed from a groin with a negative sentinel node. In addition, the importance of surgical technique and surgeon experience has been emphasized [1,18,19].

This audit demonstrates that pathology protocol compliance is critically important and variation can be associated with failure of the SN procedure. Notably, pathology protocol violation was not uncommon. The importance of meticulous systematic pathological inspection of the SN was identified by the pioneers of this technique [1]. In the original GROINSS-V report, of the 8 women who had a groin recurrence, two were reported to have micro-metastases detected in the SN at pathological review [1]. Other reports of groin recurrence associated with missed micro-metastases exist. Schutter reported 7 women with groin recurrences following 56 (12.5%) negative SN biopsies, 3 of whom had micro-metastases on pathological review which had not originally been reported [20]. Our findings are consistent with these reports and suggest that missed SN metastases of any size are associated with groin recurrence.

However, the clinical significance of metastases that may be missed at pathological node examination remains uncertain [21]. In a review of evaluable women included in the GROINSS-V study, Oonk found that micro-metastases occurred in non-sentinel groin nodes in 2 of 19 women with a SN micro-metastasis <2 mm. In those where SNs had isolated tumor cells only, one in 24 women had a metastasis in non-sentinel nodes [22]. This would suggest a low risk of recurrence in patients with missed metastases <2 mm. This is supported by the fact that following pathology review of available material, 32 nodes from 20 patients in the GROINSS-V study were considered false negative, although these false negative SNs only contained isolated tumor cells. None of these women had groin recurrences despite the fact that they had no groin treatment other than removal of the SN [22]. Missed micro-metastases may be of greater importance than missed isolated tumor cells. However, in view of the first case of groin recurrence we describe above, the missed metastasis was only 0.06 mm in diameter, isolated tumor cells should therefore be reported. Future research is required to determine appropriate management for these patients.

In the current audit, following review of all pathology specimens from women with SNs previously reported as negative, missed metastases were only seen in the two women who experienced recurrence. Although this sample is small it would imply that women with missed metastases in the SN may have tumor cells in other groin nodes or lymphatics that may or may not be detectable by routine histopathology techniques. These women appear to be at increased risk of groin recurrence and further treatment to the groin is indicated. This emphasizes the need for meticulous pathological examination of the SN that involves cutting the node appropriately, sectioning at close enough intervals to exclude micro-metastases and examining the entire node with ancillary immunohistochemistry (ultrastaging).

In this audit, failure to comply with the pathology protocol occurred despite the existence of a clearly documented protocol. The factors leading to this are considered to be the relative infrequency of SN biopsies for vulvar cancer, differing protocols for examination of SNs for vulvar cancer, breast cancer and melanoma [23], lack of understanding of the importance of detection of micro-metastases in SNs for vulvar cancer, and the large number of pathologists or trainee pathologists who may be involved with the processing of nodes from 'cut up' to reporting. It is important to note that despite centers being alerted to the risks of pathology protocol breach following the first false negative case, further protocol breaches still occurred.

When compared with other tumor streams [23], the higher workload involved in vulvar SN pathological examination, especially when multiple SNs are identified, is recognized. Approximately 30 slides need to be examined for each SN. Thus, in women with multiple SN identified, over 100 slides may need to be examined by the pathologist. The feasibility of accurately and consistently performing such a rigorous protocol is therefore questioned. Further research should be undertaken to determine the number of slides that need to be examined per node and the possibility of alternative, automated methods of identifying subclinical micro-metastases [24,25].

In this report, the risk of groin recurrence following a negative SN was low. However, false negative SNs do occur. This audit has yet to confirm that SN biopsy performed for vulvar cancer within participating centers in Australia and New Zealand is safe. However, the risks identified appear modifiable. SN biopsy is increasingly accepted internationally as an alternative to lymphadenectomy. A recent systematic review estimated the risk of groin recurrence to be 2.8% following a

negative SN biopsy, compared to 1.4% following a negative groin node dissection [19]. However, a current population-based study, comparing both cause-specific and overall survival in patients with negative SNs, who had undergone either full groin node dissection or SN biopsy, found that they were comparable [9]. The 5 year cause-specific survival and overall survival for lymphadenectomy and SN biopsy were 91.8% and 92.9% ($p = 0.912$) and 77.5% and 82.5% respectively ($p = 0.403$).

Despite the heterogeneity of other reports and the need for ongoing data collection, the participating centers involved in the current study believe that the reduced morbidity of the SN procedure justifies its ongoing use as an alternative to groin dissection in appropriately selected women. The benefits of, and need for, ongoing multicenter prospective evaluation are clear [26]. Of note, the protocol violations in this study occurred in both high and lower volume centers. Consequently, practice has improved in all participating institutions, reaffirming the importance of multicenter evaluation for infrequently performed procedures regardless of institutional volume.

In order to prevent further pathology protocol breaches, the following measures have been instituted: (1) the pathology protocol has been reworded and clarified, each center has a nominated pathologist responsible for the vulvar carcinoma SN protocols and (2) SN pathology reports are now synoptic (see Supplementary material – Updated histology protocol and synoptic report). Following review by the New Zealand Southern Health and Disability Ethics committee of the root cause analysis and report, recruitment to the study has recommenced. For gynecological oncology centers utilizing sentinel node biopsy for vulvar cancer, it is strongly advised that there is (1) well identified and agreed clinical and pathology protocol, (2) attention paid to patient selection, (3) radiological investigation of groins, (4) clear labelling of specimens from surgical procedures, (5) reference to the correct protocol on the pathology request form, (6) overseeing of pathology reporting by a designated pathologist, (7) use of a synoptic report that easily identifies that the correct protocol has been utilized, and (8) discussion of the patient at a multidisciplinary meeting where protocol violations can be identified. We also recommend outcomes should be monitored.

We conclude that missed SN metastases are associated with a significant risk of groin failure following SN biopsy for vulvar cancer; that pathology protocol violations are associated with an increased risk of missed SN metastases, and that prospective multicenter evaluation is an important aspect of quality control when new techniques are introduced into 'real world' clinical practice.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.02.012.

Conflict of interest statement

The authors report no conflict of interest.

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