

# Sentinel lymph node detection in vulvar cancer patients: A 20 years analysis

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## Abstract

*Our study aimed to analyze postoperative treatment-related morbidity after sentinel lymph node biopsy (SLNB) compared to systematic inguino-femoral lymph node dissection (ILND) and the recurrence rate in patients with vulvar cancer. This single center study included 128 patients diagnosed with vulvar cancer that underwent ILND or SLNB between January 1991 - January 2011 with intraoperative SLN detection and removal. Treatment-related morbidity, as well as recurrence rate of SLNB patients were evaluated. Preoperative sentinel node scintigraphy was successful in 82/89 (92%) of the patients. A hundred and seventy six nodes were visualized and all positive SLN were detected within 60min. Patients who were treated with ILND underwent a longer operation ( $P < 0.001$ ), required longer inguinal drainage ( $P < 0.001$ ), and had a lengthier postoperative hospital stay ( $P = 0.006$ ). The presence of lymph cysts ( $P = 0.02$ , 95% CI 3.4 (1-1-10.6)) was significantly higher in ILND patients. No groin recurrence was appreciated in SLNB patients. In conclusion, patients who underwent SLNB were at a lower risk of postoperative morbidity. No groin recurrences were observed in patients who received SLNB.*

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## Introduction

Vulvar cancer is a relatively rare disease and comprises approximately four percent of all gynecological cancers [1, 2]. While the mean age of women presenting with vulvar cancer is 70 years, recent data has shown a decline of the mean age by five to eight years [1, 3]. The most common histological form of vulvar cancer is squamous cell carcinoma (SCC), which accounts for approximately 80% [1]. The other forms including adenocarcinomas, melanomas, sarcomas and basal cell carcinomas are less frequent [1]. Inguino-femoral lymph nodes are usually the first route of spread of SCC and the most significant prognostic factor [1, 4]. Tumor grade, depth of invasion, lymph space invasion, clinical lymph node status, and age are reported risk factors for inguinal lymph node metastases [5]. Studies have shown that only 17%-32% of patients with vulvar cancer have lymph node metastases [6-8]. Treatment-related morbidities include wound infection, wound breakdown, groin swelling, lymph cysts, sensibility disturbances, sexual problems and chronic lymph edema of the lower limb, reported in up to 60% of patients [5, 6, 9-11]. While not undisputed, it is estimated in the literature that groin recurrences occur in 2%-30% of vulvar cancer cases and usually within the first two years after treatment [10, 12-14].

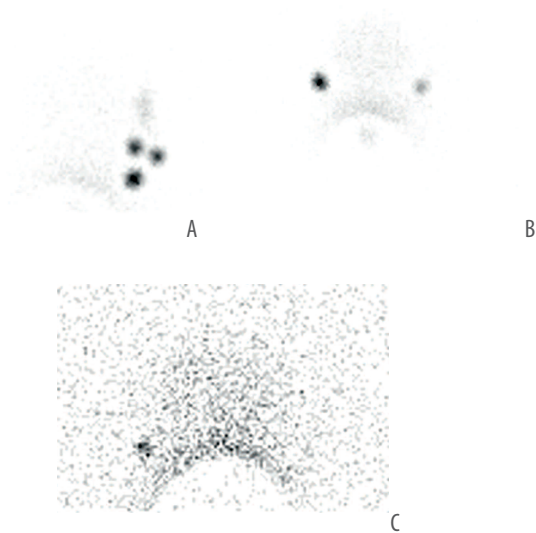
Systemic inguino-femoral lymph node dissection (ILND) is considered the standard surgical approach in patients with invasive vulvar cancer >1mm. A new operative approach, sentinel lymph node biopsy (SLNB), was first introduced in 1977 for penile cancer [15]. The sentinel lymph node is the first lymph node or group of lymph nodes draining from the primary lesion. SLNB potentially decreases the morbidity of ILND and is associated with fewer postoperative complications [16]. The first results on the detection of SLN in vulvar cancer patients were published in 1994, where blue dye was used to identify SLN in nine patients [17]. Currently, lymphatic mapping and subsequent SLNB is the standard of care in melanomas and breast cancer [14]. By combining preoperative sentinel node scintigraphy with technetium-99m and intraoperative Isosulfan blue dye, the detection rate of SLN lies between 75%-100% [18]. On the other hand, a study by Robison et al. described an SLN detection rate of 85% with <sup>99m</sup>Tc plus intraoperative handheld collimated gamma counter and 68% using blue dye [19]. A poor detection rate for the dye technique alone was discussed [20]. Therefore, the SLN detection rate widely varies depending upon the technique used.

The aim of our retrospective study was to examine postoperative treatment-related morbidity of SLNB in comparison to ILND and the recurrence rate in patients with vulvar cancer.

## Material and methods

### Patients

One hundred and twenty eight women who underwent either ILND or SLNB with/without preoperative sentinel node scintigraphy, in addition to intraoperative SLN detection and surgical removal between January 1991 and January 2011 at the Vienna General Hospital were included in the study after chart review. Inclusion criteria consisted of available data regarding operation date, preoperative sentinel node scintigraphy, type of SLN detection and subsequent removal, and follow-up were included. For patients undergoing SLNB, tumor size greater than 4cm was a contraindication. However, two patients who had tumors greater than 4cm underwent SLNB. The exact reason as to why this procedure was carried out and not ILND, could not be ascertained from their charts. Individuals were excluded if they did not receive any surgical treatment including SLNB or ILND for vulvar cancer or if they did not obtain a follow-up. Bleeding was defined as hemorrhage greater than 100mL occurring intra- or postoperatively. Infection was defined as redness, swelling, pain or positive infection parameters in the blood. Lymph cysts were defined as visible groin swelling with/-out lymph secretion from the wound. Wound breakage or dehiscence was defined as opening of the surgical incision along the suture. From 1991 until 1998, only ILND procedures were performed [21]. A SLNB algorithm was first introduced in 1998 at the Vienna General Hospital. Between 1998 and 2000, ILND was always conducted after SLNB. From 2001 up until the present, patients applicable for SLNB procedure received SLNB procedures only without any subsequent ILND [21]. Patients who initially received SLNB followed by ILND, were analyzed as an individual group for their patient characteristics, whereas for all other statistical analyses they were included in the ILND population. The sentinel lymph nodes at 90min post injection of three patients are shown in Figure 1. The present study has been approved by the local institutional review board (EK-reference number: 803/2011) and all subjects signed a written informed consent.



**Figure 1.** The sentinel lymph nodes 90min post-injection in three patients (A, B, C).

### Procedure

The guidelines for European Nuclear Medicine in SLN and breast cancer were applied and slightly modified [22]. We used a 27-gauge needle, two to three hours before surgery to inject 15MBq technetium<sup>99m</sup> microcolloidal albumin (Nanocoll®, GE Healthcare) intracutaneously 4 times around the primary tumor (3,6,9,12 o'clock) [23]. Following injection, sentinel node scintigraphy using a Philips (Picker) Axis dual-head gamma camera with a low-energy general-purpose (LEGP) collimator was conducted and results were recorded after 5, 30, 60 and 90min. Hot spots were defined as the SLN and a cutaneous marker was applied to assist the surgeon. Two experienced nuclear medicine physicians analyzed all preoperative lymphoscintigraphies. Intraoperative SLN detection was conducted with a handheld collimated gamma probe, pre-operatively injected blue dye or a combination of both methods. The hot nodes were identified before and after the inguinal regions were opened with a hand-held gamma camera. After all radioactive nodes were removed, the groins were reexamined with the hand-held gamma camera to identify any residual radioactivity [23]. All sentinel lymph nodes sent to pathology were examined intraoperatively with frozen section analysis. Final examination of the sentinel and other lymph nodes was executed with the standard techniques of hematoxylin-eosin (H&E) staining and serial sections [21, 24]. All negative or questionable nodes were then subjected to additional immunohistochemical cyto-keratin inspection [21].

### Statistical analysis

After classification of the data and analysis of normality by Kolmogorov-Smirnov tests, various parameters and surgical technique were analyzed using the Mann-Whitney *U* test. The association between surgical technique and postoperative morbidity, i.e. infection, bleeding, wound breakage, lymph cysts, swelling, edema, recurrences and death were examined by chi-square tests. Values were given as P-values and odds ratio (95% confidence interval). A univariate analysis was conducted to assess risk factors for postoperative morbidity between the two different dissection techniques. Analysis of data was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) v19 for Windows.

## Results

During the duration of the study period 1991-2011, 128 patients diagnosed with SCC underwent tumor excision and subsequent SLNB, ILND or SLNB followed by ILND. Patients' characteristics are provided in Table 1.

### Lymphoscintigraphy

Preoperative SLN visualization with a gamma camera was successful in 82/89 patients (92%), while 39 patients did not receive preoperative lymphoscintigraphies. All SLNB and SLNB+ILND patients had preoperative lymphoscintigraphies. While 14 ILND patients also received a preoperative lymphoscintigraphy, the exact circumstances as to why they were conducted could not be ascertained from chart review.

A total of 176 nodes were visualized (mean 2.0 SLN per

patient) and all of the SLN were visualized within 60min. In seven patients no SLN was visualized. One of these patients, classified with International Federation of Gynecology and Obstetrics (FIGO) stage IV, had a large tumor, which may have impeded lymphatic flow. Chart review of the remaining six patients could not identify any characteristics as to why no SLN was detected. Histological examination of the lymph nodes in these seven patients only showed signs of lymphatic tumor cell spread in the patient with FIGO IV vulvar cancer. Additional use of intraoperative hand-held gamma probe aided in the detection of the SLN in five of the seven patients. One of these seven patients received only blue dye for identification and in one patient, no additional assistance was employed.

Of the 89 patients who underwent preoperative SLN detection, the additional employment of intraoperative gamma camera was conducted in 63 patients, solely blue dye in 13 patients, a combination of these two techniques in 8 patients and in 5 patients no additional detection was used. Which detection technique employed (technetium, intraoperative gamma camera, blue-dye) was left up to the discretion of the surgeon.

**Table 1.** Patients' characteristics

	SLNB n (%)	ILND n (%)	SLNB + ILND n (%)
No. of patients	46 (36)	53 (41)	29 (23)
Mean age (yrs)	67.8	67.4	65.4
Histological grade	18.3		
Squamous cell cancer	43 (94)	49 (92)	28 (97)
Other	3 (6)	4 (8)	1 (3)
Mean tumor size (mm)	18.3	27.9	17.4
Unilateral LN dissection	-	13 (25)	3 (10)
Bilateral LN dissection	-	40 (75)	26 (90)
FIGO stage			
I	31 (68)	21 (39)	15 (51)
II	7 (15)	12 (23)	2 (7)
III	8 (17)	8 (15)	8 (28)
IV	-	12 (23)	4 (14)
Lymph node status			
N0	37 (80)	36 (68)	17 (59)
N1	9 (20)	17 (32)	12 (41)
Procedure			
Partial vulvectomy	23 (50)	29 (55)	18 (62)
Hemi-vulvectomy	7 (15)	6 (11)	5 (17)
Radical vulvectomy	2 (4)	9 (17)	-
Other	14 (31)	9 (17)	6 (21)
Total removed (LN)	206	569	367
Mean size of SLN (mm)	24.5	-	18.0

SLNB: Sentinel lymph node biopsy, ILND: Inguinofemoral lymph node dissection, FIGO: International Federation of Gynecology and Obstetrics, LN: Lymph nodes, mm: millimeters, SLN: sentinel lymph node

### SLNB patients

Overall, 46 patients underwent SLNB and a total of 206 lymph nodes were removed. Positive nodes were identified in nine patients. Given that these nodes were diagnosed postoperatively as being positive, none of these patients underwent ILND. Six patients, however, did receive adjuvant radiotherapy and three declined additional therapy.

A total of 37 patients had negative SLN. However, 29 of these 37 patients underwent further underwent ILND. In 17 of these patients, ILND produced no further positive lymph nodes. However, in the remaining 12 SLN negative patients, ILND discovered positive inguinal lymph nodes.

### ILND patients

In 82 patients (solely ILND and SLNB followed by ILND), a total of 936 lymph nodes were removed. Twenty-nine ILND patients had positive nodes, whereby 28 of these received adjuvant radiotherapy and one declined additional therapy. On the other hand, 53 patients had tumor negative lymph nodes.

### SLNB vs. ILND

Patients who received SLNB had a mean operation time of 76.2min compared to 103.3min in those who underwent ILND ( $P<0.001$ ). In addition, patients who received ILND had a longer hospital stay of 18.1 days versus 13.3 days in SLNB patients ( $P=0.006$ ). Moreover, SLNB patients had inguinal drainage for an average of 4.1 days compared to ILND patients with 6.9 days ( $P<0.001$ ). The risk of lymph cysts ( $P=0.02$ , 95% CI 3.4 (1.1-10.6)) was significantly higher with ILND. Puncture of the lymph cysts was the most common form of therapy, followed by suprapubic catheter sandbag or a disposable catheter. In addition, the risk of bleeding (95% CI 3.7 (0.8-17.7)) was higher with patients who received ILND. One ILND patient who had severe postoperative bleeding required a revision, while another ILND patient was treated with a tamponade. All other instances did not require any further treatment. The odds rate of postoperative morbidity factors determined with univariate chi-square tests for their association between the two different dissection techniques are illustrated in Table 2

**Table 2.** Postoperative morbidity of SLNB versus ILND

	SLNB n (%)	ILND n (%)	P	OR (95%CI)
No. of patients	46 (36)	82 (64)		
Bleeding	3 (7)	11 (13)	n.s.	3.7 (0.8-17.7)
Infection	8 (17)	7%	n.s.	0.7 (0.3-2.0)
Wound breakage	7 (15)	12 (15)	n.s.	1.1 (0.4-3.1)
Inguinal lymph cysts	4 (9)	20 (24)	0.02	3.4 (1.1-10.6)
Inguinal swelling	5 (11)	15 (19)	n.s.	2.5 (0.8-8.1)
No complications	19 (41)	13 (16)	n.s.	n.s.

SLNB: Sentinel lymph node biopsy, ILND: Inguinofemoral lymph node dissection, n.s.: not significant, OR (95% CI): odds ratio 95% confidence interval

### Follow-up and recurrences

Mean follow-up time was 40 months. Recurrences were observed in a total of 47 patients, 19 of which received SLNB, 16 ILND and 12 SLNB+ILND. Mean time to recurrence was 17 months (range: 1-72 months). Forty-two patients suffered a local recurrence, three women a groin recurrence, and two distant metastases. Of the three women who suffered a groin recurrence, two underwent ILND. One patient who underwent SLNB followed by ILND also experienced a groin recurrence, however, given that this patient ultimately received ILND, she was placed in the ILND group. In total, 22 of 128 patients included in this study passed away from intercurrent disease or from unknown causes and 14 succumbed to vulvar cancer. The mean survival time of patients with positive nodes was 37.1 months (standard deviation 8.5 months) and for those with negative nodes was 93.9 (standard deviation 10.8 months) ( $P=0.006$ ). Cancer specific disease free survival was 10.5 (standard deviation 3.1 months). In addition, cancer specific overall survival was 14.5 (standard deviation 3.2 months).

### Discussion

The feasibility of SLN mapping in preventing excessive lymphadenectomies has been previously confirmed in melanoma and breast cancer [25]. Given that the lymph node status in patients with vulvar cancer is an essential prognostic factor, SLN mapping and subsequent SLN removal is vital for tumor staging [10].

In 82 patients, at least one SLN was clearly identified (82/89), which is in accordance with other single, as well as multi-center studies [6, 10, 13, 16, 18, 21, 24-36]. Therefore, the sensitivity of SLN detection in this study was 92%. Interestingly, a recently published multi-center study by Coleman et al [36] was able to demonstrate a negative correlation between distance of vulva lesion from midline and the probability of detecting bilateral drainage in preoperative lymphoscintigraphy. In our patients, only in a small number and only in recent years, lesion distance from the midline is documented. Therefore, it is imperative to employ other intraoperative methods of identification, such as a gamma camera and blue dye. Current consensus for sentinel lymph node detection includes a combination of preoperative lymphoscintigraphy, as well as radioactive isotope and blue dye [35].

In contrast to the guidelines for sentinel node scintigraphy in breast cancer, which state that imaging can be acquired for up to 16-18h after application or other studies which visualized sentinel nodes within three hours [22], our data support optimal pre-operative lymph node visualization already within 60min. However, one must also take into consideration the fact that a small percentage of patients may show drainage later than 60min. Our mean number of sentinel nodes visualized is comparable to that published in the study by Martinez-Palones et al [13], despite their small patient population.

On the other hand, our results confirmed the importance of SLNB by demonstrating that patients who underwent ILND had significantly higher risk of postoperative morbidities. All

of these results are in accordance to those published in previous studies [9-11, 19, 21, 37-39]. A multi-center observational study by Van der Zee et al [37] demonstrated a significant decrease in short- and long-term morbidity, in terms of wound breakdown, cellulitis, recurrent erysipelas and lymphedema in patients who underwent SLNB compared to ILND. While these morbidity factors did not gain significance in our study, they did occur overall less frequently in SLNB patients. One reason for the lack in significance can most likely be attributed to our small population size. However, in our study, a univariate analysis determined the risk for obtaining lymph cysts following ILND to be significantly higher than in SLNB. Twenty-five percent of patients developed a lymph cyst following ILND, which is higher than the 15%-20% reported by Gould et al [9]. The increased risk of lymph cysts could be caused by co-morbidities, such as venous insufficiency of the lower extremities or cardiac insufficiency, given the older age of our patient population diagnosed with this disease [38]. Other risk factors that were associated with ILND, such as bleeding, wound breakage, infection, swelling and sensibility disturbances did not gain significance, most likely due to the small patient number. Interestingly, when assessing patient characteristics and taking FIGO stage into consideration, only the number of removed lymph nodes gained significance ( $P<0.001$ ).

Our study also demonstrated that 30% of patients had sentinel and/or inguinal lymph node metastases, which lies within the range of 17% 32% cited in the literature, depending on tumor stage [7, 8]. Our high rate of metastases could be due to the large number of patients classified at advanced FIGO stages III and IV with lymph node involvement. The majority of patients with FIGO III and IV underwent ILND or SLNB followed by ILND given that these stages of disease are more advanced with positive inguinal lymph nodes. In order to remove all positive inguinal lymph nodes, these patients must undergo complete inguinal lymph node dissection, as only removing the sentinel node would not be enough. Our study was also able to demonstrate that all patients with sentinel-node metastases have a poor prognosis, irrespective of the metastasis size, given that the majority of our node-positive patients contained macrometastatic lymph nodes. In accordance with the GROINSS-V multi-center observational study by Oonk et al [40] the risk of non-sentinel metastases increases in correlation with the size of sentinel-node metastasis. As stated in their study, there is no size cut-off of sentinel metastases under which the possibility of non-sentinel node metastases is very small [40].

Groin recurrence in vulvar cancer is positively correlated with a high mortality rate and often results in a fatal outcome, given the average age a woman is diagnosed [10]. In our study, mean follow-up time was 40 months and mean time to recurrence was 17 months. Previously published studies have demonstrated that one of the most significant prognostic factors for survival is groin node status [40, 41]. Our follow-up data are in accordance with other studies [2, 10, 37]. It is reported that groin recurrences occur in 2%-30% of vulvar cancer patients and usually within the first two years after treatment [10, 12, 42, 43]. In our study population, the groin-recurrence rate in negative nodes was 3%, which is within the 0-5.8% referenced by Van der Zee et al [37] while the overall

groin recurrence rate was 6%, which is respectively low. In their study, Van der Zee et al [37] had a groin recurrence rate of 2.3%, however, one must take into consideration that this was a multi-center study with 276 patients compared to our single-center study with 128 patients. Two of the groin recurrences in our study occurred in patients who underwent ILND, one of which was diagnosed with FIGO I and the other FIGO II. A further patient who suffered a groin recurrence received SLNB followed by ILND, therefore also considered to be an ILND patient, and was diagnosed with FIGO I. Thus, no patient who underwent SLNB suffered a groin recurrence. All of the groin recurrences were observed within two years after treatment, which is in accordance to previous studies [10, 42]. Previously published higher rates of groin recurrences could be due to undetected lymph nodes that contained micrometastases [10, 13, 14, 21, 26, 42]. In addition, tumor emboli in lymphatic channels, which were not removed during surgery, could also cause recurrences in patients with histologically verified negative nodes [12].

A limitation of this study might be the fact that it is a retrospective study. However, we believe that the long duration of this study for 20 years gives credit to its statistics. Furthermore, given the fact that patients with advanced stage vulvar cancer do not qualify for SLNB due to the extensibility of the disease, this may have led to bias in our results when comparing both methods. One must also take into consideration that a small sub-group of these patients was analyzed previously by Hefler et al [21], Sliutz et al [24], and Brunner et al [41] with regards to postoperative morbidity. However, given that this disease is so rare, and no single center study with such a large population was published thus far, we included this sub-group in order to analyze as many patients as possible. Nevertheless, we were able to show significance in postoperative morbidity in patients with vulvar cancer.

In conclusion, the results of our single-center study were able to demonstrate that in SLNB, fewer nodes were removed; operation time, inguinal drainage, and hospital stay were all reduced. No groin recurrences were observed in patients who received SLNB, even when FIGO stage was taken into consideration and not just the operational technique.

The authors declare that they have no conflicts of interest.

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