

# Number of Nodes Removed With Inguinofemoral Lymphadenectomy and Risk of Isolated Groin Recurrence in Women With FIGO Stage IB–II Squamous Cell Vulvar Cancer

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**Aim:** The aim of this study was to evaluate if the lymph node count from inguinofemoral lymphadenectomy impacted the risk of isolated groin recurrence in patients with nodenegative squamous cell vulvar cancer.

**Materials and Methods:** This is a retrospective cohort study of women with squamous cell vulvar cancer (stage IB–II according to the 2009 Revised International Federation of Gynecology and Obstetrics staging system) who underwent primary radical vulvar surgery and groin lymphadenectomy between January 2005 and December 2014. Patients' sociodemographic characteristics, the disease characteristics, the number of nodes removed from each groin, and the oncologic outcome were evaluated. A cutoff value of at least 6 nodes removed from each groin was used to define the adequacy of inguinofemoral dissection.

**Results:** Seventy-six patients, fulfilling the study inclusion criteria, were considered. The mean number of nodes removed (bilaterally) was  $14.5 \pm 5.3$ , SD), with a range of 2 to 29 nodes. Thirty-three women (43.4%) had less than 6 nodes removed from each groin. In the whole study cohort, 4 cases of isolated groin recurrence (5.3%) were detected, and all these recurrences developed in patients with less than 6 nodes removed. Considering the demographic, clinical, and histopathological characteristics potentially related to the risk of groin recurrence, only the number of nodes removed showed a significant correlation.

**Conclusions:** Women treated for vulvar cancer in which less than 6 nodes are removed from each groin are at higher risk of groin recurrence.

**Key Words:** Vulvar cancer, Inguinofemoral node dissection, Groin dissection, Lymphadenectomy, Groin recurrence, Inguinofemoral recurrence

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Vulvar cancer is a rare entity, accounting for approximately 4% of all gynecological malignancies, and most of the cases (90%) are squamous cell carcinomas (SCCs). The treatment of early-stage or locally advanced vulvar cancer is primarily by surgery, and vulvar lesions can be managed by radical wide local excision or radical vulvectomy (or hemivulvectomy), according to the site and the size of the lesions. 1–3

The inguinofemoral node status is the most important prognostic factor for patients with vulvar SCC, <sup>1,4</sup> because the 5-year survival ranges from 70% to 93% for patients without node metastasis to 25% to 41% for those with positive nodes. <sup>4-6</sup> Moreover, the presence of metastatic disease in the groin nodes determines the need for adjuvant treatments. <sup>1-3</sup> Therefore, a careful evaluation of nodal status is paramount. <sup>1</sup> Unfortunately, the poor sensitivity of imaging techniques makes them unsuitable as a substitute for staging lymphadenectomy. <sup>7</sup>

Despite the importance of lymph node status, there have been very few studies assessing the potential prognostic role of the number of nodes removed with inguinofemoral lymphadenectomy, especially in patients with node-negative disease. However, these studies had some evaluation biases; therefore a univocal cutoff of groin nodes to be removed to define the adequacy of lymphadenectomy has not been determined.

In the present study, we have retrospectively analyzed a cohort of patients with node-negative vulvar SCC who underwent a primary radical vulvar surgery and groin lymphadenectomy to evaluate if the number of nodes removed with groin dissection impacted the risk of isolated groin recurrence.

## MATERIALS AND METHODS

All the patients who underwent surgical treatment for vulvar SCC between January 2005 and December 2014 were considered. A histopathological biopsy diagnosis of SCC was obtained in each woman before the surgical intervention, and only women to whom the diagnosis of vulvar SCC was subsequently confirmed on the final histopathological specimen were included in the final analysis.

Only women diagnosed with vulvar SCC for the first time were considered. All the women were treated with a radical wide local resection or modified radical vulvectomy, as appropriate according to size, number, and location of vulvar lesions. <sup>1–3</sup> All the surgical treatments were performed by the same gynecologist with particular expertise in the management of vulvar cancer. Those cases in which a preoperative radiotherapy or a neoadjuvant combined chemoradiotherapy was used were excluded.

Consensual bilateral groin lymphadenectomy (with the removal of both superficial inguinal nodes and deep femoral nodes), according to the standardized surgical technique of preservation of femoral fascia, <sup>11,12</sup> was adopted. In selected cases with a single lateralized tumor, only an ipsilateral lymphadenectomy was performed. <sup>1-3</sup>

All the final histopathological specimens were analyzed by the same pathologist of our institute, with particular expertise in the field of gynecological cancers, avoiding potential interobserver variability. After formalin fixation of the gross specimen, the number of nodes removed was carefully evaluated through microscopic identification and manual isolation. However, to date, the minimal criteria for defining an aggregate of lymphocytes as a lymph node have not been determined, and no one has constructed a set of minimum histological criteria that define a lymph node. Hence, as a working definition, we have considered lymphoid aggregates of greater than approximately 1 mm in diameter, delimited by a capsule and with an identifiable germinal center, to be lymph nodes.

For the present analysis, only patients with tumor stage IB and II, according to the 2009 Revised International Federation of Gynecology and Obstetrics (FIGO) staging system, <sup>14</sup> were considered; therefore, those with positive inguinofemoral nodes were excluded. Women diagnosed and treated before the introduction of the 2009 Revised FIGO staging system were revised accordingly, through the revision of surgical and histopathological reports.

After surgery, all the women treated for vulvar cancer were recommended to adhere to our institutional follow-up program, with gynecological evaluation and vulvoscopy every 3 months for the first 2 years, every 6 months for another 3 years, and then annually. For the present study, only women with at least 2 years of follow-up were considered.

The patients eligible for the present study were identified by searching the clinical databases of our institution, and the medical records of women fulfilling the study inclusion criteria were retrospectively analyzed in an observational cohort study, evaluating all the pertinent clinical, surgical, and histopathological data.

According to previous published studies, <sup>8</sup> for the present analysis, we stratified the cohort of patients by the number of lymph nodes removed, using a cutoff value of at least 6 nodes removed from each groin (based on the 20th percentile value in our dataset) to define the adequacy of inguinofemoral dissection. Therefore, we have considered a surgical groin dissection in which 6 or more nodes were removed from each groin as adequate.

Statistical software IBM SPSS Statistics 22 (IBM Corp, Armonk, NY) was used for data analysis. All continuous variables were tested for normality with the D'Agostino-Pearson test; normally distributed variables were expressed as mean  $\pm$  SD, whereas skewed variables were reported as median and interquartile range. The t test or the Mann-Whitney U test was used for comparison as appropriate. Qualitative variables were expressed as proportions and were compared with  $\chi^2$  or Fisher exact test as appropriate.

Institutional review board approval (CRO IRB no. 07/2014) was obtained.

## **RESULTS**

From January 2005 to December 2014, a total of 179 patients underwent surgery for vulvar cancer at our institution. Among them, 76 patients with FIGO stage IB and II SCC, fulfilling the study inclusion criteria, were considered for the present analysis.

The mean age of the included patients was  $68.9 \,(\pm 12.7, \mathrm{SD})$  years (range, 38-89 years), and most of them were in menopause at the time of diagnosis (88.2%). In 3 cases, a cardiovascular comorbidity (ASA 2 classification) was reported.

Among the patients of the study cohort, 72 (94.7%) had a FIGO stage IB vulvar cancer, whereas a FIGO stage II tumor was observed in the remaining 4 cases (5.3%).

The diameter of the vulvar lesion ranged from 5 to 110 mm, with a median (interquartile range) value of 20 (5–63.5 mm); in 12 cases, the vulvar lesion was 40 mm or larger. A lateralized lesion (a lesion located  $\geq$ 2 cm from the vulvar midline)<sup>1</sup> was observed in 17 patients (22.4%), and 11 patients (14.5%) had multifocal lesions.

At the histopathological examination of the vulvar specimen, 34 patients (44.7%) had a grade I tumor, 32 patients (42.1%) had a grade II tumor, and the remaining 10 patients (13.2%) had a grade III tumor. A lymphovascular space invasion (LVSI) or perineural space invasion (PNI) was reported in 11 cases. A close surgical margin (tumor-free margin <8 mm after formalin fixation)<sup>1</sup> was reported in 25 patients (32.9%), whereas 3 patients had at least one positive surgical margin.

In 4 cases (5.3%) with lateralized lesions, only ipsilateral inguinofemoral lymphadenectomy was performed (with the surgical removal of both superficial and deep nodes), whereas in the remaining patients, a complete bilateral inguinofemoral lymphadenectomy was performed.

In the whole study cohort, a total of 148 groins were surgically dissected.

The mean number of nodes removed (bilaterally) was  $14.5 \pm 3.3$  SD), with a range of 2 to 29 nodes detected (bilaterally).

For the present study, we have considered a surgical groin dissection in which 6 or more nodes were removed from each groin as adequate. Therefore, 33 women (43.4%) had an inadequate dissection. Considering the total number of dissected groins, 43 (29.1%) of 148 groins had an inadequate dissection.

The main demographic and clinical characteristics of women with inadequate lymphadenectomy compared with those with adequate dissection are reported in Table 1.

A total of 11 patients (14.5%) developed a tumor recurrence detected during the routine follow-up examinations. More precisely, 7 cases of local recurrence (9.2%) and 4 cases of isolated groin recurrence (5.3%) were detected. No case of distant metastasis was observed.

Considering the total number of dissected groins (n = 148), the rate of isolated groin recurrence was 2.7%.

The mean time from surgery to recurrence was 30.3 months ( $\pm28.9$ , SD), with a range between 3 and 240 months. Patients who developed an isolated groin recurrence showed a significantly lower mean time from surgery to recurrence compared with patients with local recurrence ( $7.8 \pm 3.7$  months vs  $43.1 \pm 29.3$  months; P = 0.04).

The characteristics of the 11 patients who developed a tumor recurrence are reported in Table 2.

All the cases of recurrence were reported in women with FIGO stage IB vulvar cancer, and all of them underwent a complete bilateral inguinofemoral lymphadenectomy.

Four patients developed an isolated groin recurrence, and in all of these cases, the inguinofemoral lymphadenectomy was inadequate, with the removal of less than 6 lymph nodes per groin. Interestingly, in all these cases, the recurrence developed in the very groin in which the dissection was inadequate (Table 2).

Comparing the 33 patients with inadequate inguinofemoral dissection with those who received an adequate lymphadenectomy, the risk of isolated groin recurrence was significantly higher (12.1% vs 0%, P = 0.03). Such a difference persisted even when considering not only the 76 patients but also the 148 dissected groins and comparing the 43 groins with inadequate dissection with the remaining 105 with adequate dissection (9.3% vs 0%, P = 0.006).

Table 3 reports the main demographic, clinical, and histopathological characteristics of the study population with respect to the risk of isolated groin recurrence. Among all the evaluated characteristics, only the number of nodes removed (adequate dissection) showed a significant correlation with the risk of groin recurrence.

As a secondary analysis, we evaluated the rate of surgical complications after groin dissection in the study cohort. A total of 20 cases of postoperative complications were detected (26.3%). More precisely, we reported 3 cases of chronic lymphedema

**TABLE 1.** Demographic and clinical characteristics of the study cohort with respect to the number of nodes removed with inquinofemoral lymphadenectomy

Characteristics	Inadequate Lymphadenectomy (n = 33)	Adequate Lymphadenectomy (n = 43)	P
Age, y	69.1 ± 13.9	68.8 ± 11.8	0.9
Menopause	29 (87.9%)	38 (88.4%)	0.8
Comorbidity (ASA score 2+)	1 (3%)	2 (4.7%)	0.6
BMI	$25.9 \pm 5.4$	$26.9 \pm 3.7$	0.4
FIGO stage II	_	4 (9.3%)	0.2
Dimension, mm	$25.8 \pm 16.5$	$24.8 \pm 19.6$	0.8
Diameter ≥40 mm	6 (18.2%)	6 (13.9%)	0.8
Lateralized lesions	6 (18.2%)	11 (25.6%)	0.6
Multifocal lesions	5 (15.2%)	6 (13.9%)	0.9

Data are expressed as mean ± SD or n (%) as appropriate.

Inadequate lymphadenectomy means groin dissection in which less than 6 nodes have been removed in at least one groin; lateralized lesion means a lesion located  $\geq 2$  cm from the vulvar midline.

BMI indicates body mass index.

Clinical and histopathological characteristics of women with recurrence of vulvar cancer TABLE 2.

								Nodes	Nodes		Time From
Patient			Dimension of	į.	Histopathological	LVSI	Close	Removed	Removed	Site of	Surgery to
Number Age, y BMI	Age, y	BMI	the Lesion	Lesion	Grading	or PNI	Margins	(Right)	(Left)	Recurrence	Recurrence, mo
9	99	31.3	20 mm	Central	1	No	No	10	10	Local	59
11	42	27	15 mm	Lateralized	2	No	Yes	6	6	Local	75
22	4	21.8	25 mm	Central (multifocal)	2	No	Yes	10	5	Left groin	12
28	89	26.1	15 mm	Central	1	No	No	9	9	Local	83
33	74	22.3	60 mm	Central (multifocal)	1	No	No	3	7	Local	13
45	82	23.6	8 mm	Central	2	No	No	9	3	Local	36
49	70	27.3	35 mm	Lateralized	1	No	Yes	10	3	Left groin	3
51	81	28.3	15 mm	Central	2	No	No	9	S	Left groin	∞
52	87	23	45 mm	Central	2	No	Yes	3	3	Right groin	∞
53	49	32.5	10 mm	Central	2	Yes	Yes	7	S	Local	24
59	89	26	35 mm	Central (multifocal)	1	No	Yes	3	6	Local	12
Close	naroins me	ean filmo	r-free maroin <8	Oose maroins mean nimor-free maroin <8 mm after formalin fixation. Jateralized Jesion means a Jesion Jocated >7 cm from the vulvar midline	ion: lateralized lesion r	neans a le	ion located	>2 cm from t	oe vulvar mid	lline	

vulvar midline. cm mom me 4 mm after formalln fixation; lateralized lesion means a lesion located  $\geq 2$ Ciose margins mean unnor-tree margin ' BMI indicates body mass index.

**TABLE 3.** Demographic, clinical, and histopathological characteristics of the study cohort with respect to the risk of isolated groin recurrence

Characteristics	Isolated Groin Recurrence (n = 4)	No Groin Recurrence (n = 72)	P
Age, y	70.5 ± 19.1	68.9 ± 12.4	0.8
BMI	$25.1 \pm 3.2$	$26.7\pm3.1$	0.3
Comorbidity		3 (4.2 %)	0.4
FIGO stage II	_	4 (5.6%)	0.5
Dimension, mm	$30 \pm 12$	$25 \pm 19$	0.6
Diameter ≥40 mm	1 (25%)	11 (15.3%)	0.8
Positive margins	_	3 (4.2 %)	0.4
Close margins	3 (75%)	22 (30.6%)	0.2
Grading G2/G3	3 (75%)	39 (54.2%)	0.8
LVSI or PNI		11 (15.3%)	0.9
Central lesions	3 (75%)	56 (77.8%)	0.6
Multifocal lesions	1 (25%)	10 (13.9%)	0.9
Inadequate lymphadenectomy	4 (100%)	29 (40.3%)	0.03

Data are expressed as mean  $\pm$  SD or n (%) as appropriate.

Close margins mean tumor-free margin <8 mm after formalin fixation; central lesion means a lesion located on the vulvar midline or <2 cm from the midline; inadequate lymphadenectomy means groin dissection in which less than 6 nodes have been removed in at least 1 groin.

BMI indicates body mass index.

(3.9%); 9 cases of lymphocele (11.8%), 4 cases of surgical site infection (5.3%), 2 cases of cellulitis with cutaneous necrosis (2.6%), and 2 cases of suture dehiscence (2.6%). These 20 cases of postoperative groin complications were detected in 6 patients with inadequate groin dissection and in 14 patients with adequate groin dissection, with a similar rate (18.2% vs 32.5%, P = 0.3). The complications rates observed in our cohort in comparison to other publications are reported in Table 4.

### DISCUSSION

Vulvar SCC is a rare gynecological malignancy, and in the last decades, its standard surgical treatment has changed dramatically from aggressive, disfiguring surgery to a more focused and conservative radical approach. The search for more conservative techniques derives both from the well-recognized psychosexual sequelae associated with radical vulvectomy and from the morbidity related to the groin node dissection. 2,15

The status of inguinofemoral nodes is the most important prognostic factor in patients with vulvar SCC, <sup>1,4–6</sup> thus a proper surgical and histopathological evaluation is mandatory. Moreover, an appropriate groin node dissection is considered the greatest single factor in reducing the mortality from vulvar cancer.<sup>2</sup>

To date, the groin dissection with preservation of femoral fascia<sup>11,12</sup> is the most commonly used procedure for radical inguinofemoral lymphadenectomy in women with vulvar SCC.

TABLE 4. Comparison between the incidence of wound complications in the current cohort and other published data

<b>Wound Complications</b>	<b>Current Study</b>	Soliman et al (2012)	Gaarenstroom et al (2003)	<b>Gould et al (2001)</b>
Wound cellulitis	2.6%	24.2%	Not studied	35.4%
Wound breakdown	2.6%	9.7%	11%	19.4%
Wound infection	5.3%	3.2%	27%	Not studied
Groin lymphocele	11.8%	12.5%	27%	13.1%
Chronic lymphedema	3.9%	4.8%	21%	4.8%

This surgical procedure preserves normal tissues and structures in the groins, whereas removing only the inguinal and femoral nodes potentially involved in the spread of metastatic cells from vulvar lesions. <sup>11</sup> Thus, this surgical technique provides optimal oncologic outcomes with a relatively low rate of postsurgical complications. <sup>11</sup>

According to the most recent international guidelines, <sup>1–3</sup> even the sentinel node (SLN) biopsy can be proposed as an alternative standard-of-care approach in selected women with vulvar SCC, because prospective trials have demonstrated feasibility, safety, validity, and low risk of groin recurrence. <sup>16,17</sup> However, only patients with negative groins on clinical examination or imaging, primary unifocal vulvar tumor of less than 4 cm maximum diameter, and no previous vulvar surgery can be suitable for SLN biopsy. <sup>1</sup> In addition, if SLN biopsy is considered, it ideally should be performed by a high-volume SLN surgeon, as high-volume surgeons exhibit improved SLN detection rates. <sup>1</sup> Thus, only well-selected patients with vulvar SCC could really benefit from this minimally invasive approach, and this is probably the main limitation of this technique.

Therefore, due to the restricted field of application of SLN in daily clinical practice, in our opinion, it is important to focus on the traditional surgical approach with radical inguino-femoral lymphadenectomy, which can be used even in women unsuitable for SLN biopsy. Furthermore, data about women treated with SLN biopsy were not available for the present analysis because such an evaluation was not routinely performed in our institution during the study period.

The currently available guidelines do not provide a univocal and explicit definition of appropriate or adequate groin dissection, only assessing the importance of a radical dissection of both superficial and deep inguinofemoral nodes. <sup>1–3</sup> The anatomical boundaries of such a dissection are widely described elsewhere, <sup>11,12</sup> and the inguinofemoral lymphadenectomy with preservation of femoral fascia has become a standardized and widely used surgical technique.

Unfortunately, even the most recent guidelines do not define the number of nodes to be removed to consider the groin dissection as adequate. 1–3

Furthermore, there have been very few studies assessing the potential prognostic role of the number of nodes removed, especially in patients with node-negative disease. Also, these studies have some conceptual biases: most of them considered the total count of lymph nodes removed, regardless of whether a unilateral or bilateral lymphadenectomy was performed. Moreover, evaluating the potential prognostic impact of the number of nodes removed, women with node-negative and node-positive vulvar SCC were often considered together. In

addition, the end point considered was the overall survival rate or the disease-specific survival rate. Obviously, this would include patients with local recurrence and patients whose death was not related to groin disease. We believe that the detection of isolated groin recurrence is a more appropriate end point for such an evaluation. Interestingly, the authors of the aforementioned studies reported different cutoff of nodes to be removed for an adequate groin lymphadenectomy.

Moreover, it is important to highlight that the lack of consensus about the number of nodes to be removed to obtain an adequate groin dissection could not only reflect the variation in individual anatomy but also differences in surgical techniques and skills, and pathologists' efforts to identify and analyze the nodes within the surgical specimen.<sup>4,11</sup>

In the present study, to avoid the potential bias due to interindividual variability, all the surgical procedures were performed by the same senior gynecologist, with particular expertise in the surgical treatment of vulvar SCC. For the same reason, all the surgical specimens were analyzed by the same senior pathologist of our institution, with particular expertise in vulvar malignancies.

Obviously, the adequacy of lymphadenectomy should be firstly obtained anatomically by dissection boundaries: it is indeed well known that the surgical groin dissection with preservation of femoral fascia<sup>11,12</sup> offers a better oncological outcome compared with the dissection of only superficial inguinal nodes. <sup>18–20</sup> However, the maximum surgical effort should be made to obtain also an adequate node count from groin dissection, even if this goal it is not always easy to reach.

In the present study, we have considered a surgical groin dissection in which 6 or more nodes were removed from each groin as adequate, and we observed a significantly higher risk of isolated groin recurrence in patients with inadequate inguinofemoral dissection.

Interestingly, none of patients' demographic and clinical characteristics evaluated seems to be related to the adequacy of groin dissection (Table 1).

In our cohort, we found 4 cases of isolated groin recurrence, all of them occurring in women who underwent bilateral groin dissection; interestingly, all the recurrences developed in the very groins with inadequate dissection. Moreover, among all the variables potentially involved, only the number of nodes removed appeared to be related to the risk of groin recurrence in our cohort. It is also interesting to observe that all the isolated groin recurrences developed in the first year after the surgical treatment.

However, it is not easy to define a univocal cutoff of nodes to be removed to consider the inguinofemoral dissection in every single patient as adequate, especially because of the potential anatomical interindividual variability. For this reason, in our opinion, to date, there is no sufficient evidence to suggest an adjuvant therapy in women with inadequate groin dissection. Further studies on large cohorts assessing this topic would be of particular relevance.

Nevertheless, considering the higher risk of groin recurrence in women with less than 6 nodes removed from each groin, they could benefit from closer follow-up evaluations, especially in the first months after surgery.

In our cohort, almost 30% of groins did not undergo an adequate surgical dissection. This datum reflects the surgical difficulty of groin dissection (and thus the necessity of an experienced gynecologist) but could even be an expression of the lack of well-defined histopathological criteria for lymph node identification, <sup>13</sup> thus the identification of univocal and shared pathological criteria would be desirable.

As a secondary analysis, we evaluated the rate of surgical complications after groin dissection in our study cohort. It is interesting to observe that, if the surgical procedure is properly performed by an experienced gynecologist, the rate of postsurgical complication seems not to be related to the number of nodes removed. In our cohort, a total of 20 cases of postoperative complications were detected. Compared with previous published data (Table 4), a lower rate of wound cellulitis and wound breakdown emerged. This might be explained by the routine use of prophylactic antibiotics and daily wound cleansing. Interestingly, we reported only 3.9% of patients with chronic lymphedema. Probably the routine use of compression stockings led to this result. However, proper well-designed randomized trial could be useful to clarify if these procedures really led to a reduction of early and late postsurgical complications in women treated with inguinofemoral lymphadenectomy.

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