

Lymph Node Count at Inguinofemoral Lymphadenectomy and Groin Recurrences in Vulvar Cancer

Heleen J. van Beekhuizen, MD, PhD,* Maria Auzin, MD,† Loes C.G. van den Einden, MD,‡
Johanna A. de Hullu, MD, PhD,‡ Jacobus van der Velden, MD, PhD,§ Mark F. Wildhagen, PhD,||
and Helena C. van Doorn, MD, PhD*

Objective: The objective of the study is to determine the risk factors for groin recurrence (GR) in patients with primary vulvar squamous cell carcinoma (SCC) after inguinofemoral lymphadenectomy (IFL) without lymph node metastases and/or adjuvant chemoradiotherapy.

Methods: The study is a multicenter retrospective review of clinical and histopathological data of patients with lymph node-negative vulvar SCC who underwent an IFL. Patients with and without GRs were compared to identify risk factors.

Results: In 134 patients, 252 groins were eligible for the analyses—16 patients underwent ipsilateral IFL and 118 patients underwent bilateral IFL. Groin recurrences occurred in 4 (1.6%) of the 252 dissected groins. Besides, 1 patient who underwent ipsilateral IFL had a recurrence in the nonoperated contralateral groin; this groin was left out of analysis. The median number of dissected nodes per groin was 9.8 (range, 1–38) in all patients and 6.5 (range, 5–8) in patients with GR. Multivariate analyses showed that GR was related to poor differentiation ($P = 0.04$), and node count less than 9 ($P = 0.04$), no association with age, tumor localization, tumor diameter, focality, invasion depth, or stage was found. Nineteen patients with both low node count and poor differentiation had 19% GRs. Survival analyses showed less favorable survival in patients with poor differentiation.

Conclusions: The overall risk of developing GR after negative IFL in patients with vulvar SCC is low (1.6% per groin) but significantly higher in patients with tumors with a poor differentiation and lymph node count less than 9 at IFL. A large well-designed prospective study is needed to evaluate closer surveillance in patients at risk.

Key Words: Vulvar cancer, Groin recurrences, Inguinofemoral lymphadenectomy, Squamous cell carcinoma

Received January 2, 2014, and in revised form February 16, 2014.

Accepted for publication February 18, 2014.

(*Int J Gynecol Cancer* 2014;24: 773–778)

*Erasmus MC Cancer Centre, Rotterdam, the Netherlands; †ZNA Middelheim, Antwerp, Belgium; ‡Radboud University Medical Center, Nijmegen; §Center for Gynaecologic Oncology Amsterdam, Academic Medical Center, Amsterdam; and ||Erasmus Medical Center, Rotterdam, the Netherlands.

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ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000000125

Address correspondence and reprint requests to
Heleen J. van Beekhuizen, MD, PhD, Department of
Obstetrics and Gynecology, Erasmus MC Cancer Centre,
PO Box 5201, 3008 AE Rotterdam, the Netherlands.
E-mail: h.vanbeekhuizen@airpost.net.

Disclosure of funding: no funds were received for
this research.

The authors declare no conflicts of interest.

Inguinofemoral lymphadenectomy (IFL) plays a central role in the surgical treatment of squamous cell carcinoma (SCC) of the vulva as part of the staging procedure and to remove metastatic disease.¹ Surgical management of SCC of the vulva is tailored; in tumors larger than 4 cm and in multifocal tumors, an IFL is performed. In many European countries, IFL is currently replaced by sentinel node (SN) procedure in patients with unifocal lesions less than 4 cm because of the low groin recurrence (GR) risk after negative SN and the reduction of morbidity.^{2,3}

Groin recurrences in previously dissected groins (without lymph node metastases) infrequently occur with a reported incidence of about 1.3% to 4.3%.⁴ Nevertheless, they carry a very poor prognosis, with reported median survival of only 9 months.⁵ As a result, great efforts should be made at the time of primary treatment to minimize the risk of GR, and it may be advantageous to select patients that have a high risk for GR after IFL.

It is suggested that the number of dissected lymph nodes correlates with GRs. In 2010, a SEER analysis in patients with node-negative SCC of the vulva showed that overall survival (OS) and disease-free survival differed between patients with 10 or less versus patients with 11 or more dissected lymph nodes; a hazards ratio of 1.5 (95% confidence interval [CI], 1.16–1.94) for OS and 1.71 (95% CI, 1.08–2.71) for disease-free survival was reported.⁶ However, from this study, it is unclear whether lymph nodes were counted per groin, where the recurrences were located, and what type of primary surgery was performed. Butler et al⁴ published a retrospective study of 139 patients (228 groins) with IFL for SCC of the vulva. In 3 of the 89 patients who underwent a bilateral IFL and in 3 of the 50 who underwent unilateral IFL, a GR occurred. Based on these 6 GRs, a node count below 8 was found to be a risk factor for GR ($P=0.03$). However, the 3 GRs in the patients who underwent unilateral IFL were located in the contralateral, undissected groin. It is not clear if and how this affected the node count. Other studies involve GR after superficial IFL only,^{7,8} a technique that is currently abandoned in favor of complete (superficial plus deep) IFL or SN assessment.^{1,9}

We present a study that investigates whether there is a minimal nodal count that can be considered to represent an adequate IFL with a low rate of GRs. Furthermore, we studied other tumor characteristics that may give increased risk for GRs.

MATERIALS AND METHODS

A retrospective review of clinical and histopathological data was performed of patients with primary SCC of the vulva who have been treated at 3 Dutch university hospitals—the Cancer Center at the Erasmus Medical Center in Rotterdam, the Academic Medical Center of Amsterdam, and the Radboud University Medical Center in Nijmegen, the Netherlands—between January 2000 and December 2010. Patients underwent ipsilateral IFL in lateralized and bilateral IFL in central (medial margin <1 cm from midline) SCC of the vulva. In patients with unilateral IFL, only GRs in the dissected groin were analyzed. The uniform technique of complete IFL was performed via separate incisions, and all lymph nodes

superficial to the inguinal ligament and lymph nodes under the cribriform fascia were removed. The upper limit of the dissection was 2 cm above the inguinal ligament to include all the inguinal nodes. All subcutaneous tissues superficial to Scarpa's fascia were preserved to minimize skin necrosis. In general, the saphenous vein was spared. The fascia lata overlying the femoral blood vessels was opened, and the fatty tissue containing the femoral lymph nodes was removed from within the fossa ovalis.¹

Patients with stage I and II vulvar cancer (FIGO 2009)¹⁰ who underwent IFL, had negative groin nodes, and did not receive adjuvant chemoradiotherapy were included in the analyses. Patients were identified through a national pathological data base (PALGA). Clinical data included age, tumor localization, tumor diameter, and unifocality or multifocality. Pathological data included depth of invasion, grade, vascular space invasion, tumor-free margin, and nodal disease. Pathologists with special interest in gynecologic oncology examined the specimen in a similar way in all institutions. Information on the time and site of recurrences and the vital status were retrieved, and in case of death, the cause and date of death were registered. The end point of this study was the first recurrence in a groin that was clinically and pathologically confirmed. Groin recurrence was defined as a recurrence located in the anatomic site where the previous IFL took place; bridge recurrences were not considered as GRs.

In 2009, the FIGO classification for SCC of the vulva changed. To compare our data with existing literature, we have used the FIGO (1988) classification in our analyses for all patients.^{10,11}

From 2000 onwards, the SN dissection was introduced and practiced in the Netherlands in the setting of a clinical trial; nearly all “low risk” patients (unifocal tumor ≤ 4 cm) were included.² As a result, most of the patients in our study have either a tumor greater than 4 cm or multifocal disease. Patients who declined to enter the SN trial, and patients in the trial in whom SN detection was not possible because of technical failure, underwent an IFL and were included in our study as well.

Statistical analyses were performed using SPSS version 20.0. The risk factors of recurrence were tabulated, and descriptive statistics and histograms were used to summarize empirical distributions of negative node counts by GR status. Statistical significance of association between risk factors and GR status were assessed by Fisher exact test and Pearson χ^2 test. The multivariate analysis was conducted using backwards logistic regression and the survival analyses by Kaplan-Meier analyses. In the multivariate analysis, we used a model with all parameters with a P value of 0.20 or less in the univariate analysis. A P value of less than 0.05 was considered to be significant.

According to Dutch law on ethics and research, retrospective research that does not involve administration of study medication or interventions are exempted from obtaining permission from an ethical committee.

RESULTS

In the study period (2000–2010), 134 patients with primary SCC of the vulva met our inclusion criteria; 4 patients

TABLE 1. Patient characteristics of 134 patients with SCC of the vulva and negative IFL

	No GR (n = 130)	GR (n = 4)
Age, mean (SD), y	68.8 (13.6); range, 27–95	62.8 (18.2); range, 38–78
Diameter of vulvar tumor, mean (SD), mm	35.4 (18.6); range, 7–90	39.3 (14.1); range, 25–47
Tumor ≤20 mm, n	36	0
Tumor >20 mm, n	94	4
Depth of invasion, mm	7.3; range, 0.7–35	7.5; range, 3–15
Multifocal tumor, n	35	2
Unifocal tumor, n	95	2
Follow-up, mean (SD), mo	44.6 (33.2); range, 1–145	25.8 (21.0); range, 12–35
Lost to follow-up	0	0
Local recurrence	25 (19.2%); 1 skin bridge (0.8%)	0
Death of disease	10 (7.7%)	3 (75%)
Local recurrence	5	
Skin bridge	1	
Pelvic recurrence	2	
Distant recurrences	2	
GR	N/A	3
Death of other causes	20 (15.3%)	0

had GRs and 130 patients had not. One patient had a recurrence in a contralateral, not dissected groin, so this groin was left out of the analysis. Patient characteristics are displayed in Table 1. Age at diagnosis ranged from 27 to 95 years (mean, 68.6 years) and follow-up duration from 1 to 145 months (mean, 44.0 months). The 4 patients with lymph node recurrence had additional imaging to discover concomitant metastatic disease; in 2 of the 4 patients, positive pelvic lymph nodes were discovered.

A total number of 252 groins were dissected in 134 patients (118 bilateral and 16 unilateral) with a wide variation in the number of negative nodes collected per groin ranging from 1 to 38 (mean [SD], 9.8 [4.7]; median, 9.0) (Fig. 1). Node count less than 9 was present in 112 (44.4%) of the 252 IFLs.

Four patients (1.6%) had a unilateral GR in the 252 previously dissected groins. The number of negative nodes dissected in patients with GR ranged from 5 to 8 (2 patients had 5 and 2 patients had 8 nodes dissected; mean [SD], 6.5 [1.7]). In patients with GR, a significantly lower number of nodes ($P = 0.038$) were dissected in comparison with patients that did not have a GR. All GRs occurred between 5 and 17 months (mean, 12.5 months). Of the 4 patients with GR, 3 died of disease and one is still alive (follow-up time, 57 months) without evidence of disease.

A univariate analysis was conducted including clinical and histopathological parameters of 252 IFLs (Table 2). A node count less than 9 ($P = 0.038$) and a poor differentiation ($P = 0.038$) were significantly related to GR. All other parameters such as age, diameter, depth of invasion, or focality were not significantly different between patients with or without a GR.

In the multivariate analysis, the 3 univariate risk factors for GR with a $P < 0.20$ were included. Both node count less

than 9 and differentiation grade were significant ($P < 0.05$) whereas invasion depth was not ($P = 0.48$).

Of the 52 patients with a poorly differentiated tumor, GR occurred in 3 (5.7%). When both risk factors (poor differentiation grade and node count <9) were present, GR occurred even more frequent, in 3 (19%) of 16 groins ($P = 0.025$).

The Kaplan-Meier survival curves showed that the disease-specific survival (DSS) was similar in the group with node count less than 9 and node count 9 or more (Fig. 2). The DSS was shorter in the group with poor differentiation compared with well and moderately differentiated tumors

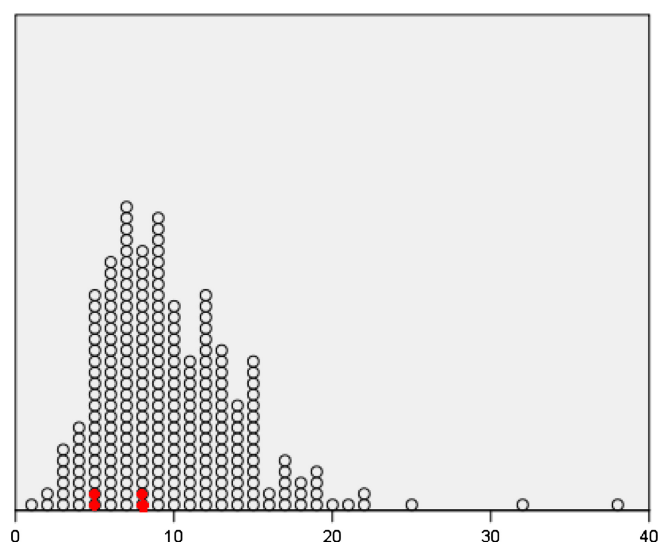
**FIGURE 1.** Histogram of the number of lymph nodes removed in 252 groins in 134 patients with SCC of the vulva. The red dots represent groins with GR.

TABLE 2. Univariate analysis of 252 dissected groins

	No GR (n = 248)	GR (n = 4)	P
Node count <9	108	4	0.038
Largest diameter, mean (SD)	35.4 (18.6); range, 7–90	39.3 (14.1); range, 25–47	0.54
Focality			0.30
Unifocal	180	2	
Multifocal	66	2	
Missing	2		
FIGO (1988) stage			1.00
<T2	78	1	
T2	138	3	
>T2	32		
Localization tumor			0.41
Central	168	2	
Lateral	74	2	
Missing	6		
Surgical margin tumor, mm			0.65
<8 mm	76	2	
≥8 mm	149	2	
No margin	7		
Missing	16		
Depth of invasion, mean (SD), mm	7.5 (6.3); range, 1–35	12.0 (8.0); range, 3–21	0.19
LVI			1.00
No	84	2	
Yes	17	0	
Missing	149	2	
Differentiation grade			0.038
Well	82	0	
Moderate	113	1	
Poor	49	3	
Missing	4		

(Fig. 3). Figure 4 displays the DSS of patients with poorly differentiated tumors with a node count 9 or more and less than 9, and the latter had a poorer DSS.

DISCUSSION

Groin recurrence is a rare but often fatal complication in SCC of the vulva. In this study, we conclude that in T_{any} N0 M0 vulvar tumor, a node count less than 9 lymph nodes and poor differentiation of the tumor are risk factors for GR in SCC of the vulva in previously dissected groins.

An isolated GR in a groin with negative lymph nodes after inguinofemoral lymph node dissection can theoretically be caused by either remaining nodal tissue, which could be considered as inadequate surgery or histopathology at which micrometastasis in nodes where not resected, or in transit metastases in afferent lymph channels that can hardly be influenced by more radical surgery. Our study involved patients who underwent complete groin dissection. A recurrence rate

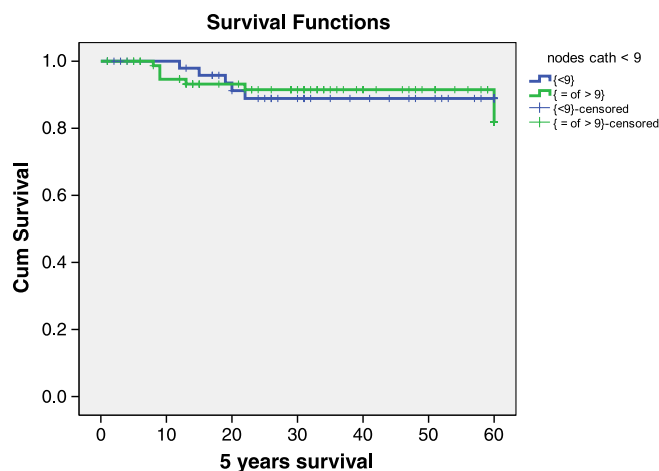


FIGURE 2. Disease-specific survival for patients with node count less than 9 and 9 or more lymph nodes per groin ($P = 0.40$).

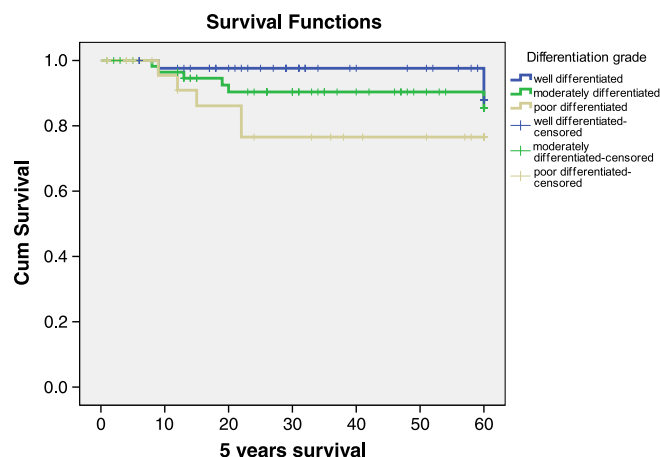


FIGURE 3. Disease-specific survival for patients according to differentiation grade ($P = 0.03$).

of 1.6% per groin was found, which is similar to the 1.3% GR reported by Butler et al.⁴ Both are in contrast to a review on superficial IFL where a recurrence rate of 5.3% (95% CI, 3.2%–8.2%) was found.⁷ This confirms the importance of performing a complete IFL in SCC of the vulva.

The mean number of lymph nodes dissected in our study was 9.8, slightly higher than in the study of Butler et al.⁴ (mean, 8.7). A major drawback of the study of Butler et al.⁴ is that 3 of the 6 GRs occurred in the contralateral non-dissected groin, and therefore, this does not reflect a possible inadequacy of the surgical technique. A large variation of the number of resected nodes was observed in our study, with the 25 and 75 percentiles at 7 and 12 nodes. Overall survival was independent of the number of removed nodes. Therefore, the conclusion of an “adequate” node dissection cannot be made based on the number of nodes removed, so the surgical limitations should be leading in this respect. This is in contrast with the epidemiological SEER study,⁶ in which the authors concluded that the removal of more than 10 nodes was associated with a significantly higher OS. Moreover, the SEER study was different from ours in primary outcome, namely, OS versus GRs. Substantial information about adjuvant treatment, number of recurrences, site of recurrences, and the number of nodes per groin were missing in the SEER publication.

In the present study, no patients with a node count of 9 or more did have a GR. It should be noted that in only 140 (56%) of the 252 of the groins, 9 or more nodes were removed. Butler et al.⁴ reported no GR in groins with a node count of 8 or greater. Both results are in the same (clinical) range.

A second identified risk factor for GR was a poor differentiation of the tumor; in 3 (5.8%) of the 52 groins with poor differentiation, a GR occurred ($P = 0.038$). These data are in line with the study of Butler et al.⁴; they found 1 (2.2%) of 46 GR in well-differentiated tumors compared with 5 (5.4%) of 93 in moderately/poorly differentiated tumors ($P = 0.66$). We found that when both risk factors (node count <9 and poor differentiation) were present, the incidence of GR was the highest (19%).

A concern raised is that in 1 (6.3%) of 16 patients developed a GR in the contralateral, undissected groin after ipsilateral IFL. This is in concordance with Butler et al.⁴, who reported 3 contralateral recurrences (6.0%) of 50 undissected groins after ipsilateral IFL. This percentage is much higher than reported previously.^{9,12,13} The first studies on ipsilateral IFL showed that recurrence rate was low (<1%) in patients with lateralized (>1 cm from midline), unifocal tumors less than or equal to 2 cm without ipsilateral metastasis located posterior from the clitoris,^{9,12} whereas a later published study showed a risk of recurrence after ipsilateral IFL of 2.5%.¹³ The recommendation to perform only an ipsilateral lymph node dissection in lateralized tumors in which the ipsilateral groin nodes are negative is based on these studies.^{9,12,13} A recent publication of the GOG 173 group showed a significant reduction in drainage of vulvar cancer to the contralateral groin when the tumor was more lateralized—70% of midline tumors, 58% of lateral/ambiguous tumors, and 22% of lateral tumors drained to the contralateral groin.¹⁴ The 6% contralateral recurrences that were reported in our study and in the study of Butler et al.⁴ can be due to a sliding scale; more patients underwent ipsilateral IFL who did not strictly fulfill the original stringent criteria of a unifocal lateral small (diameter, ≤ 2 cm) tumor dorsal of the clitoris.

The analysis of the role of lymphovascular space invasion (LVSI) was not possible because of the missing data in about 60% of our patients. In previous studies, the role of LVSI on OS were inconclusive; 2 studies showed reduced OS,^{15,16} whereas in another study, the presence of LVSI was not significantly associated with a shorter OS.¹⁷ In the study of Butler et al.,⁴ there was only a trend in association between LVSI and GR ($P = 0.08$).⁴

Both the retrospective design and the lack of central pathology review are weak points of our study. Until now, no prospective studies about risk factors for GRs are available most likely because of the low incidence of both SCC of the vulva and GR after deep and superficial dissection. Although a central pathology review was not performed, all specimens were examined by dedicated gynecological pathologists in

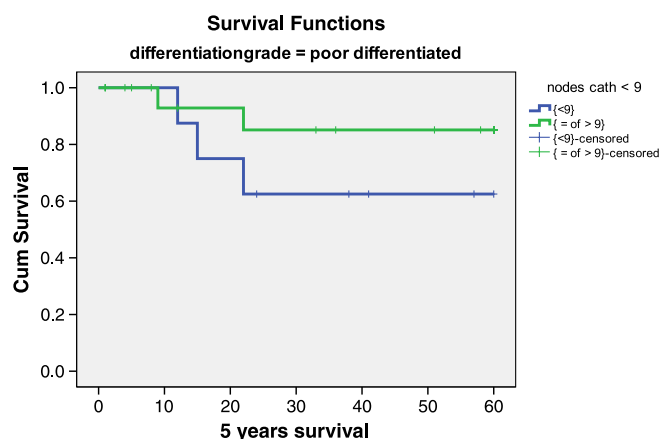


FIGURE 4. Disease-specific survival for patients with poorly differentiated tumors in relation to node count ($P = 0.025$).

university cancer centers according a standardized protocol. It is generally assumed that the number of lymph nodes found is related to the efforts of the pathologists,¹⁸ but proof is lacking.

Three of 4 patients with GR died. Kaplan-Meier survival analyses showed that poor differentiation of the primary tumor decreased the 5-year DSS although node count less than 9 lymph nodes did not. This may be due to the high incidence of node count less than 9 (44%) in relation to the relative low incidence of GR (1.3%). Disease-specific survival was lower in poorly differentiated tumors with a node count less than 9 than in a node count 9 or more.

In conclusion, the risk of developing an isolated GR after a negative IFL in patients with vulvar SCC is low (1.6% per dissected groin). A significant relation between a node count less than 9 ($P = 0.038$) and/or poorly differentiated tumor ($P = 0.038$) with isolated GRs was found. A combination of both risk factors was present in 3 of 4 patients with GRs. A properly performed complete inguinofemoral lymph node dissection is warranted to avoid remaining nodal tissue potentially harboring metastatic foci. A strict selection of patients for ipsilateral or bilateral groin dissection is important to prevent GR in the contralateral undissected groin. For current practice, we would not yet like to suggest adjuvant treatment in the high risk group. Further studies are needed to confirm these findings and to define patients who can benefit from adjuvant treatment.

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