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Vulvar cancer : pathogenesis, molecular genetics and treatment

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CHAPTER 3

Groin surgery and risk of recurrence in lymph node positive patients with vulvar squamous cell carcinoma

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Abstract

Objectives: Treatment of groin metastasis in vulvar squamous cell carcinoma (VSCC) patients consists of surgery, often combined with (chemo)radiotherapy, and is associated with significant morbidity. Our aim was to compare the risk of groin recurrence and morbidity in patients with lymph node positive VSCC after standard full inguinofemoral lymphadenectomy (IFL) versus less radical debulking of clinically involved lymph nodes or removal of sentinel nodes only followed by radiotherapy.

Methods: A retrospective cohort study of 68 patients with primary VSCC and proven lymph node metastasis to the groin(s) was conducted. Patients were divided into three subgroups by type of initial groin surgery (84 groins): sentinel node (SN), IFL, and debulking of clinically involved nodes. Most patients (82%) received adjuvant radiotherapy. Overall survival was analyzed using time dependent cox regression. Analysis of morbidity and groin recurrence-free time was performed per groin with the generalized estimating equation model and Kaplan Meier method.

Results: There was no significant difference in the risk of developing a groin recurrence (SN 25%, debulking 16%, IFL 13%, $p=0.495$). Despite the fact that more patients received radiotherapy after debulking (90% vs 67%), the complication rate was significantly lower ($p=0.003$) compared to IFL, especially regarding lymphocysts and lymphedema ($p=0.032$ and $p=0.002$ respectively).

Conclusions: The risk of groin recurrence was similar in all treatment groups. Debulking of clinically involved lymph nodes was related to a significant lower risk of complications compared to IFL. These findings support that the preferred treatment of patients with clinically involved lymph nodes is debulking followed by radiotherapy.

Introduction

Vulvar cancer is a rare disease, representing about 4% of all female genital cancers. The majority of these tumors (90%) are vulvar squamous cell carcinomas (VSCC)(1). Most patients present with early stage disease, which has an excellent 5-year survival rate of up to 90% (2, 3). The presence of groin metastases is the most significant negative predictor for survival (2, 4, 5) with reported 5-year survival rates ranging from 0 to 51% (3, 6, 7). In VSCC patients with early stage disease the incidence of groin metastases is 20-30%, whereas in patients with advanced disease, the incidence can be as high as 60% (2, 3, 8, 9). Patients with groin metastases have an increased risk of groin recurrence (2, 8-11), which is fatal in almost all patients (12-14).

The cornerstone of treatment for vulvar cancer is surgery(1, 5). Surgery for all VSCC stages used to be extensive before 1980, consisting of en-bloc radical vulvectomy and bilateral dissection of the groins and enlarged pelvic nodes, leading to a high risk of morbidity, such as wound infections, wound breakdown, lymphocysts and lymphedema. Last decades, treatment consisted of local radical excision with separate groin incisions, with still high morbidity rates (9, 15-20). For patients with a unifocal tumor of 4 cm or less, without suspicious groin nodes on ultrasonography or CT-scan, the sentinel node (SN) procedure has proven to be a safe treatment, with reported groin recurrence rates of 2,3 – 3% (8, 9, 12, 21). These changes in surgical approach have resulted in a significant decrease in morbidity without causing an increase in mortality rate or recurrence risk (8, 15, 22). However, patients with multifocal disease, a tumor size larger than 4 cm, or clinically involved lymph nodes of the groin should receive radical treatment of the groin, consisting of either debulking of enlarged lymph nodes with postoperative radiotherapy, or inguinofemoral lymphadenectomy (IFL) (8, 21). After IFL, postoperative radiotherapy is advised for patients with two or more positive groin nodes or extracapsular spread of groin nodal involvement (1, 23).

Treatment of groin metastases of patients with VSCC remains a major challenge, because affected patients are mainly women over 60 years of age and have a high risk of developing complications after surgery (24-26). Extensive groin surgery as well as radiotherapy, and in particular the combination of these treatments, are associated with significant morbidity (5, 9, 16, 17, 20, 27-29). At present, it remains uncertain which surgical approach for the treatment of groin metastases has the best overall outcome with both lowest risk of groin recurrence and of complications. In 2007 Hyde et al. performed a retrospective study on a series of 40 VSCC patients with lymph node metastases to the groin who underwent either lymph node debulking or IFL followed by radiotherapy. In this study surgical treatment was performed in three different clinics in the Netherlands and in Australia. The results showed no difference in overall survival when groin surgery was followed by inguinal and pelvic radiation (30).

Our study aimed to investigate the risk of groin recurrences and overall survival in relation to surgical treatment in a larger group of patients with VSCC and cytologically or histologically proven metastases to the groin treated within one center. We investigated three different surgical approaches in case of proven metastases to the groin in patients with VSCC: SN procedure; debulking of clinically involved lymph nodes; or IFL. Additionally, we investigated the differences in morbidity between the different surgical groin treatment approaches.

Methods

Patients and treatment

A single-institution retrospective study was performed. Clinical and histopathological data of patients with newly diagnosed VSCC who were referred to the Leiden University Medical Center between January 2000 and December 2012 were collected. Only patients with cytologically or histologically proven lymph node metastases to the groin were included. Data collection was carried out according to the guidelines of the Ethics Committee of the Leiden University Medical Center.

Local vulvar cancer treatment consisted of radical vulvectomy, wide local excision or primary chemoradiation. Groin surgery consisted of either IFL, debulking of clinically involved groin nodes, SN procedure, or a combination of these treatment modalities to both groins. During the study period surgery was performed by the same four experienced gynecologic oncologists. IFL is defined as removal of all lymph node bearing fatty tissue between the inguinal ligament, the sartorius muscle and the adductor longus muscle and dissection of the femoral lymph nodes located in the fossa ovalis medial to the femoral vein (16, 30-32). Debulking is defined as selectively removing clinically involved or cytological/histological proven positive and enlarged groin nodes (30). The sentinel node procedure was performed using the radioactive tracer ^{99m}Tc -labelled colloid and blue dye as reported previously according to the GROINSS-V protocol (8, 33). From 2000 until 2010 we performed a debulking of clinically involved nodes generally followed by radiotherapy when metastases were detected pre- or intra-operatively by ultrasonography or frozen section or when the SN was tumor positive. An IFL was performed in patients with tumors larger than 4 cm when there were no clinically involved lymph nodes. From July 2010 onwards, patients with a macrometastasis of >2 mm in the SN underwent IFL, because this was reported to be a risk factor for groin recurrence (19). Patients with a micrometastasis < 2 mm in the SN without enlarged lymph nodes on ultrasound or CT scan were treated with additional radiotherapy, as well as patients with more than one groin metastasis and/or extracapsular spread at IFL. Patients with locally advanced disease were treated with concurrent chemoradiation as primary treatment after IFL or debulking of clinically involved nodes. Radiotherapy was

administrated to the inguinal and external iliacal regions, and in case of close margins also to the vulva, to a total dose of 46-50.5 Gy in 23-28 daily fractions of 1.8-2 Gy, 5 times a week, with a boost dose to 56-60 Gy to the involved groin in case of extracapsular extension. If primary chemoradiation was used, radiotherapy was combined with either oral capecitabine 825 mg/m² on days 1-14 every 3 weeks (within a national phase 2 study) or with 5-fluorouracil (5FU) 1000 mg/m² i.v 4x24 hr continuous infusion in weeks 1 and 5 of radiotherapy and mitomycin-C 10 mg/m² i.v on day 1 of 5FU administration (unless clinically contraindicated). Patients were followed at 2-3 month intervals in the first two years after treatment, 4 to 6-monthly in the third and fourth year and annually thereafter.

Tumor characteristics that were analysed were tumor location, size, depth of infiltration and lymphovascular space invasion (LVSI). LVSI was considered positive when cancer cells were present within endothelium-lined spaces on regular hematoxylin and eosin stained slides. Furthermore, the total number of removed lymph nodes, the number of tumor positive lymph nodes, the size of groin metastases and intra- or extranodal growth were documented. In case of missing histopathological data, pathological slides were reviewed by a gynaecological pathologist (TB).

To study treatment-related morbidity, overall complication rate, the presence of lymphocysts, lymphedema, wound dehiscence, wound infection and wound hematoma were documented. These data were collected retrospectively from the patient charts. Complications were defined according to an earlier study performed in our clinic regarding complications after IFL procedure (16). Lymphocysts were documented if greater than 4 cm in diameter and generally confirmed by cytology and/or ultrasound. Lymphedema was defined when clinically relevant and/or if lymphedema treatment using manual compression therapy and compression stockings were required from three months after surgery onwards. Wound dehiscence was defined as disruption of the groin wound over more than one-third of the length of the incision. A wound infection was noted if a purulent exudate was present and/or if a patient had a positive wound culture with erythema, edema and localized pain requiring antibiotics (16).

Statistical analysis

Statistical analysis was performed using SPSS Statistics 20. Clinical and histopathological characteristics of all patients were analysed with the with the Fisher exact test and one way ANOVA. Groin recurrence-free time was defined as the time from date of primary surgery until the date of histologically proven groin recurrence or date of last follow up or death. Overall survival is defined as the time from surgery until date of death, irrespective of the cause, with censoring at date of last follow up. Groin recurrence-free time was analysed per groin and estimated with the Kaplan-Meier method. Groins of the

patients were subdivided into three groups regarding the analysis of surgical treatment to the groin and groin recurrence: 1) SN procedure only, 2) lymph node debulking, 3) IFL. If a SN procedure was followed by either a debulking or IFL, the final surgical treatment was leading. Overall survival was analysed for the whole patient group, subdivided into patients who did and patients who did not develop a recurrence in the groin(s). Analysis of overall survival was done with cox regression, using a time dependent covariate to take the time to develop a recurrence into account.

Because some patients received different groin treatment modalities to both groins, a per groin analysis for the statistical analyses of the groin characteristics was performed. To take the possible correlation of both groins in one patient into account, analyses were done using the generalized estimating equations model. In this model we corrected for age.

A univariate and multivariate analysis was performed using the cox regression model in order to determine risk factors for groin recurrence. Clinicopathological variables that were considered in the analysis are: primary surgical treatment of the groin, age, FIGO stage, tumor size, LVSI, intact or extracapsular nodal growth of the groin metastasis, depth of infiltration of the primary tumor, the number of removed lymph nodes during groin surgery, the number of tumor positive lymph nodes, the size of the groin metastases and adjuvant groin treatment after initial surgery (i.e. radiotherapy). These variables are regarded as known risk factors influencing prognosis (10, 34-36). In the multivariate analysis we analysed primary groin treatment and all prognostic variables with a p-value of <0.1.

A p-value of <0.05 was considered to be statistically significant.

Results

Patients and treatments

From January 2000 to December 2012, 289 patients were treated for primary vulvar cancer at Leiden University Medical Center, of whom 232 (80%) presented with VSCC. Seventy-two (31%) of these 232 patients had histological proven metastases to the groin nodes, either diagnosed before or after surgery by cytological or histological examination. Of these 72 patients, one patient refused initial surgical treatment of groin metastasis and 3 patients received primary radiotherapy to the groins. These four patients were excluded from the analysis. Subsequently, the study group consisted of 68 patients with VSCC and cytologically or histologically proven lymph node metastases to the groin who underwent surgery of the groin as their initial treatment.

Table 1: Clinical and histopathological characteristics of 68 lymph node positive VSCC patients

		N (Range)	%	
Mean age		70,8 (35-94)		
FIGO stage (2009)	III	54	79,4%	
	IV	14	20,6%	
Location vulva tumour	Midline	15	22%	
	Unilateral	43	63,3%	
	Bilateral	6	8,8%	
	Multifocal	3	4,4%	
	Not specified	1	1,5%	
Size vulva tumour	≤ 2 cm	15	22,1%	
	2 – 4 cm	27	39,7%	
	≥ 4 cm	26	38,2%	
Depth of infiltration vulva tumour	1-4 mm	21	30,9%	
	≥ 4 mm	47	69,1%	
Lymph vascular space invasion (LVSI)	No	45	66,2%	
	Yes	19	27,9%	
	Unknown	4	5,9%	
Primary treatment vulva tumor	Wide local excision	53	77,9%	
	Radical vulvectomy	12	17,7%	
	Chemoradiation	3	4,4%	
Primary groin treatment	SN unilateral	7	10,3%	
	SN bilateral	5	7,4%	
	Debulking unilateral	11	16,2%	
	Debulking bilateral	7	10,3%	
	IFL unilateral	2	2,9%	
	IFL bilateral	18	26,5%	
	Combination in both groins			
	IFL and debulking	13	19,1%	
	IFL and SN	3	4,4%	
	Debulking and SN	2	2,9%	
Adjuvant treatment groin metastasis	None	12	17,6	
	Radiotherapy	51	75%	
	Chemoradiation	5	7,4%	
Location groin metastasis	Unilateral	52	76,5%	
	Bilateral	16	23,5%	
Size of groin metastasis	Isolated tumour cells	7	10,3%	
	≤2 mm	8	11,8%	
	>2 mm	53	77,9%	
Nodal growth groin metastasis	Intact	37	54,4%	
	Extra capsular	30	44,1%	
	Not assessable	1	1,5%	
Patients with groin recurrence		14	20,6%	
Mean time until groin recurrence (months)		14,4 (2-39)		
Current patient status at end of follow up or last visit	Alive, recurrence free	17	25%	
	Alive, recurrent disease	2	2,9%	
	Death because of tumour	34	50%	
	Death, other cause	14	20,6%	
	Death, unknown cause	1	1,5%	

VSCC: vulvar squamous cell carcinoma

Clinical and histopathological characteristics of the study group are shown in table 1. Mean age was 70.8 years. Initial surgical treatment of the groins consisted of a SN procedure only in 12 patients; debulking of clinically involved or enlarged lymph nodes in 18 patients; IFL in 20 patients; and a combination of surgical procedures to both groins in 18 patients. Sixty-five of the 68 patients (96%) underwent primary surgical treatment of the vulva tumor. Three patients with locally advanced disease were treated with primary chemoradiation on the vulva in combination with lymph node debulking of one groin. Fifty-one (75%) of the 68 patients received adjuvant radiotherapy to the groins and 5 patients (7%) underwent chemoradiation. In all patients who received adjuvant (chemo)radiation a CT-scan was performed for planning of the radiotherapy. In the rare cases that borderline residual nodes were seen on a radiotherapy planning CT scan, a repeat ultrasound with cytology was done that was negative in all cases. In 9 of 12 patients who did not receive adjuvant therapy, pre-operative imaging had been performed to exclude enlarged lymph nodes consisting of an ultrasound in 7 patients, a CT-scan in 1 patient and MRI-scan in 1 patient. Adjuvant treatment was started as soon as possible after surgery. Forty-three patients (77%) started with radiotherapy within six weeks after surgery. For thirteen patients (23%) radiotherapy was started later than six weeks after treatment. Eleven of these patients started adjuvant treatment within eight weeks after surgery. The reason for delay for the other two patients was that one patient refused adjuvant radiotherapy at first and the other patient had prolonged wound recovery. For three patients a break during radiation therapy was needed: one patient had a break of two days on her own request; one had a break of one week due to extensive moist desquamation, after which the radiotherapy was completed according to the normal schedule. The third patient discontinued radiotherapy shortly after the start due to a rapid deterioration of her condition because of metastatic disease. Twelve (18%) of the 68 patients did not receive adjuvant radiotherapy, despite the presence of lymph node metastases: for 8 patients this was not considered necessary because of a single metastasis to the groin node without extracapsular growth. Four of these patients had a micrometastasis. The four patients who had a metastasis of >2 mm after IFL were all treated before the GROINSS-V-II amendment in 2010 and therefore did not receive radiotherapy. One patient died shortly after primary surgical treatment and 2 patients refused adjuvant radiotherapy. These three patients underwent a SN procedure. Finally, 1 out of these 12 patients underwent debulking to one groin and IFL to the other groin. In the latter patient, a total of 20 lymph nodes in the groin were excised, all of which were tumor positive with extensive extranodal growth. Additional radiological imaging showed pulmonary metastasis. Therefore it was decided to start palliative treatment. Mean follow up time of all patients was 33,4 months (range 0-146 months, median follow up time 20,5 months).

Clinical outcome: overall survival and groin recurrences

Forty-nine (72%) of 68 patients died, 34 of whom due to recurrent or progressive disease. For 1 patient in the IFL group the cause of death was unknown. Fourteen (21%) of 68 patients developed a groin recurrence, with a mean time until recurrence of 14 months (range 2-39 months). Three out of these fourteen patients (21,4%) had an ipsilateral vulvar recurrence at the same time of the groin recurrence.

Twelve (86%) out of 14 patients with a groin recurrence died. Mean and median overall survival for patients with a groin recurrence was 20 and 18 months, respectively (range 6-43 months). Eleven patients with a groin recurrence (79%) died because of the disease. In the group of patients without a groin recurrence 37 patients (69%) died, 23 (42,6%) due to disease. Mean and median overall survival in this group was 37 and 23 months (range 0-146 months). The hazard ratio (HR) of dying was nine (8,995) times higher for patients who developed a groin recurrence compared to patients who did not develop a groin recurrence ($p < 0.001$).

Per-groin analysis

In 68 patients, 116 groins were treated surgically. Eighty-four of these groins had lymph node metastases and were eligible for analysis (Table 2). In 16 groins (19%) a SN procedure was performed, 38 groins (45%) were treated with debulking surgery, and thirty groins (36%) with IFL. The size of the primary vulva tumor was significantly larger in the debulking group compared to the other treatment groups ($p = 0.005$). Pre-operative suspicious lymph nodes were present in 34 patients (89,5%) of the debulking group versus 17 patients (56,7%) in the IFL group. This difference remained significant when comparing these last two treatment groups ($p < 0.001$). As expected, the number of removed lymph nodes was significantly higher in the IFL group compared to the other treatment groups ($p < 0.001$). The number of tumor-positive lymph nodes was not significantly different between the treatment groups ($p = 0.140$). The number of groin metastases with extra capsular growth was significantly higher in the debulking group compared to the SN procedure only and IFL group (68% versus 19% and 47% respectively, $p = 0.002$). Macro-metastases (> 2 mm) were found significantly more often in the debulking (95%) and IFL groups (93%) compared to the SN group (25%) ($p < 0.001$). More patients in the debulking group (90%) received adjuvant radiotherapy compared to the SN (69%) and IFL (67%) groups ($p = 0.013$).

Table 2: Groin characteristics, complications and recurrences among 84 surgically treated groins in 68 patients

Variables		SN procedure N=16	Debulking N=38	IFL N=30	P value
Size vulva tumor	≤ 2 cm	6 (37,5%)	3 (7,9%)	6 (20%)	0.005
	2 – 4 cm	9 (56,2%)	12 (31,6%)	13 (43,3%)	
	≥ 4 cm	1 (6,2%)*	23 (60,5%)	11 (36,7%)	
Infiltration depth vulva tumor	1-4 mm	5 (31,2%)	7 (18,4%)	10 (33,3%)	0.347
	≥ 4 mm	11 (68,8%)	31 (81,6%)	20 (66,7%)	
Focality vulva tumor	Unifocal	16 (100%)	27 (71,1%)	22 (73,3%)	0.369
	Multifocal	0 (0%)	11 (28,9%)	8 (26,7%)	
Pre-operative suspicious lymph nodes **	No	16 (100%)	4 (10,5%)	13 (43,3%)	< 0.001
	Yes	0 (0%)	34 (89,5%)	17 (56,7%)	
Number of removed lymph nodes (median and range)		1 (1-4)	3 (1-15)	8 (3-19)	< 0.001
Number of positive nodes		1,1	2,1 (1-12)	2,6 (1-19)	0.007
N stage ***	N1	12 (75%)	5 (13,2%)	7 (23,3%)	< 0.001
	N2	3 (18,8%)	32 (84,2%)	21 (70%)	
	N3	0 (0%)	0 (0%)	0 (0%)	
	Unknown	1 (6,2%)	1 (2,6%)	2 (6,7%)	
Size of groin metastases	ITC	5 (31,2%)	1 (2,6%)	0 (0%)	< 0.001
	≤ 2 mm	7 (43,8%)	0 (0%)	2 (6,7%)	
	>2 mm	4 (25%)*	36 (94,8%)	28 (93,3%)	
	Unknown	0 (0%)	1 (2,6%)	0 (0%)	
Nodal growth	Intact	13 (81,2%)	11 (29%)	16 (53,3%)	0.005
	Extra capsular	3 (18,8%)	26 (68,4%)	14 (46,7%)	
	Unknown	0 (0%)	1 (2,6%)	0 (0%)	
Adjuvant treatment groin metastasis	None	5 (31,2%)*	1 (2,6%)	7 (23,3%)	0.005
	Radiotherapy	11 (68,8%)	34 (89,5%)	20 (66,7%)	
	Chemoradiation	0 (0%)	3 (7,9%)	3 (10%)	

Complication groin surgery		2 (12,5%)	5 (13,2%)	16 (53,3%)	0.003
Type of complication groin surgery	Lymphocyst	1 (6,2%)	0 (0%)	8 (26,7)	0.032
	Lymphedema	1 (6,2%)	0 (0%)	13 (43,3%)	0.002
	Wound dehiscence	0 (0%)	2 (5, 3%)	3 (10%)	0.649
	Wound infection	1 (6,2%)	1 (2,6%)	7 (23,3%)	0.091
	Hematoma	0 (0%)	2 (5,3%)	0 (0%)	0.765
Number of complications	None	14 (87,6%)	33 (86,9%)	14 (46,7%)	0.010
	One	1 (6,2%)	4 (10,5%)	9 (30%)	
	Two	1 (6,2%)	1 (2,6%)	2 (6,7%)	
	Three	0 (0%)	0 (0%)	5 (16,6%)	
Number of groin recurrences		4 (25%)	6 (15,8%)	4 (13,3%)	0.495
Mean time until groin recurrence (months)		9,3 (7-14)	17,3 (3,8-37)	5,8 (2,1-12,6)	0.601

* This patient underwent a SN procedure because the size of the vulva tumor turned out to be larger than clinically assessed. In the SN ITC's were found. After multidisciplinary consultation it was decided to treat this patient with postoperative radiotherapy instead of an IFL.

** Based on physical examination or pre-operative imaging

*** N stage according to the TNM classification of the American Cancer Society 2010. N1: the cancer has spread to 1 or 2 lymph nodes in the groin and the areas of cancer spread are both less than 5 mm in size or the cancer has spread to one lymph node and the area of cancer spread is 5 mm or greater. N2: the cancer has spread to 3 or more lymph nodes, but each area of spread is less than 5 mm or the cancer has spread to 2 or more lymph nodes with each area of spread 5 mm or greater or the cancer has spread to lymph nodes and has extracapsular spread in at least one lymph node. N3: the cancer has spread to the lymph nodes causing ulceration or causing the lymph node to be fixed to the tissue below it.

**** These four patients with a macrometastasis in the SN all underwent their SN procedure before 2010. Three patients received adjuvant radiotherapy and one patient refused radiotherapy. Before 2010 the SN procedure was not followed by IFL.

***** Five patients in the SN procedure group did not receive adjuvant radiotherapy. One patient with pre-existent cardiac disease died two weeks after surgery due to an acute myocardial infarction. Two patients refused adjuvant radiotherapy (one patient with a micrometastasis and one patient with a macrometastasis, both patients developed a groin recurrence). For two patients with one lymph node metastasis with ITC's it was decided in a multidisciplinary meeting that further treatment was not desirable because of their high age, comorbidity and the small chance on additional metastases in the non-sentinel nodes.

ITC: isolated tumor cells (considered as tumor positive lymph nodes)

SN: sentinel node

IFL: inguinofemoral lymphadenectomy

In 14 of the 84 groins a groin recurrence occurred. One patient with lymph node metastases in both groins treated with bilateral IFL and chemoradiation developed a groin recurrence in both groins. Four groin recurrences (25%) occurred in the sixteen groins which were initially treated with SN only. In two of these four cases no adjuvant radiotherapy was given because of refusal, one groin contained isolated tumor cells and was treated with adjuvant radiotherapy, and one groin contained a macrometastasis and was treated with adjuvant radiotherapy. Six groin recurrences (16%) occurred in the 38 groins treated with debulking and four groin recurrences (13%) in the 30 groins in which IFL was performed. The number of groin recurrences was not significantly different between the initial surgical modality groups ($p=0.495$). There was also no significant difference in groin recurrence-free time between the different surgical modality groups ($p=0.904$) (Figure 1). The mean time until recurrence was 9,3 months in the SN procedure group, 17,3 months in the debulking group, and 5,8 months in the IFL group ($p=0.156$). When the SN group was excluded, the difference between the number of groin recurrences and the mean time until groin recurrence remained non-significant.

Morbidity after groin surgery

The risk of complications after groin surgery was significantly lower in the debulking and SN groups compared to IFL (13% and 13% versus 53% , $p=0.003$). Lymphocysts and lymphedema occurred less often in the debulking and SN groups compared to the IFL group (0% and 6% versus 27% , $p=0.032$ and 0% and 6% versus 43%, respectively, $p=0.002$). In addition, significant more patients suffered from more than one complication in the IFL group than in the other treatment groups ($p=0.010$). The occurrence of lymphocysts, lymphedema and overall complication rate remained significantly higher in the IFL group compared to the debulking group ($p=0.011$, $p=0.002$, $p=0.005$, respectively) after excluding the SN group from the analysis.

Univariate and multivariate analysis

Univariate and multivariate analyses on groin recurrence-free time were performed in the 84 groins with lymph node metastases. In the univariate analysis we found no significant prognostic variables for groin recurrence-free time. Importantly, the type of primary surgical treatment of the groin was not significantly related to groin recurrence-free time. In multivariate analysis we also found no significant prognostic variables for groin recurrence-free time (Table 3). Again, initial surgical groin treatment modality, either SN, debulking or IFL, was not significantly related to groin recurrence-free time ($p=0.650$).

Table 3: Univariate and multivariate analysis of groin recurrence free time in 84 groins

Variable	Univariate analysis		Multivariate analysis	
	Hazard (CI)	P-value	Hazard (CI)	P-value
Primary groin treatment		0.905		0.650
IFL versus debulking	0.898 (0.253 – 3.193)	0.868	1.782 (0.447 – 7.102)	0.413
SN-procedure versus debulking	0.754 (0.344 – 4.371)	0.754	1.618 (0.449 – 5.826)	0.462
SN-procedure versus IFL	2.075 (0.529 – 10.989)	0.255	1.101 (0.259 – 4.683)	0.896
Age	0.984 (0.953 – 1.017)	0.339	0.976 (0.946 – 1.007)	0.127
FIGO stage	0.982 (0.273 – 3.530)	0.982		
Tumor size		0.903		
< 2 cm versus 2-4 cm	0.760 (0.203 – 2.849)	0.684		
2-4 cm versus >4 cm	1.257 (0.363 – 4.347)	0.717		
< 2 cm versus >4 cm	0.956 (0.253 – 3.607)	0.947		
LVSI (yes versus no)	0.174 (0.023 – 1.337)	0.093	0.131 (0.016 – 1.038)	0.054
Nodal growth (extracapsular versus intact)	1.734 (0.593 – 5.076)	0.315		
Depth of infiltration (>4 mm versus 1-4 mm)	3.681 (0.810 – 16.730)	0.092	4.447 (0.893 – 22.154)	0.069
Number of removed lymph nodes	1.063 (0.956 – 1.182)	0.256		
Number of tumor positive lymph nodes	1.052 (0.877 – 1.263)	0.585		
Size lymph node metastases		0.678		
ITC versus micrometastases	0.597 (0.037 – 9.592)	0.716		
ITC versus macrometastases	1.433 (0.186 – 11.045)	0.730		
Micrometastases versus macrometastases	2.398 (0.308 – 18.519)	0.403		
Adjuvant groin treatment		0.359		
No treatment versus radiotherapy	0.612 (0.164 – 2.280)	0.464		
No treatment versus chemoradiation	1.778 (0.296 – 10.688)	0.529		
Radiotherapy versus chemoradiation	2.906 (0.625 – 13.513)	0.174		

IFL: inguinofemoral lymphadenectomy
 SN: sentinel node
 LVSI: lymphovascular space invasion

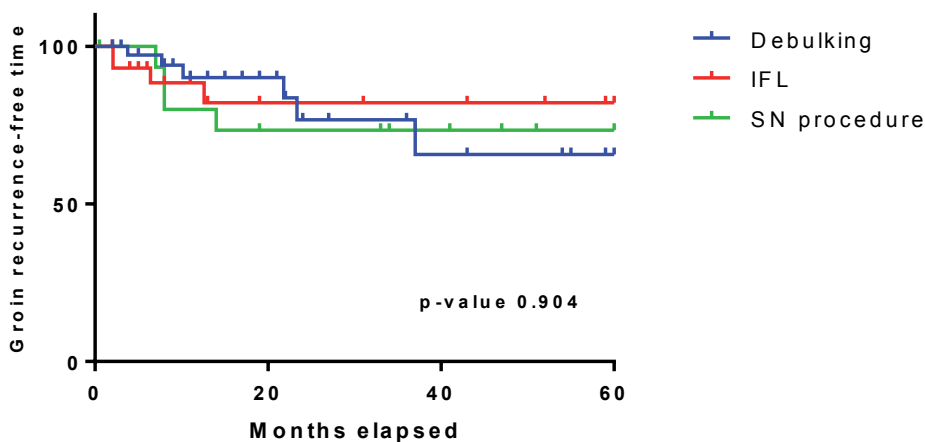


Figure 1: groin recurrence free time in 84 groins of 68 patients who had primary surgical treatment of lymph node positive groins.

IFL: inguinofoemoral lymphadenectomy

SN: sentinel node

Discussion

Most patients with VSCC and proven metastases to the groin nodes are treated with extensive IFL surgery and adjuvant radiotherapy or chemoradiation, resulting in high morbidity rates. Thus far, there is no consensus whether groin metastases can best be treated with debulking surgery of clinically involved or enlarged nodes followed by radiotherapy, or with more radical removal of all inguinofoemoral lymph nodes (IFL), with radiotherapy when indicated (30). In this study we analysed whether the type of initial surgical procedure of the groin influenced groin recurrence-free time in patients with VSCC and cytologically or histologically proven groin metastases. Furthermore, we analysed the negative impact of a groin recurrence on overall survival, and compared the morbidity of the different initial surgical groin treatment modalities. Our results show that patients with a groin recurrence have a nine times higher risk of dying of disease compared to patients who do not develop a groin recurrence. These findings emphasise the importance of obtaining groin control at first treatment. Because VSCC patients are often fragile and elderly, it is also of major importance to choose a treatment modality with the lowest risk of morbidity and complications. We found that there was no significant difference regarding the risk of groin recurrence between the initial surgical treatment groups with proven lymph node metastases. Furthermore, it was shown that both debulking surgery and SN procedure had a significantly lower complication rate compared to IFL. Especially the risk of developing lymphocysts or lymphedema was

significantly lower after debulking or SN procedure compared to IFL, regardless of postoperative radiotherapy.

The SN procedure has led to a major decrease in morbidity compared to IFL without influencing prognosis (8, 19, 37-39). However, this procedure is only suitable and reliable in early stage vulvar cancer patients with unifocal lesions, tumor size less than 4 cm and clinically negative lymph nodes (1, 8, 21). Therefore, a selected group of patients still needs extensive surgery of the groins, consisting of either IFL or debulking of clinically involved lymph nodes followed by radiotherapy. The preferred treatment of proven metastases to the groin, especially in case of macrometastases >2 mm, remains to be answered. In a retrospective study, Hyde et al. (30) compared IFL with nodal debulking regarding groin recurrence and survival in forty patients with VSCC and clinically involved groin nodes. They found no difference in groin recurrence rate, and concluded that nodal debulking does not jeopardize survival in comparison to IFL when both are followed by groin and pelvic radiation. These results are confirmed by our study. We did not find a significant difference in groin recurrence rate when only comparing the debulking group with the IFL group. This is especially important because these groups are more homogenous in contrast to the SN group (Table 2), and reflect patients with more advanced disease. In addition to the study of Hyde et al. we also analysed postoperative morbidity and found that postoperative morbidity was worse in patients who received IFL, as also found in a previous study (16). We found a complication rate as low as 13% in patients who underwent debulking compared to 53% in patients who underwent IFL (Table 2). Even despite the fact that significant more patients received adjuvant radiotherapy in the debulking group, which is regarded to be associated with a higher complication rate.

Although we confirmed the results of Hyde et al. in a larger series of patients and supplemented our results with morbidity rates, our study group remains relatively small. This remains a limitation for all studies on VSCC because of the rarity of the disease. Also, retrospective analyses have the inherent limitations of differences in treatment selection and outcomes over time. Diagnostic and therapeutic procedures have significantly improved, and have likely increased the rate of patients treated to all involved and clinically relevant lymph node regions with radiotherapy. Radiotherapy techniques have improved both in terms of dose distribution, accuracy, and reduction of late complications by use of more conformal, and in later years also image-guided, intensity modulated treatment techniques. This could have led to better outcomes in more recent years, and contributed to the lower rate of complications in the debulking group as compared to IFL despite the more frequent use of radiotherapy (98 vs 77%).

The treatment of patients with VSCC and proven groin metastases remains a clinical challenge, as these patients need additional treatment in order to improve their prognosis. With the current treatment modalities, prognosis of patients with proven lymph node metastases is still poor while treatment-associated morbidity rates are high. For patients with clinically suspicious inguino-femoral lymph nodes and/or macrometastases >2 mm our findings suggest that nodal debulking followed by radiotherapy is the preferred mode of treatment. Debulking of pathologic or enlarged nodes is related to a lower risk of complications, also in combination with postoperative radiotherapy, without increasing the risk of recurrence, compared to IFL. These findings are a relevant contribution to the growing body of data that will help to individualize the surgical treatment of patients with VSCC. Because of the low incidence of node-positive vulvar cancer, larger, prospective studies are needed.

Conflict of interest statement

There are no conflicts of interest.

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