Citation

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/62866

Cover Page

Universiteit Leiden

Leiden University
Repository

The handle http://hdl.handle.net/1887/62866 holds various files of this Leiden University dissertation

Author: Nooij, Linda
Title: Vulvar cancer : pathogenesis, molecular genetics and treatment
Date: 2018-06-28

CHAPTER 4

Risk factors and treatment for recurrent vulvar squamous cell carcinoma

Linda S. Nooij
Fernande A.M. Brand
Katja N. Gaarenstroom
Carien L. Creutzberg
Joanne A. de Hullu
Mariette I.E. van Poelgeest

Abstract

Recurrent disease occurs in 12–37% of patients with vulvar squamous cell carcinoma (VSCC). Decisions about treatment of recurrent VSCC mainly depend on the location of the recurrence and previous treatment, resulting in individualized and consensus-based approaches. Most recurrences (40–80%) occur within 2 years after initial treatment. Currently, wide local excision is the treatment of choice for local recurrences. Isolated local recurrence of VSCC has a good prognosis, with reported 5-year survival rates of up to 60%. Groin recurrences and distant recurrences are less common and have an extremely poor prognosis. For groin recurrences, surgery with or without (chemo)radiotherapy is a treatment option, depending on prior treatment. For distant recurrences, there are only palliative treatment options. In this review, we give an overview of the available literature and discuss epidemiology, risk factors, and prognostic factors for the different types of recurrent VSCC and we describe treatment options and clinical outcome.

1. Introduction

Vulvar cancers account for 3–5% of all gynecological malignancies, with an annual incidence of 1–2 per 100,000 women (1-4). The incidence of vulvar cancer increases with age, with a peak incidence in the seventh decade (1, 3). The overall incidence of vulvar cancer has risen over the last decade, probably because of an increase in human papilloma virus (HPV) infections and higher life expectancy (5). Around 80–90% of these tumors are squamous cell carcinomas. Malignant melanoma, Bartholin gland carcinoma, invasive Paget's disease, and basal cell carcinoma are less frequent. Other tumor types, such as sarcomas and verrucous carcinomas, are extremely rare (1-3).

Five-year survival for early-stage VSCC is about 80–90% (1, 6). Prognosis is strongly dependent on the presence of lymph node metastases (3, 6-9). Therefore, the International Federation of Gynecology and Obstetrics (FIGO) staging system was changed in 2009 (Table 1) (10). Tumors with negative lymph node status can be regarded as low risk, regardless of tumor diameter and expansion to the vagina and/or urethra. By contrast, the number, size, and extranodal growth of involved lymph nodes are important prognostic factors. An increasing number of positive lymph nodes, a larger diameter of nodal metastases, and extranodal growth are significantly related to worse survival (11).

Table 1: FIGO staging system of vulvar cancer

Stage	
I	Tumours confined to the vulva or perineum, no nodal metastasis Ia: Tumour ≤ 2 cm with stromal invasion ≤ 1 mm Ib: Tumour > 2 cm or stromal invasion > 1mm
II	Tumour of any size with extension to adjacent perineal structures (lower urethra, lower vagina, anus), no nodal metastasis
III	Tumour of any size with or without extension to adjacent perineal structures (lower urethra, lower vagina, anus), with inguino-femoral nodal metastasis IIIa: 1 node metastasis (≥ 5 mm) or 1-2 node metastasis(es) (< 5 mm) IIIb: ≥ 2 node metastases (≥ 5 mm) or ≥ 3 node metastases (< 5 mm) IIIc: node metastases with extra-capsular spread
IV	Iva: Tumour invades any of the following: upper urethra and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or fixed or ulcerated inguinofemoral nodes IVb: Any distant metastasis including pelvic nodes

Carcinogenesis of VSCC can be subdivided into two different pathways. One pathway is associated with lichen sclerosus (LS) and usually occurs in older patients (55–85 years) (4, 12-18). This pathway accounts for around 70% of all VSCC. Differentiated vulvar intraepithelial neoplasia (dVIN) is the presumed precursor lesion found in this type of VSCC. It has been suggested that untreated dVIN has a high malignant potential, probably as high as 80% (19). The other known pathway is human papilloma virus (HPV) dependent and accounts for around 30% of all VSCC. The most prevalent HPV

types found in VSCC are HPV16 in 60–78% of cases followed by HPV18 in 5–16% (13, 14, 16-18, 20-25). This pathway usually occurs in younger patients (35–65 years) and is associated with vulvar high grade squamous intraepithelial lesions (HSIL, formerly referred to as usual type VIN) and smoking. Untreated vulvar HSIL has a lower rate of progression to VSCC (9–16%) (15, 19) compared to dVIN. Although most VSCC are HPV independent, dVIN accounts for only 2–10% of all reported VIN lesions (15, 25). The low prevalence of dVIN may be explained by the belief that it progresses rapidly to VSCC. Another explanation may be that dVIN is an underdiagnosed and therefore underreported lesion due to its subtle clinical and histological features. Although dVIN has been described already in 1961 by Abell et al. (26), it is only recently that dVIN has been recognized and regarded as a distinctive diagnosis by clinicians as well as pathologists (15). Recently, the International Society for the Study of Vulvar Disease (ISSVD) published a new classification system for VIN. The new terminology discriminates between HPV-dependent low-grade squamous intraepithelial lesions (LSIL; i.e., flat condyloma or HPV effect) and high-grade squamous intraepithelial lesions (HSIL) on the one hand, and the HPV-independent precursor dVIN on the other (Table 2) (27). Because precursor lesions are frequently found in the presence of VSCC, clinicians should take the phenomenon of "field cancerization" into account: the majority of "recurrences" maybe considered "de novo" tumors in a background of epithelial changes already at risk for the development of malignancy (19, 28, 29).

Table 2: Old and new terminology of vulvar squamous intraepithelial lesions

ISSVD 1986	ISSVD 2004	ISSVD 2015
VIN 1	Flat condyloma or HPV effect	LSIL
VIN 2	VIN, usual type (uVIN)	HSIL
VIN 3		
Differentiated VIN (dVIN)	VIN, differentiated type (dVIN)	VIN, differentiated type (dVIN)

ISSVD: International Society for the Study of Vulvovaginal Disease
VIN: Vulvar Intraepithelial Neoplasia
LSIL: Low grade squamous intraepithelial lesion
HSIL: High grade squamous intraepithelial lesion

Surgery is the cornerstone of treatment for primary VSCC (1, 2, 4). Surgery for tumors infiltrating >1 mm generally consists of wide local excision with full uni- or bilateral inguinofemoral lymphadenectomy (IFL) or sentinel lymph node (SLN) biopsy. A full IFL is defined as the surgical removal of all lymph node–bearing fatty tissue of the superficial inguinal and deep femoral loge medial to the fossa ovalis. SLN biopsy is considered safe in a selected group of patients with VSCC: those with a unifocal vulvar tumor <4 cm without enlarged or clinically suspected groin lymph nodes upon palpation

and imaging (30). Adjuvant radiation therapy is indicated for close or involved surgical margins and lymph node involvement depending on the size and number of nodal metastases and the presence of extranodal growth. Concurrent chemoradiotherapy in a neoadjuvant setting is recommended, especially for downsizing of bulky disease, in particular when the urethra or anus are involved (2, 3, 30-33). Despite these treatment modalities, recurrence rates are still high: 12–37% (7, 34). Furthermore, prognosis of patients with recurrent VSCC has not improved over the past decades, with a reported 5-year survival rate of 25–50% (34-38).

There are several challenges in the treatment of recurrent VSCC. Most VSCC patients are over 60 years of age, with significant comorbidity. Moreover, treatment of recurrent VSCC is associated with a high risk of developing complications (5, 25). The choice of treatment for recurrent VSCC is determined by the localization of recurrence and prior treatment (8, 34, 39). Nevertheless, the literature is relatively scarce and clear guidelines for the treatment of recurrent VSCC are lacking (40-42). In this review, we present an overview of the available literature on known risk factors for recurrence and treatment options for recurrent VSCC, including associated morbidity and clinical outcome.

1.1 Data sources

We performed an extensive search on PubMed, Embase, Web of Science, Cochrane, and ScienceDirect. After consulting a medical librarian, we formulated a combination of Medical Subject Headings (MeSH) and free text words. Our search included the terms vulvar neoplasm, vulvar carcinoma, vulvar neoplasia, groin, metastasis, and recurrence. The electronic search was complemented by a manual search of reference lists for relevant publications. In addition, we collected information from national and international oncological guidelines and checked study books for further data (4, 40-44).

A total of 1303 articles were identified. All articles were assessed by two independent authors (LN and FB) on title, abstract, or full article. Inclusion criteria were original articles that reported on treatment of recurrent VSCC (either local, groin or distant recurrences). To avoid inclusion of too small studies we chose to only report studies that included a minimum of respectively 20 or 10 patients (local or groin recurrence). After exclusion of articles based upon title and abstract 67 articles remained of which the full article was judged. Finally, twenty-four articles met our inclusion criteria and were included in this review.

1.2 Terminology

There is no clear definition of local VSCC recurrence in the current literature. There is no consensus on the minimum or maximum time span until local recurrence and on the distance between recurrent disease and the initial or primary vulvar tumor. Some authors define local recurrence as the new appearance of a tumor after therapy with radical intent

and a disease-free period of at least 6 months (45). Rouzier et al. defined three patterns of local recurrence: primary tumor site recurrence, remote vulvar recurrence (>2 cm from the primary tumor site), and skin bridge recurrence (9). Because documentation of the exact location of the primary tumor is often equivocal, the distance to the primary site to define recurrence is difficult to assess. In ongoing and future prospective studies, introduction of digital cameras may be helpful in reporting the exact location of the tumor. Another point of discussion addresses the time span that should be used to define tumor recurrence versus de novo tumor. Most recurrences occur within 2 years after primary treatment, so recurrences after 2–3 years might be considered de novo tumors (34, 46).

For this review, we defined a local recurrence as a "new or de novo" tumor on the vulva after primary treatment of VSCC, irrespective of location on the vulva, distance from the primary tumor, or time interval from initial therapy to recurrence. We stand by this definition because differences in these features were not described clearly in the available literature. A groin recurrence is defined as any (recurrent) lymph node metastasis in the groin(s) with or without the presence of a local recurrence after initial treatment for VSCC. A skin bridge recurrence is considered a special type of locoregional recurrence and is defined as a new tumor in the dermis in the intervening skin between the operated-on vulva and the ipsilateral groin region. Distant or metastatic recurrence is defined as any recurrence beyond the vulva or groins, whether or not asynchronous with a local or groin recurrence. Pelvic recurrences are considered distant recurrences.

2. Epidemiology and risk factors

Recurrences of VSCC occur in 12–37% of patients after initial treatment, depending on tumor stage at initial diagnosis (7, 34); 40–80% of all recurrences occur within 2 years of initial treatment (1, 34). Outcome for patients who had recurrences within 2 years after initial surgery is worse compared to patients who had recurrences >2 years after initial treatment (8, 47). In a prospective study of 143 patients with VSCC, Stehman et al. found a median time until local recurrence of 35.9 months: 19% of the VSCC recurred in the first year after therapy, and 28.6% recurred in the first 2 years after therapy. All patients included in this study underwent surgery to remove the local tumor, consisting of a modified radical hemivulvectomy or radical vulvectomy. Primary groin treatment consisted of superficial inguinal lymphadenectomy in 120 patients and groin irradiation in 23 patients (38). Another study identified local recurrences in the first year after treatment in 39% of patients, with an equal distribution during the following years (45). A recently published study reporting long term follow-up data of the GROINSS-VI study in patients with unifocal VSCC found a local recurrence rate of 27% after 5 years, with a median time to local recurrence of 33 months (range 2–128 months). The reported local recurrence rate at 10 years was as high as 40%. This 'recurrence' rate after 10 years was even higher than expected later in the course of disease (48). Mean follow-up after initial treatment was shorter in most previous studies compared to the long-term follow-up of the GROINSS-VI study. This might have underestimated the true incidence of recurrent disease. Furthermore, it still can be argued whether recurrent disease after several years must be regarded as true recurrence or de novo disease. Because of late "recurrences", several guidelines advise lifelong follow-up after treatment for VSCC (41, 42). Routinely scheduled follow-up leads to detection of smaller local recurrences in a considerable proportion of patients (49). The median time until recurrence in the groin is 7 months. The majority of the groin recurrences (67–73%) occur in the first year after initial treatment (38, 45, 48). Distant recurrences predominantly occur within 2 years after initial treatment (45, 48).

2.1 Local recurrence

The incidence of isolated local recurrences is 20–23% (45, 48, 50). More than 50% of all recurrences are local (7, 8, 34, 38, 45, 51); they are mainly isolated or associated with the groin or distant recurrences (7, 38, 45, 51). Univariate risk factors for local recurrence are higher age (50, 51), greater tumor size (34, 51-53), a multifocal tumor (52), depth of invasion >2 mm (9, 51, 54, 55), lymphovascular space invasion (52), and the presence of lymph node metastases at initial treatment (6, 45, 51). Except for greater tumor size, all of these risk factors are independent risk factors for local recurrence in multivariate analyses. A recent study identified the presence of perineural invasion as an independent pathological risk factor for local recurrence (56). The presence of lymph

node metastases at initial treatment may reflect a more aggressive biological behavior of the tumor and therefore also a poor prognostic factor for local recurrence. Few studies have reported on the presence of precursor lesions as risk factors for local recurrence. Two studies found that LS is a risk factor for recurrent disease (50, 57). One study compared the presence of associated HSIL as a prognostic factor for recurrence with the absence of associated HSIL (relative risk 2.30, *p*<0.019) (52). Another study found that the presence of HSIL in the surgical margins resulted in a 3-fold higher risk of recurrence (*p*=0.03) (58). The width of the tumor-free margin status is one of the most clinical important and controversial topics in vulvar cancer treatment. Although it is obvious that a tumour positive margin is associated with an increased local recurrence rate, the association of the width of the tumor-free margin and local recurrence rate is less clear (46, 59-63). Heaps et al. (59) found that increasing tumor-free margins were associated with a decrease in the local recurrence rate in a group of 135 patients. In patients with a tumor-free margin of <8 mm, there was a 48% risk of local recurrence, compared to a 0% local recurrence rate for patients with a tumor-free margin of >8 mm (59). However, subsequent studies yielded varying results with regard to the tumor-free margin and the risk of local recurrence (46, 60-63). Moreover, in most of these studies, the difference between "true recurrences" and "de novo" tumors was not taken into account. Future studies should focus on investigating the optimal tumor-free margin for prevention of local recurrences.

2.2 Groin recurrence

In 9–38% (average 22%) of patients with recurrent VSCC, the groin is the site of recurrence (6, 34, 38, 50, 51, 64-66). Patients with lymph node involvement at initial diagnosis have a higher risk of developing a groin recurrence (6, 38, 50, 51, 64, 66). In patients with negative lymph nodes at initial diagnosis, the groin recurrence rate is estimated to be extremely low (0–2%), while for patients with positive lymph nodes, this risk is as high as 29–40% (30, 51, 64, 65). SLN procedure of the groin is the preferred staging in patients with unifocal disease <4 cm without enlarged or clinically suspected lymph nodes (30). In all other primary cases and local recurrences without earlier IFL a full IFL should be performed. The risk of groin recurrence can be reduced considerably with adjuvant radiotherapy to the inguinofemoral and pelvic region (3, 67-69). Because radiotherapy was not always applied routinely in case of positive nodes, in particular in older studies, the groin recurrence risk could be overestimated compared to today's standard treatment. Adjuvant radiotherapy is recommended in patients with lymph node involvement when there are two or more positive lymph nodes or in case of extracapsular extension (3).

The number of positive lymph nodes is also a strong risk factor for groin recurrences (7, 62, 65, 70, 71). Hacker et al. found that patients with more than three positive lymph

nodes had a 33% risk of groin recurrence, compared to 2.9% for patients with less than three positive lymph nodes (70). Three studies described the impact of the number of removed lymph nodes at IFL on groin recurrence rate, with higher risk of groin recurrences and/or poorer survival after removal of less than 9–12 lymph nodes (72-74). However, it should be taken into account that removal of more lymph nodes and/or ultrastaging will lead to the identification of more and possibly otherwise-undetected lymph node metastases (72, 75). This could be a possible source of bias in the reported results. Other prognostic clinicopathological variables for groin recurrences are advanced FIGO stage (50), size of the lymph node metastases (7, 31, 76), and extracapsular nodal spread (7, 54, 71). In addition, groin treatment limited to superficial groin node dissection instead of a full IFL is associated with an increase in groin recurrences (77). The SLN procedure has been proven safe in these patients (403 patients in the GROINSS-V-I study), with a recurrence rate of 2.3% in patients with a negative SLN (30). In addition, the risk of groin recurrence is associated with the size of lymph node metastasis. Oonk et al. found lower disease-specific survival for patients with SLN metastases >2 mm (69.5%) compared to patients with SLN metastases ≤2 mm (94.4%, p=0.001) (31).

2.3 Distant recurrence

Distant recurrences are found in approximately 8% of patients with recurrent disease, and most distant recurrences occur within the first 2 years after treatment (84%) (6, 34, 45). The most common distant recurrence is pelvic recurrence (5–19% of the recurrences), which nearly always occurs together with a groin recurrence. Incidence of pelvic recurrence is dependent on treatment strategy as was shown by Homesley et al (68). In this study, 114 eligible patients with VSCC and positive groin nodes after radical vulvectomy and bilateral lymphadenectomy were randomized to receive either radiation therapy or pelvic node resection. In the radiotherapy group 68% remained free of recurrence, and rates of groin and pelvic recurrence were 5.1 and 6.8%, respectively. In the pelvic node dissection group, 55% remained recurrence-free, while rates of groin and pelvic recurrence were 23.6 and 1.8%. The estimated two-year survival rates were 68% for the radiation therapy group and 54% for pelvic node resection group (68). Multiple-site recurrences are described in about 14% of patients with recurrent disease (34, 45). Advanced stage of disease is a risk factor for the development of distant as well as multiple-site recurrences (7, 45, 50, 66).

2.4 HPV as a risk factor

In the last few years, more data have become available on the role of HPV in carcinogenesis. Infections with HPV have been linked to the development of vulvar, vaginal, cervical, anal and head and neck cancer, especially oropharyngeal malignancies (78-82). Like squamous cell carcinoma of the head and neck, VSCC can be subdivided into two different types: HPV independent and HPV dependent (13, 17, 19). For head

and neck carcinomas, it has become clear that these two types are clinically distinct with regard to response to treatment and survival outcome, with HPV positivity as a favorable prognostic biomarker (78-80).

There are conflicting data about the role of HPV status as a prognostic factor in VSCC. An overview of studies on the presence of HPV and impact on prognosis is given in table 3 (13, 16-18, 20, 22-25). The presence of HPV DNA can be detected by PCR (sequencing or INNO-LiPA) or in situ hybridization. HPV-independent VSCC are more common and seem to have a higher recurrence rate (mean 44%) and worse overall survival (mean 60%) compared to HPV-dependent VSCC (mean 26% and 78%, respectively), although no definitive conclusions can be drawn because of varying results and different definitions of HPV positivity (16, 17, 20, 22). VSCC associated with HSIL have a better prognosis with regard to local recurrence, disease-free survival, and overall survival compared to VSCC associated with LS and/or dVIN (15, 25, 83). One possible explanation for the prognostic difference between HPV-dependent and HPV-independent VSCC might be due to a better response to treatment of HPV-dependent cancers as has been shown in head and neck squamous cell carcinoma (78, 79). Of the studies included in table 3, only the study of Alonso et al. reported on the specific treatments in HPV+ and HPV- VSCC and found no differences between the two groups (13).

2.5 Prognosis
In general, 5-year survival for recurrent VSCC is reported to be 25–50% compared to 50–90% for patients with primary VSCC (40, 47, 52, 84, 85). Prognosis is mainly influenced by the presence of groin metastases at initial diagnosis. In addition, age, comorbidity, advanced FIGO stage, and tumor characteristics are important factors for prognosis and outcome (8, 9, 45, 46, 48, 50, 51, 64, 76, 84, 86). More recently, morphological factors such as spindle cell morphology and molecular changes, especially mutations in HRAS, were shown to be associated with poor prognosis in VSCC (87-89). Furthermore, prognosis is influenced by the site of recurrence and the time interval between initial diagnosis and recurrent disease. Five-year survival after diagnosis of recurrent disease for patients with early local recurrence (<24 months after primary treatment) was 53%, compared to 76% for patients with late local recurrence (>24 months after primary treatment) (p=0.05) (48, 90). The prognosis for patients with groin and/or skin bridge recurrence of VSCC is very poor with 5-year survival rates of only 0–10% (34-36, 50, 85, 91-94). However, a recently published study found an overall survival rate of 50% after 7 years for patients with a groin recurrence (95).

Risk factors and treatment for recurrent vulvar squamous cell carcinoma

Table 3: Prevalence of HPV in VSCC and influence of HPV presence on prognosis

Author	N° of patients	N° HPV positive	N° HPV negative	Clinical outcome HPV positive	Clinical outcome HPV negative	Clinical outcome p-value
Larsson et al. 2012[22]	130	31%	69%	RR 30% / OS 67%	RR 44% / OS 43%	RR p = 0.121 / OS **p = 0.029**
Alonso et al. 2011[13]	98	19%	81%	RR 60% / OS 67%	RR 50% / OS 71%	RR p = 0.885. Number of local recurrences lower in HPV positive VSCC (16% vs 37%, **p = 0.049**) / OS p = 0.789
Lindell et al. 2010[16]	75	31%	69%	RR NS / OS 100%	RR NS / OS 65%	RR HPV positive better disease free survival; **p = 0.004** / OS **p = 0.001**
Van de Nieuwenhof et al. 2009[19]	130	35%	65%	RR NS / OS NS	RR NS / OS NS	RR NS / OS p = 0.646
Pinto et al. 2004[23]	161	24%	76%	RR 50% / OS 63%	RR 35% / OS 71%	RR p = 0.055 / OS p = 0.447
Rouzier et al. 2001*[83]	77	32% vulvar HSIL adjacent to the VSCC	68% LS or dVIN adjacent to the VSCC	RR 10% / OS 87%	RR 35% / OS 42%	RR **p < 0.05** / OS **p < 0.01**
Monk et al. 1995[17]	55	60%	40%	RR 27% / OS 72%	RR 55% / OS 44%	RR **p = 0.041** / OS **p = 0.01**
Ansink et al. 1994[20]	60	32%	68%	RR NS / OS NS	RR NS / OS NS	RR NS / OS HPV positive better OS; **p = 0.003**
Hording et al. 1993[24]	62	31%	69%	RR NS / OS NS	RR NS / OS NS	RR not significant / OS NS
Bloss et al. 1991[18]	21	48%	52%	RR 20% / OS 90%	RR 45% / OS 82%	RR not significant / OS not significant

*Determination of the presence of precursor lesions based on morphology.

HPV: human papilloma virus
VSCC: vulvar squamous cell carcinoma
RR: recurrence rate
OS: overall survival
NS: not specified

Chapter 4

Table 4: Treatment of local recurrence of VSCC

Study	Total	Local	Local & groin	Beyond vulva*	Surgery	Surgery + RT	RT only	C-RT	No treatment/ palliative	Re-recurrences	5- year survival**	Note
Weikel, 2006[39]	N=201	Ns	ns	Ns	N=201 (100%)					68% after 5 years.	45%	Authors did not specify treatment for location of recurrent disease
Chakalova, 1993[94]	N=102	N=72 (70%)	N=18 (18%)	N=12 (12%)	N=81 (79%)	N=21 (21%)				NS	61%	79% of patients with a local recurrence were free of disease at last follow-up
Kohler, 1997[107]	N=82	N=39 (47%)	N=27 (33%)	N=16 (20%)	N=33 (40%)		N=16 (20%)		N=33 (40%)	17 (35%)	46.9%	Re-recurrence occurred after 12,8 months on average.
Piura, 1993[47]	N=73	N=39 (53%)		N=34 (47%)	N=41 (56%)	N=7 (10%)	N=5 (7%)		N=20 (27%)	NS	35.2%	At last follow up, 73% of all patients treated surgically were alive versus 25% of all patients treated with RT.
Schmidt, 1992[90]	N=51	N=28 (55%)	N=3 (6%)	N=20 (39%)	N=19 (37%)	N=20 (39%)	N=7 (14%)		N=5 (10%)	19 (37%)	61%	
Faul, 1998[84]	N=47	N=47 (100%)			N=31 (66%)	N=6 (13%)	N=6 (13%)	N=2 (4%)	N=2 (4%)	13 (28%) local, 6 (13%) groin or distant	40%	Mean time to re-recurrence 1,1 yr.
Frischbier, 1985[106]	N=41	N=41 (100%)			N=41 (100%)					NS	19.5%	All patients received radiotherapy as treatment for their primary tumor.
Strauß, 1994[108]	N=37	N=28 (76%)	N=4 (11%)	N=5 (13%)	N=18 (49%)	N=8 (22%)	N=7 (19%)			50%	56%	For 4 patients treatment was NS

Study	Total	Local	Local & groin	Beyond vulva*	Surgery	Surgery + RT	RT only	C-RT	No treatment/ palliative	Re-recurrences	5- year survival**	Note
Hopkins, 1990[36]	N=34	N=24 (71%)	N=6 (17%)	N=4 (12%)	N=27 (79%)	N=7 (21%)				15 (44%)	61%	
Simonsen, 1984[91]	N=32	N=29 (91%)	N=3 (9%)		N=25 (78%)	N=5 (16%)	N=1 (3%)	N=1 (3%)		NS	NS	34% had no evidence of disease at last follow up.
Buchler, 1979[109]	N=21	N=18 (86%)	N=3 (14%)		N=13 (62%)	N=1 (5%)	N=7 (33%)			5 (38%) after S, 2 (29%) after RT	NS	Survival 43 months after S and 26 months after RT.
Raffetto, 2003[102]	N=20	N=6 (30%)	N=6 (30%)	N=8 (40%)			N=9 (45%)	N=11 (55%)		NS	20%	

Only studies that reported on a minimum of 20 patients were included

S:	Surgery
RT:	Radiotherapy
CT:	Chemotherapy
C-RT:	Chemoradiotherapy
NS:	Not specified
CR:	Complete response
PR:	Partial response

*: Beyond vulva: all VSCC recurrences without a local component.
** For all patients: local, groin and distant recurrences
*** Radiotherapy sometimes combined with chemotherapy: not specified

3. Diagnosis and clinical evaluation

Symptoms of local recurrences differ, and patients may be asymptomatic. The diagnostic workup of patients with recurrent VSCC includes a complete medical history and full gynecological examination. All clinically suspect vulvar areas should be biopsied to confirm diagnosis and to glean information about the extent of disease. Fine-needle aspiration of suspected groin lymph nodes is needed to confirm the diagnosis (2, 4, 34, 96). For assessment of regional and distant metastases, computed tomography (CT) scans of the pelvis, abdomen, and chest are recommended (2, 4, 96). A positron emission tomography–CT scan may be considered for patients in whom other radiological imaging is inconclusive (2, 34, 96). If there is locally advanced recurrent VSCC, a cystoscopy and/or proctoscopy should be considered (40, 41).

4. Local recurrence

Surgery is the cornerstone of treatment for local recurrent VSCC (4, 8, 34, 96). Surgical treatment of local recurrences becomes more difficult with increasing tumor size, especially when the tumor is close to the anus or urethra. Furthermore, prior surgery with changed anatomy and, in particular, earlier radiotherapy can influence skin healing and the risk of wound dehiscence or infection. Reconstructive surgery can be an indispensable component of surgical treatment, for example by using local (fasciocutaneous) skin flaps (97) or V-Y reconstruction skin flaps from the upper posterior thighs (98-100) or split-skin grafts (101). Surgery may be contraindicated based on comorbidity and/or extensive previous surgery (1, 8, 34). In these cases, radiotherapy with or without concurrent chemotherapy may be considered, if not administered previously, preferably with the option of surgery for residual disease after downsizing (4, 102). Radiotherapy can be considered as an adjuvant or primary treatment (84). Chemotherapy is only indicated in combination with radiotherapy or as palliative treatment (102-104). A full IFL is considered standard treatment for the groins in cases of local recurrence infiltrating >1 mm, where primary treatment of VSCC did not comprise full IFL (8, 34, 36). A recent article on the safety of SLN biopsy in local recurrent VSCC showed that a repeat SLN biopsy is technically challenging, but feasible. The safety of the procedure should and will be further investigated before it is implemented in the treatment of local recurrent VSCC (105). We found 12 retrospective studies on the treatment of local recurrent VSCC. Table 4 provides an overview of these studies, with characteristics, reported number of re-recurrences, and 5-year overall survival (36, 39, 47, 84, 90, 91, 94, 102, 106-109).

4.1. Surgery

Patients who have an isolated local recurrence are good candidates for surgical treatment, unless there is a threat for the necessity of a colostomy. Eleven of the 12 studies on the treatment of local recurrent VSCC evaluated surgery alone as treatment for local recurrent VSCC. All 11 studies had a retrospective design. The largest study, published in 2006 by Weikel et al., included 201 patients (39). The other studies evaluated 13–81 patients. Surgery consisted of wide local excision, hemivulvectomy, or radical vulvectomy, with or without groin surgery. The type of surgery was based on the location and extent of the recurrence. The percentage of patients who developed a second recurrence was 28–50% (36, 39, 84, 90, 107-109), and 5-year survival was 20–79% (36, 39, 47, 84, 90, 94, 106-108). The most often encountered complications were wound infection (40%), vaginal stricture, and urinary incontinence (91, 109).

In seven studies, 5-21 patients with local recurrent VSCC were treated with surgery and adjuvant radiotherapy (36, 47, 84, 90, 91, 94, 108). The indications for adjuvant radiotherapy are unclear. In these studies, the percentage of subsequent recurrences was 35–50%, with a 5-year survival of 35–79%. Most reported complications after radiotherapy were skin reactions, such as moist desquamation and skin ulceration. In some cases, interruption of radiation treatment was necessary (102).

Pelvic exenteration may be a curative treatment option when patients have extensive locally recurrent VSCC that is otherwise untreatable. Four studies have reported on pelvic exenteration as a treatment option in cases of local recurrent VSCC. Pelvic exenteration achieved good symptom control, with a reported mean overall survival of 11 months and 2-year overall survival of 57%. This extensive surgical procedure is associated with considerable morbidity, and most patients develop psychological problems due to major alterations in body image and loss of sexual function. Patient selection and extensive counselling is of utmost importance before pelvic exenteration is performed (110-113).

4.2 (Chemo)radiotherapy

When surgery is not possible or may lead to high morbidity, (chemo)radiotherapy can be considered as a primary treatment for locally recurrent VSCC, but only if patients have not previously undergone radiotherapy. Therapy plans are individualized depending on the extent of disease and prior therapy, but they most often involve external beam radiotherapy (EBRT), in some cases with a brachytherapy boost. Seven retrospective studies were performed that included 5–20 patients treated with primary (chemo)radiotherapy for locally recurrent VSCC (47, 84, 90, 102, 107-109). In general, treatment with primary (chemo)radiotherapy yields less favorable treatment results than surgery with respect to 5-year survival (20–60% versus 20–79%, respectively) (47, 109). It should, however, be emphasised that there is a high risk of bias with regard to therapy

selection and associated outcomes. Although most studies do not report on the selection of therapy, it is plausible that patients with worse clinical or tumor characteristics were selected more often for (chemo)radiotherapy instead of surgical therapy. Radiotherapy-associated side effects were severe skin desquamation (20%) (102), radiation fibrosis (10%) (102), lymphedema (10%) (102), and, more rarely, radiation proctitis (3%). The additional value of concurrent chemoradiotherapy in recurrent VSCC is not well documented. However, this treatment strategy has been suggested to improve salvage of bulky locally advanced disease, with complete response rates as high as 64% (102, 114-116). One study evaluated the efficacy and toxicity of chemotherapy alone (cisplatin and vinorelbine); it included nine patients with local recurrent VSCC and seven patients with a groin recurrence. A complete response was recorded in 27% of the patients and a partial response in 13%. Stable disease was observed in 27% of the patients and progressive disease in 33%. The median progression-free survival was 10 months (range 3–17 months), and overall survival was 19 months (1–30 months). Toxicity of the treatment was high, especially hematological toxicity; 31% of the patients experienced WHO grade 3/4 leukopenia, 69% had neutropenia, and 24% had anemia. Other WHO grade 3/4 toxicities included nausea/vomiting in 62% of the patients, neurotoxicity in 38%, and alopecia in 62% (117). Chemotherapy as treatment for locally recurrent VSCC should only be considered as a last resort in a palliative treatment setting, with a small chance of response.

5. Groin recurrence

Nearly all VSCC patients with a groin recurrence die of disease, and management is challenging (4, 6, 34, 38, 50, 51, 64-66). However, a recently published study on groin recurrences found a 50% survival rate after 7 years and the authors suggest that a groin recurrence should therefore no longer be considered a palliative situation (95). Choice of treatment is individualized and determined by the size of the tumor, previous treatment, and time interval to recurrence (34, 38, 64, 66). We found a total of 7 studies that reported on the treatment of groin recurrences in VSCC patients. All studies had a retrospective design (35, 36, 85, 91-93, 95). Patients included in the studies had local and groin recurrences, isolated groin recurrences or groin and pelvic recurrence. An overview of the studies and their results is provided in table 5. Median survival was 3–19 months, with overall survival rates of 0–50%.

Surgery, followed by radiotherapy when possible, is currently the treatment of choice if the patient is in good general health. Primary radiotherapy for a groin recurrence can be considered as alternative treatment, but almost never leads to a cure (35, 118, 119). Five studies report on surgery, either alone or in combination with radiotherapy, as a treatment for groin recurrences. Surgical treatment consisted of full IFL or debulking of the groin recurrence(s). Radiotherapy consisted of external beam therapy. Some patients in these studies received primary radiotherapy. In general, the recommended dose for radiotherapy is 46–50 Gy in fractions of 1.8–2.0 Gy, with a boost to 56–60 Gy to the site of the involved lymph node(s), especially in cases of extracapsular extension, and to 64–66 Gy to macroscopic residual disease. One study combined surgery with chemo- and radiotherapy in 10 of the 30 included patients. Which chemotherapy was not specified by the authors (95). Progression-free survival and overall survival was low, with median survival rates varying from 6 to 16 months. Only a few patients survived for >5 years without evidence of disease after treatment (35, 36, 85, 91). However, in the most recently published study a five-year survival of 50% was found. Especially patients who underwent combined therapy, surgery with (chemo)radiotherapy had a better overall survival after groin recurrence in comparison to patients with single-mode therapy (HR 0.25, p=0.037)(95). Earlier studies already suggested better outcomes for concurrent chemoradiotherapy, also based on efficacy of the treatment for advanced primary disease (115, 120). Concurrent chemoradiotherapy is recommended for treatment of (bulky) groin recurrence, followed by resection of the residual tumor if feasible (120-122). Chemotherapy as a stand-alone treatment for groin recurrence is only considered in a palliative setting, when surgery or radiotherapy are not advisable (92, 93). Two studies evaluated palliative treatment of a groin recurrence with chemotherapy alone. These studies found a median progression-free survival of 2.6–4 months, with a median overall survival of 7–9 months (92, 93). In other words, palliative chemotherapy for groin recurrences yields short response rates with substantial side effects.

5.1 Skin bridge recurrence

Skin bridge recurrence can be considered a special type of locoregional recurrence, with a clinical course comparable to groin recurrence and an extremely poor prognosis, despite treatment with surgery and/or radiotherapy. It has been hypothesized that skin bridge recurrences evolve from metastatic tumor emboli in lymphatic vessels arrested in their migration (9). Skin bridge recurrences in vulvar cancer are uncommon, but they are relevant because of the poor outcome. The incidence has been described as 0–9% (9, 36, 46, 47, 50, 123). Since the introduction of a surgical approach with separate incisions (instead of "en-bloc" surgery), there has been an increased incidence of skin bridge recurrences (46). De Hullu et al. investigated the prevalence of groin and skin bridge recurrences in 253 VSCC patients primarily treated with surgery. Group I underwent radical vulvectomy with en bloc IFL, and group II underwent wide local excision with

Table 5: Treatment of groin recurrence of VSCC

Study	Total	Local & groin	Isolated groin	Surgery	Surgery + RT	RT	CT	Response	Progression-free survival	Overall survival	Note
Frey, 2016[95]	N=30	N=4 (21%), 2 local, groin & distant recurrence	N=30* (7 patients had groin and pelvic recurrence)	N=7 (23%)	N=20 (66%), 10 patients received surgery and C-RT	N=1 (3%)	N=1 (3%)	NS	NS	50% 5-year survival	Patients with multimodal groin treatments performed better than tose with single-mode treatment (hazard ratio 0.25, p=0.037) * No data available of 1 patient
Cormio, 2010[35]	N=21	N=4 (21%)	N=17 (81%)	N=3 (14%)	N=7 (34%)	N=2 (10%)	N=3 (14%)	NS	NS	Median: 9 months (range 3-30)	95% of the patients died, 1 patient alive after 60 months after surgical treatment. 3 (14%) patients received surgery and CT and 3 (14%) patients refused treatment.
Hopkins, 1990[36]	N=10	N=6 (60%)	N=4 (40%)	N=4 (40%)	N=6 (60%)			NS	0/10	10% 5-year survival	
Simonsen, 1984[91]	N=12	N=3 (25%)	N=9 (75%)	N=1 (8%)	N=4 (34%)	N=7 (58%)		NS	NS	Median: 6 months (0.1-3.5 years). 8.3% 5-year survival	1 patient had NED after 6 years. She was treated with surgery and RT.
Tilmans, 1992[85]	N=12		N=12 (100%)		N=5 (42%)	N=5 (42%)	N=1 (8%)	NS	17%	Median: 10 months	2 patients received cyclophosphamide & cisplatin after S+RT. 1 patient received supportive care
Wagenaar, 2001[92]	N=13		N=13 (100%)				N=13 (100%)	PR: 54%, 7/13	Median: 4 months (range 2-22)	Median: 9 months (range 2-31)	CT: bleomycin, methotrexate & CCNU.
Study	**Total**	**Local & groin**	**Isolated groin**	**Surgery**	**Surgery + RT**	**RT**	**CT**	**Response**	**Progression-free survival**	**Overall survival**	**Note**

| Witteveen, 2009[93] | N=11 | N=5 (45%) | N=6 (55%) | N=11 (100%) | CR + PR 27%, 3/11 | Median: 2,6 months (2-4,2 months). 10,3% 1-year progression free-survival | Median: 6,9 months (range 3,5-12,4). 31% 1-year OS | Patients were not amenable to surgery or radiotherapy. Response and overall survival is for all patients included in the study (total 29, all patients with locally advanced or recurrent VSCC) |
| | | | | | | | | CT: paclitaxel. |

Only studies that reported on a minimum of 10 patients were included

S: Surgery
RT: Radiotherapy
CT: Chemotherapy
C-RT: Chemoradiotherapy
CT: Chemotherapy
NS: Not specified
CR: Complete response
PR: Partial response
SD: Stable disease
PD: Progressive disease
NED: no evidence of disease

Chapter 4

IFL through separate incisions. The prevalence of skin bridge recurrences was 6.3% in group II compared to 1.3% in group I (p=0.029)(46). Rose et al. found five skin bridge recurrences in a group of 126 patients (3.9%) with VSCC (123). Rouzier et al. investigated relapses and prognostic factors associated with skin bridge recurrences. They found that margin status (p=0.001) and tumor size >2 cm (p<0.05) were significantly associated with the occurrence of skin bridge recurrences. Seven patients had a skin bridge recurrence out of a group of 215 VSCC patients. None of the seven patients were alive after 1 year (9). On the other hand, Woolderink et al. reported on 125 patients with VSCC; none had a skin bridge recurrence (50). In conclusion, literature on skin bridge recurrences is limited and prognosis is still very poor.

6. Distant recurrence

Patients with distant recurrence have a very poor prognosis. There is no standard therapy for these patients, and treatment is always palliative (85, 96). In cases of isolated recurrence in the pelvis, radiotherapy or concurrent chemoradiotherapy can be considered. Patients with para-aortic nodal recurrences can be treated with radiation therapy to relieve symptoms. Radiation can also be used for palliation of pain due to bone metastasis. Some studies have evaluated chemotherapy for patients with metastatic vulvar cancer, often as a last resort if patients are not amenable to surgery or radiotherapy. These studies are summarized in table 6 (85, 93, 102, 124). The most commonly used agents are paclitaxel, bleomycin, cisplatin and 5-fluorouracil, but large series are lacking. Although some regimens were associated with limited clinical activity, response rates were low, with complete response rates of 7–20% (93, 102) and partial response rates of 7–80% (93, 102, 124). Other patients had stable or progressive disease during chemotherapy (85, 93, 124). Response was usually short, with a median survival of 4–7 months. Response rates of recurrences in irradiated areas are even lower.

Recently, EGFR targeting therapy has been suggested as a therapeutic option in the treatment of patients with distant recurrences. In a phase II trial on the effect of erlotinib (an inhibitor of the EGFR tyrosine kinase) 32 patients with distant recurrences were included. Eight patients were treated with one cycle of 28 days oral erlotinib followed by surgery or chemoradiation (cohort 1) and 24 patients were treated with multiple cycles of oral erlotinib (cohort 2, mean 3.3 cycles). In cohort 1 35% of the patients showed a partial response to erlotinib therapy and in cohort 2 22% of the patients. Progressive disease was seen in 6% and 23% of the patients, respectively. Other patients had stable disease or were unevaluable, because they failed to complete a minimum number of cycles of therapy due to serious adverse events. Adverse events included an allergic reaction, diarrhoea, dehydration, electrolyte abnormalities, gastro-intestinal bleed and ischemic colitis (all grade 3 toxicity). Two patients experienced grade 4 acute renal

Table 6: Chemotherapy for patients with distant recurrent VSCC

Study	N° patients distant recurrent disease	CT regimen	Response	Survival	Note
Witteveen, 2009[93]	8 distant (22 total)	Paclitaxel	CR 7% PR 7% Overall response 14%	Median 6.9 months 1-year survival 31%	4 patients discontinued treatment for toxicity
Raffetto, 2003[102]	7 distant	Cisplatin or Cisplatin with 5 FU	CR 20% (1/5) PR 80% (4/5)	Median; 6 months (range 2-16). Mean; 8,2 months.	All patients also got radiotherapy. Five patients were treated with chemotherapy concomitantly or neo-adjuvant.
Tilmans, 1992[85]	11 distant	5 FU, Cisplatin, Aziridinyl-benzequinone, etoposide, doxorubicin, cyclophosphamide	PD 100%	Median; 4 months pelvic recurrence and 5 months distant recurrence	All treated with a palliative intention
Durrant, 1990[24]	10 distant	Bleomycin, methotrexate and lomustine	6/10 (60%) showed a partial or complete response	ns	Administered to patients ineligible for surgical treatment. 33 % of the patients discontinued treatment due to severe toxicity.

CT: Chemotherapy
OS: Overall Survival
CR: Complete Response
PR: Partial Response
SD: Stable disease
PD: Progressive disease
NS: not specified

Chapter 4

failure (125). These results are promising and new studies regarding targeted therapies in VSCC patients with distant recurrences are expected in the next future.

7. Summary and recommendations

In cases of local recurrence, surgical resection is the treatment of choice. If needed, combined with reconstructive and/or groin surgery. If primary surgery is not an option because of tumor growth adjacent to the urethra or anus, (chemo)radiotherapy can be a good alternative, either as definitive treatment or prior to surgery for downsizing the tumor. Chemotherapy alone is considered palliative treatment and is not recommended due to the low response rates and short duration of response. The preferred treatment for groin and skin bridge recurrence is surgery, followed by radiation therapy if not previously irradiated. Concurrent chemoradiotherapy can be considered if primary resection does not seem feasible, either preoperatively for downsizing of a bulky groin recurrence or as definitive or palliative treatment. Distant recurrences of VSCC are rare, and treatment is only palliative. Chemotherapy can be considered, but it has low response rates. Future studies regarding targeted treatment in patients with metastatic VSCC are expected. Management of recurrent VSCC should be individualized and requires an experienced, multidisciplinary team approach in an oncological center.

References

1. Gadducci A, Cionini L, Romanini A, Fanucchi A, Genazzani AR. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. Crit RevOncolHematol. 2006;60(3):227-41.

2. Hacker NF, Eifel PJ, van d, V. Cancer of the vulva. IntJGynaecolObstet. 2012;119 Suppl 2:S90-S6.

3. de Hullu JA, van der Zee AG. Surgery and radiotherapy in vulvar cancer. Crit RevOncolHematol. 2006;60(1):38-58.

4. Berek JS, Hacker N.F. Berek and Hacker's Gynecologic Oncology. 2014;6 ed Philadelphia LWW.

5. Schuurman MS, van den Einden LC, Massuger LF, Kiemeney LA, van der Aa MA, de Hullu JA. Trends in incidence and survival of Dutch women with vulvar squamous cell carcinoma. EurJCancer. 2013;49(18):3872-80.

6. Gonzalez BJ, Magrina JF, Gaffey TA, Hernandez JL, Webb MJ, Cliby WA, et al. Long-term survival and disease recurrence in patients with primary squamous cell carcinoma of the vulva. GynecolOncol. 2005;97(3):828-33.

7. Gadducci A, Tana R, Barsotti C, Guerrieri ME, Genazzani AR. Clinico-pathological and biological prognostic variables in squamous cell carcinoma of the vulva. Crit RevOncolHematol. 2012;83(1):71-83.

8. Salom EM, Penalver M. Recurrent vulvar cancer. Curr TreatOptions Oncol. 2002;3(2):143-53.

9. Rouzier R, Haddad B, Plantier F, Dubois P, Pelisse M, Paniel BJ. Local relapse in patients treated for squamous cell vulvar carcinoma: incidence and prognostic value. Obstet Gynecol. 2002;100(6):1159-67.

10. Oncology FCoG. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. 2014;125(2):97-8.

11. van der Steen S, de Nieuwenhof HP, Massuger L, Bulten J, de Hullu JA. New FIGO staging system of vulvar cancer indeed provides a better reflection of prognosis. GynecolOncol. 2010;119(3):520-5.

12. Al-Ghamdi A, Freedman D, Miller D, Poh C, Rosin M, Zhang L, et al. Vulvar squamous cell carcinoma in young women: a clinicopathologic study of 21 cases. GynecolOncol. 2002;84(1):94-101.

13. Alonso I, Fuste V, Del PM, Castillo P, Torne A, Fuste P, et al. Does human papillomavirus infection imply a different prognosis in vulvar squamous cell carcinoma? GynecolOncol. 2011;122(3):509-14.

14. Canavan TP, Cohen D. Vulvar cancer. AmFamPhysician. 2002;66(7):1269-74.

15. Kokka F, Singh N, Faruqi A, Gibbon K, Rosenthal AN. Is differentiated vulval intraepithelial neoplasia the precursor lesion of human papillomavirus-negative vulval squamous cell carcinoma? IntJGynecolCancer. 2011;21(7):1297-305.

16. Lindell G, Nasman A, Jonsson C, Ehrsson RJ, Jacobsson H, Danielsson KG, et al. Presence of human papillomavirus (HPV) in vulvar squamous cell carcinoma (VSCC) and sentinel node. GynecolOncol. 2010;117(2):312-6.

17. Monk BJ, Burger RA, Lin F, Parham G, Vasilev SA, Wilczynski SP. Prognostic significance of human papillomavirus DNA in vulvar carcinoma. ObstetGynecol. 1995;85(5 Pt 1):709-15.

18. Bloss JD, Liao SY, Wilczynski SP, Macri C, Walker J, Peake M, et al. Clinical and histologic features of vulvar carcinomas analyzed for human papillomavirus status: evidence that squamous cell carcinoma of the vulva has more than one etiology. HumPathol. 1991;22(7):711-8.

Chapter 4

19. van de Nieuwenhof HP, van der Avoort IA, de Hullu JA. Review of squamous premalignant vulvar lesions. Crit RevOncolHematol. 2008;68(2):131-56.

20. Ansink AC, Krul MR, De Weger RA, Kleyne JA, Pijpers H, Van TH, et al. Human papillomavirus, lichen sclerosus, and squamous cell carcinoma of the vulva: detection and prognostic significance. GynecolOncol. 1994;52(2):180-4.

21. Coleman RL, Santoso JT. Vulvar carcinoma. CurrTreatOptionsOncol. 2000;1(2):177-90.

22. Larsson GL, Helenius G, Andersson S, Elgh F, Sorbe B, Karlsson MG. Human papillomavirus (HPV) and HPV 16-variant distribution in vulvar squamous cell carcinoma in Sweden. Int J Gynecol Cancer. 2012;22(8):1413-9.

23. Pinto AP, Schlecht NF, Pintos J, Kaiano J, Franco EL, Crum CP, et al. Prognostic significance of lymph node variables and human papillomavirus DNA in invasive vulvar carcinoma. Gynecol Oncol. 2004;92(3):856-65.

24. Hording U, Kringsholm B, Andreasson B, Visfeldt J, Daugaard S, Bock JE. Human papillomavirus in vulvar squamous-cell carcinoma and in normal vulvar tissues: a search for a possible impact of HPV on vulvar cancer prognosis. IntJCancer. 1993;55(3):394-6.

25. van de Nieuwenhof HP, Massuger LF, van der Avoort IA, Bekkers RL, Casparie M, Abma W, et al. Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age. EurJCancer. 2009;45(5):851-6.

26. Abell MR, Gosling JR. Intraepithelial and infiltrative carcinoma of vulva: Bowen's type. Cancer. 1961;14:318-29.

27. Bornstein J. The 2015 Internation Society for the Study of Vulvovaginal Disease Terminology of Vulvar Squamous Intraepithelial Lesions. 2015.

28. Torezan LA, Festa-Neto C. Cutaneous field cancerization: clinical, histopathological and therapeutic aspects. AnBrasDermatol. 2013;88(5):775-86.

29. Braakhuis BJ, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. Cancer Res. 2003;63(8):1727-30.

30. van der Zee AG, Oonk MH, de Hullu JA, Ansink AC, Vergote I, Verheijen RH, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. JClinOncol. 2008;26(6):884-9.

31. Oonk MH, van Hemel BM, Hollema H, de Hullu JA, Ansink AC, Vergote I, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol. 2010;11(7):646-52.

32. Oonk MH, de Hullu JA, van der Zee AG. Current controversies in the management of patients with early-stage vulvar cancer. CurrOpinOncol. 2010;22(5):481-6.

33. van den Einden LC, Aben KK, Massuger LF, van Spronsen DJ, de Hullu JA. Successful centralisation of patients with vulvar carcinoma: a population-based study in The Netherlands. EurJCancer. 2012;48(13):1997-2003.

34. Coulter J, Gleeson N. Local and regional recurrence of vulval cancer: management dilemmas. Best Pract Res Clin Obstet Gynaecol. 2003;17(4):663-81.

35. Cormio G, Loizzi V, Carriero C, Cazzolla A, Putignano G, Selvaggi L. Groin recurrence in carcinoma of the vulva: management and outcome. EurJCancer Care (Engl). 2010;19(3):302-7.

36. Hopkins MP, Reid GC, Morley GW. The surgical management of recurrent squamous cell carcinoma of the vulva. Obstet Gynecol. 1990;75(6):1001-5.

37. Oonk MH, Hollema H, de Hullu JA, van der Zee AG. Prediction of lymph node metastases in vulvar cancer: a review. IntJGynecolCancer. 2006;16(3):963-71.

38. Stehman FB, Bundy BN, Ball H, Clarke-Pearson DL. Sites of failure and times to failure in carcinoma of the vulva treated conservatively: a Gynecologic Oncology Group study. AmJObstetGynecol. 1996;174(4):1128-32.

39. Weikel W, Schmidt M, Steiner E, Knapstein PG, Koelbl H. Surgical therapy of recurrent vulvar cancer. Am J Obstet Gynecol. 2006;195(5):1293-302.

40. Guideline vulvar cancer, national cancer institute. 2015.

41. Guideline vulvar cancer, oncoline. 2011.

42. Guidelines for the Diagnosis and Management of Vulval Carcinoma, RCOG. 2014.

43. N.F. H, J.C. G, C.J. H. Essentials of Obstetrics and Gynecology. Philadelphia: Elsevier inc.; 2010 2010.

44. A A, M G, P D. Textbook of gynaecological oncology. 2nd ed ed. Ankara: Günes Publishing; 2010 8/2010.

45. Maggino T, Landoni F, Sartori E, Zola P, Gadducci A, Alessi C, et al. Patterns of recurrence in patients with squamous cell carcinoma of the vulva. A multicenter CTF Study. Cancer. 2000;89(1):116-22.

46. de Hullu JA, Hollema H, Lolkema S, Boezen M, Boonstra H, Burger MP, et al. Vulvar carcinoma. The price of less radical surgery. Cancer. 2002;95(11):2331-8.

47. Piura B, Masotina A, Murdoch J, Lopes A, Morgan P, Monaghan J. Recurrent squamous cell carcinoma of the vulva: a study of 73 cases. Gynecol Oncol. 1993;48(2):189-95.

48. Te Grootenhuis NC, van der Zee AG, van Doorn HC, van d, V, Vergote I, Zanagnolo V, et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. GynecolOncol. 2016;140(1):8-14.

49. Oonk MH, de Hullu JA, Hollema H, Mourits MJ, Pras E, Wymenga AN, et al. The value of routine follow-up in patients treated for carcinoma of the vulva. Cancer. 2003;98(12):2624-9.

50. Woolderink JM, de Bock GH, de Hullu JA, Davy MJ, van der Zee AG, Mourits MJ. Patterns and frequency of recurrences of squamous cell carcinoma of the vulva. GynecolOncol. 2006;103(1):293-9.

51. Woelber L, Mahner S, Voelker K, Eulenburg CZ, Gieseking F, Choschzick M, et al. Clinicopathological prognostic factors and patterns of recurrence in vulvar cancer. Anticancer Res. 2009;29(2):545-52.

52. Preti M, Ronco G, Ghiringhello B, Micheletti L. Recurrent squamous cell carcinoma of the vulva: clinicopathologic determinants identifying low risk patients. Cancer. 2000;88(8):1869-76.

53. Rutledge FN, Mitchell MF, Munsell MF, Atkinson EN, Bass S, McGuffee V, et al. Prognostic indicators for invasive carcinoma of the vulva. Gynecol Oncol. 1991;42(3):239-44.

54. Bogani G, Cromi A, Serati M, Uccella S, Donato VD, Casarin J, et al. Predictors and Patterns of Local, Regional, and Distant Failure in Squamous Cell Carcinoma of the Vulva. AmJClinOncol. 2014.

55. Yoder BJ, Rufforny I, Massoll NA, Wilkinson EJ. Stage IA vulvar squamous cell carcinoma: an analysis of tumor invasive characteristics and risk. Am J Surg Pathol. 2008;32(5):765-72.

Chapter 4

56. Holthoff ER, Jeffus SK, Gehlot A, Stone R, Erickson SW, Kelly T, et al. Perineural Invasion Is an Independent Pathologic Indicator of Recurrence in Vulvar Squamous Cell Carcinoma. Am J Surg Pathol. 2015;39(8):1070-4.

57. Regauer S. Residual anogenital lichen sclerosus after cancer surgery has a high risk for recurrence: a clinicopathological study of 75 women. GynecolOncol. 2011;123(2):289-94.

58. Modesitt SC, Waters AB, Walton L, Fowler WC, Jr., Van LL. Vulvar intraepithelial neoplasia III: occult cancer and the impact of margin status on recurrence. Obstet Gynecol. 1998;92(6):962-6.

59. Heaps JM, Fu YS, Montz FJ, Hacker NF, Berek JS. Surgical-pathologic variables predictive of local recurrence in squamous cell carcinoma of the vulva. Gynecol Oncol. 1990;38(3):309-14.

60. Viswanathan AN, Pinto AP, Schultz D, Berkowitz R, Crum CP. Relationship of margin status and radiation dose to recurrence in post-operative vulvar carcinoma. Gynecol Oncol. 2013;130(3):545-9.

61. Groenen SM, Timmers PJ, Burger CW. Recurrence rate in vulvar carcinoma in relation to pathological margin distance. Int J Gynecol Cancer. 2010;20(5):869-73.

62. Dakubo GD, Jakupciak JP, Birch-Machin MA, Parr RL. Clinical implications and utility of field cancerization. Cancer Cell International. 2007;7 :15 Mar 2007.

63. Woelber L, Choschzick M, Eulenburg C, Hager M, Jaenicke F, Gieseking F, et al. Prognostic value of pathological resection margin distance in squamous cell cancer of the vulva. Ann Surg Oncol. 2011;18(13):3811-8.

64. Deka P, Barmon D, Shribastava S, Kataki AC, Sharma JD, Bhattacharyya M. Prognosis of vulval cancer with lymph node status and size of primary lesion: A survival study. JMidlifeHealth. 2014;5(1):10-3.

65. Woelber L, Eulenburg C, Choschzick M, Kruell A, Petersen C, Gieseking F, et al. Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment. IntJGynecolCancer. 2012;22(3):503-8.

66. Lataifeh I, Nascimento MC, Nicklin JL, Perrin LC, Crandon AJ, Obermair A. Patterns of recurrence and disease-free survival in advanced squamous cell carcinoma of the vulva. GynecolOncol. 2004;95(3):701-5.

67. Mahner S, Jueckstock J, Hilpert F, Neuser P, Harter P, de Gregorio N, et al. Adjuvant therapy in lymph node-positive vulvar cancer: the AGO-CaRE-1 study. Journal of the National Cancer Institute. 2015;107(3).

68. Homesley HD, Bundy BN, Sedlis A, Adcock L. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. Obstet Gynecol. 1986;68(6):733-40.

69. Kunos C, Simpkins F, Gibbons H, Tian C, Homesley H. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. ObstetGynecol. 2009;114(3):537-46.

70. Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG. Management of regional lymph nodes and their prognostic influence in vulvar cancer. ObstetGynecol. 1983;61(4):408-12.

71. Aragona AM, Cuneo NA, Soderini AH, Alcoba EB. An analysis of reported independent prognostic factors for survival in squamous cell carcinoma of the vulva: is tumor size significance being underrated? GynecolOncol. 2014;132(3):643-8.

72. Courtney-Brooks M, Sukumvanich P, Beriwal S, Zorn KK, Richard SD, Krivak TC. Does the number of nodes removed impact survival in vulvar cancer patients with node-negative disease? GynecolOncol. 2010;117(2):308-11.

73. van Beekhuizen HJ, Auzin M, van den Einden LC, de Hullu JA, van d, V, Wildhagen MF, et al. Lymph node count at inguinofemoral lymphadenectomy and groin recurrences in vulvar cancer. IntJGynecolCancer. 2014;24(4):773-8.

74. Baiocchi G, Cestari FM, Rocha RM, Faloppa CC, Kumagai LY, Fukazawa EM, et al. Does the count after inguinofemoral lymphadenectomy in vulvar cancer correlate with outcome? Eur J Surg Oncol. 2013;39(4):339-43.

75. Chen SL, Iddings DM, Scheri RP, Bilchik AJ. Lymphatic mapping and sentinel node analysis: current concepts and applications. CA Cancer JClin. 2006;56(5):292-309.

76. Paladini D, Cross P, Lopes A, Monaghan JM. Prognostic significance of lymph node variables in squamous cell carcinoma of the vulva. Cancer. 1994;74(9):2491-6.

77. Ansink A, van d, V. Surgical interventions for early squamous cell carcinoma of the vulva. Cochrane Database Syst Rev. 2000(2):CD002036.

78. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. ClinCancer Res. 2009;15(22):6758-62.

79. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. JNatlCancer Inst. 2008;100(4):261-9.

80. Ragin CC, Taioli E. Survival of squamous cell carcinoma of the head and neck in relation to human papillomavirus infection: review and meta-analysis. IntJCancer. 2007;121(8):1813-20.

81. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The Lancet Oncology. 2012;13(6):607-15.

82. Mensah FA, Mehta MR, Lewis JS, Jr., Lockhart AC. The Human Papillomavirus Vaccine: Current Perspective and Future Role in Prevention and Treatment of Anal Intraepithelial Neoplasia and Anal Cancer. The oncologist. 2016.

83. Rouzier R, Morice P, Haie-Meder C, Lhomme C, Avril MF, Duvillard P, et al. Prognostic significance of epithelial disorders adjacent to invasive vulvar carcinomas. GynecolOncol. 2001;81(3):414-9.

84. Faul C, Miramow D, Gerszten K, Huang C, Edwards R. Isolated local recurrence in carcinoma of the vulva: Prognosis and implications for treatment. International Journal of Gynecological Cancer. 1998;8(5):409-14.

85. Tilmans AS, Sutton GP, Look KY, Stehman FB, Ehrlich CE, Hornback NB. Recurrent squamous carcinoma of the vulva. Am J Obstet Gynecol. 1992;167(5):1383-9.

86. Onnis A, Marchetti M, Maggino T. Carcinoma of the vulva: critical analysis of survival and treatment of recurrences. Eur J Gynaecol Oncol. 1992;13(6):480-5.

87. Trietsch MD, Peters AA, Gaarenstroom KN, van Koningsbrugge SH, ter Haar NT, Osse EM, et al. Spindle cell morphology is related to poor prognosis in vulvar squamous cell carcinoma. BrJCancer. 2013;109(8):2259-65.

Chapter 4

88. Trietsch MD, Spaans VM, ter Haar NT, Osse EM, Peters AA, Gaarenstroom KN, et al. CDKN2A(p16) and HRAS are frequently mutated in vulvar squamous cell carcinoma. GynecolOncol. 2014;135(1):149-55.

89. Drew PA, al-Abbadi MA, Orlando CA, Hendricks JB, Kubilis PS, Wilkinson EJ. Prognostic factors in carcinoma of the vulva: a clinicopathologic and DNA flow cytometric study. IntJGynecolPathol. 1996;15(3):235-41.

90. Schmidt W, Villena-Heinsen C, Schmid H, Engel K, Jochum N, Muller A. [Recurrence of vulvar cancer--treatment, experiences and results]. Geburtshilfe Frauenheilkd. 1992;52(8):462-6.

91. Simonsen E. Treatment of recurrent squamous cell carcinoma of the vulva. Acta Radiol Oncol. 1984;23(5):345-8.

92. Wagenaar HC, Colombo N, Vergote I, Hoctin-Boes G, Zanetta G, Pecorelli S, et al. Bleomycin, methotrexate, and CCNU in locally advanced or recurrent, inoperable, squamous-cell carcinoma of the vulva: an EORTC Gynaecological Cancer Cooperative Group Study. European Organization for Research and Treatment of Cancer. Gynecol Oncol. 2001;81(3):348-54.

93. Witteveen PO, van d, V, Vergote I, Guerra C, Scarabeli C, Coens C, et al. Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer--Gynaecological Cancer Group). Ann Oncol. 2009;20(9):1511-6.

94. Chakalova G, Karagiozov A. The surgical management of recurrent carcinoma of the vulva. Eur J Gynaecol Oncol. 1993;14(4):318-22.

95. Frey JN, Hampl M, Mueller MD, Gunthert AR. Should Groin Recurrence Still Be Considered as a Palliative Situation in Vulvar Cancer Patients?: A Brief Report. Int J Gynecol Cancer. 2016;26(3):575-9.

96. Fonseca-Moutinho JA. Recurrent vulvar cancer. ClinObstetGynecol. 2005;48(4):879-83.

97. Weikel W, Hofmann M, Steiner E, Knapstein PG, Koelbl H. Reconstructive surgery following resection of primary vulvar cancers. GynecolOncol. 2005;99(1):92-100.

98. Lee PK, Choi MS, Ahn ST, Oh DY, Rhie JW, Han KT. Gluteal fold V-Y advancement flap for vulvar and vaginal reconstruction: a new flap. PlastReconstrSurg. 2006;118(2):401-6.

99. Saito A, Minakawa H, Saito N, Isu K, Hiraga H, Osanai T. Posterior thigh flap revisited: clinical use in oncology patients. SurgToday. 2014;44(6):1013-7.

100. Rinaldi M, Cormio G, Bucaria V, Di TP, Marino F, Altomare DF. [Reconstruction with skin flaps of the posterior aspect of the thighs after total pelvic evisceration with removal of vulvo-perineal soft tissues in recurrent vulvar squamous carcinoma]. Suppl Tumori. 2005;4(3):S208.

101. Thomas SS, Chenoy R, Fielding JW, Rollason TP, Jordan JA, Bracka A. Vulvoperineal reconstruction after excision of anogenital multifocal intraepithelial neoplasia ("MIN"). BrJPlastSurg. 1996;49(8):539-46.

102. Raffetto N, Tombolini V, Santarelli M, Valeriani M, Galla DA, Enrici RM. Radiotherapy alone and chemoirradiation in recurrent squamous cell carcinoma of the vulva. Anticancer Res. 2003;23(3C):3105-8.

103. Whitaker SJ, Kirkbride P, Arnott SJ, Hudson CN, Shepherd JH. A pilot study of chemo-radiotherapy in advanced carcinoma of the vulva. BrJObstetGynaecol. 1990;97(5):436-42.

104. Russell AH, Mesic JB, Scudder SA, Rosenberg PJ, Smith LH, Kinney WK, et al. Synchronous radiation and cytotoxic chemotherapy for locally advanced or recurrent squamous cancer of the vulva. Gynecol Oncol. 1992;47(1):14-20.

105. Doorn HC, van Beekhuizen HJ, Gaarenstroom KN, van d, V, van der Zee AG, Oonk M, et al. Repeat sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma is feasible. GynecolOncol. 2016.

106. Frischbier HJ, Wenn K. [Secondary vulvectomy treatment results in local recurrence of a vulvar carcinoma following electron irradiation]. Geburtshilfe Frauenheilkd. 1985;45(7):494-6.

107. Kohler U, Schone M, Bilek K. Experience and results in the treatment of vulvar carcinoma relapses. [German]

Erfahrungen und Ergebnisse bei der Behandlung von Rezidiven des Vulvakarzinoms. Geburtshilfe und Frauenheilkunde. 1997;57(8):453-7.

108. Strauss HG, Lampe D. [Recurrent vulvar carcinoma at the Halle/S. University Gynecologic Clinic 1971-1990--diagnosis and results of therapy]. Zentralbl Gynakol. 1994;116(12):675-8.

109. Buchler DA, Kline JC, Tunca JC, Carr WF. Treatment of recurrent carcinoma of the vulva. GynecolOncol. 1979;8(2):180-4.

110. Miller B, Morris M, Levenback C, Burke TW, Gershenson DM. Pelvic exenteration for primary and recurrent vulvar cancer. GynecolOncol. 1995;58(2):202-5.

111. Kaur M, Joniau S, D'Hoore A, Van CB, Van LE, Leunen K, et al. Pelvic exenterations for gynecological malignancies: a study of 36 cases. IntJGynecolCancer. 2012;22(5):889-96.

112. Pathiraja P, Sandhu H, Instone M, Haldar K, Kehoe S. Should pelvic exenteration for symptomatic relief in gynaecology malignancies be offered? ArchGynecolObstet. 2014;289(3):657-62.

113. Tan KK, Pal S, Lee PJ, Rodwell L, Solomon MJ. Pelvic exenteration for recurrent squamous cell carcinoma of the pelvic organs arising from the cloaca--a single institution's experience over 16 years. Colorectal Dis. 2013;15(10):1227-31.

114. Blake P. Radiotherapy and chemoradiotherapy for carcinoma of the vulva. BestPractResClinObstetGynaecol. 2003;17(4):649-61.

115. Beriwal S, Shukla G, Shinde A, Heron DE, Kelley JL, Edwards RP, et al. Preoperative intensity modulated radiation therapy and chemotherapy for locally advanced vulvar carcinoma: analysis of pattern of relapse. IntJRadiatOncolBiolPhys. 2013;85(5):1269-74.

116. Moore DH, Ali S, Koh WJ, Michael H, Barnes MN, McCourt CK, et al. A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study. GynecolOncol. 2012;124(3):529-33.

117. Cormio G, Loizzi V, Gissi F, Serrati G, Panzarino M, Carriero C, et al. Cisplatin and vinorelbine chemotherapy in recurrent vulvar carcinoma. Oncology. 2009;77(5):281-4.

118. Tewari K, Cappuccini F, Syed AM, Puthawala A, DiSaia PJ, Berman ML, et al. Interstitial brachytherapy in the treatment of advanced and recurrent vulvar cancer. Am J Obstet Gynecol. 1999;181(1):91-8.

119. Perrone AM, Galuppi A, Cima S, Pozzati F, Arcelli A, Cortesi A, et al. Electrochemotherapy can be used as palliative treatment in patients with repeated loco-regional recurrence of squamous vulvar cancer: a preliminary study. Gynecol Oncol. 2013;130(3):550-3.

120. Gill BS, Bernard ME, Lin JF, Balasubramani GK, Rajagopalan MS, Sukumvanich P, et al. Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer: A National Cancer Data Base (NCDB) analysis. GynecolOncol. 2015;137(3):365-72.

121. Reade CJ, Eiriksson LR, Mackay H. Systemic therapy in squamous cell carcinoma of the vulva: current status and future directions. GynecolOncol. 2014;132(3):780-9.

122. Montana GS, Thomas GM, Moore DH, Saxer A, Mangan CE, Lentz SS, et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study. IntJRadiatOncolBiolPhys. 2000;48(4):1007-13.

123. Rose PG. Skin bridge recurrences in vulvar cancer: frequency and management. Int J Gynecol Cancer. 1999;9(6):508-11.

124. Durrant KR, Mangioni C, Lacave AJ, George M, van der Burg ME, Guthrie D, et al. Bleomycin, methotrexate, and CCNU in advanced inoperable squamous cell carcinoma of the vulva: a phase II study of the EORTC Gynaecological Cancer Cooperative Group (GCCG). GynecolOncol. 1990;37(3):359-62.

125. Horowitz NS, Olawaiye AB, Borger DR, Growdon WB, Krasner CN, Matulonis UA, et al. Phase II trial of erlotinib in women with squamous cell carcinoma of the vulva. Gynecol Oncol. 2012;127(1):141-6.