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# Risk factors and treatment for recurrent vulvar squamous cell carcinoma

L.S. Nooij[a], F.A.M. Brand[a], K.N. Gaarenstroom[a], C.L. Creutzberg[b], J.A. de Hullu[c], M.I.E. van Poelgeest[a,*]

[a] Department of Gynecology, LUMC, Netherlands
[b] Department of Radiation Oncology, LUMC, Netherlands
[c] Department of Gynecology, Radboud UMC, Netherlands

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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 (Gadducci

* Corresponding author at: Dept. of Gynecology, Room K-06-020, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, Netherlands.
*E-mail address:* M.I.E.van_Poelgeest@lumc.nl (M.I.E. van Poelgeest).

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**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 >1 mm |
| 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 |

et al., 2006; Hacker et al., 2012; de Hullu and van der Zee, 2006; Berek and Hacker, 2014). The incidence of vulvar cancer increases with age, with a peak incidence in the seventh decade (Gadducci et al., 2006; de Hullu and van der Zee, 2006). 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 (Schuurman et al., 2013). 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 (Gadducci et al., 2006; Hacker et al., 2012; de Hullu and van der Zee, 2006).

Five year survival for early-stage VSCC is about 80–90% (Gadducci et al., 2006; Gonzalez et al., 2005). Prognosis is strongly dependent on the presence of lymph node metastases (de Hullu and van der Zee, 2006; Gonzalez et al., 2005; Gadducci et al., 2012; Salom and Penalver, 2002; Rouzier et al., 2002). Therefore, the International Federation of Gynecology and Obstetrics (FIGO) staging system was changed in 2009 (Table 1) (FIGO, 2014). 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 (van der Steen et al., 2010).

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) (Berek and Hacker, 2014; Al-Ghamdi et al., 2002; Alonso et al., 2011; Canavan and Cohen, 2002; Kokka et al., 2011; Lindell et al., 2010; Monk et al., 1995; Bloss et al., 1991). 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% (van de Nieuwenhof et al., 2008). 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% (Alonso et al., 2011; Canavan and Cohen, 2002; Lindell et al., 2010; Monk et al., 1995; Bloss et al., 1991; Ansink et al., 1994; Coleman and Santoso, 2000; Larsson et al., 2012; Pinto et al., 2004; Hording et al., 1993; van de Nieuwenhof et al., 2009). 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%) (Kokka et al., 2011; van de Nieuwenhof et al., 2008) compared to dVIN. Although most VSCC are HPV independent, dVIN accounts for only 2–10% of all reported VIN lesions (Kokka et al., 2011; van de Nieuwenhof et al., 2009). 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. (Abell and Gosling, 1961), it is only recently that dVIN has been recognized and regarded as a distinctive diagnosis by clinicians as well as pathologists (Kokka et al., 2011). 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) (Bornstein, 2015). 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 (van de Nieuwenhof et al., 2008; Torezan and Festa-Neto, 2013; Braakhuis et al., 2003).

Surgery is the cornerstone of treatment for primary VSCC (Gadducci et al., 2006; Hacker et al., 2012; Berek and Hacker, 2014). 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 (van der Zee et al., 2008). 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 (Hacker et al., 2012; de Hullu and van der Zee, 2006; van der Zee et al., 2008; Oonk et al., 2010a; Oonk et al., 2010b; van den Einden et al., 2012). Despite these treatment modalities, recurrence rates are still high: 12–37% (Gadducci et al., 2012; Coulter and Gleeson, 2003). Furthermore, prognosis of patients with recurrent VSCC has not improved over the past decades, with a reported 5-year survival rate of 25–50% (Coulter

**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 3 | VIN, usual type (uVIN) | HSIL |
| 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.