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Paget disease of the vulva

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ABSTRACT

In this review, we provide an overview of the clinical aspects, histopathology, molecular genetics, and treatment options for Vulvar Paget's Disease (VPD), a rare skin disease, most commonly found in postmenopausal Caucasian women. The underlying cause of VPD remains not well understood. VPD is rarely associated with an underlying urogenital, gastrointestinal or vulvar carcinoma. In approximately 25% of the cases, VPD is invasive; in these cases, the prognosis is worse than in non-invasive cases. Recurrence rates in invasive VPD are high: 33% in cases with clear margins, and even higher when surgical margins are not clear, regardless of invasion. Historically, surgical excision has been the treatment of choice. Recent studies show that imiquimod cream may be an effective and safe alternative.

1. Introduction

Sir James Paget (1814–1899) was a surgeon with a special interest in pathology and physiology. In addition to his work as a surgeon for the English royal family and his practice in London, he wrote 'Lectures on Surgical Pathology', a work that established him as one of the founders of modern pathology along with Rudolf Virchow (Paget, 1853). Sir James Paget is best known for his paper describing a nipple ulceration that was associated with an underlying breast carcinoma (Paget, 1874). That paper reported a series of 15 cases of chronic skin eruption of the nipple and areola, a condition that is now referred to as mammary Paget disease. In 1889, shortly after James Paget's report, Crocker described the first case of Paget disease on extramammary skin, a case involving penoscrotal Paget disease (Crocker, 1889). In 1901, Paget disease of the vulva was described for the first time by a French dermatologist, William Dubreuilh (Dubreuilh, 1901). Mammary and extramammary Paget disease are characterized by the presence of intraepithelial mucin-producing neoplastic cells known as Paget cells. However, the exact origin of these cells remains unclear (Demopoulos, 1971). This review presents an overview of the current literature on invasive and non-invasive VPD, including its epidemiology, clinical aspects, histopathology, treatment options, and survival.

2. Methods

2.1. Data sources

Relevant publications were identified by a computer search in the PubMed database (date of last search April 9th, 2015). We searched the database using combinations of the following terms: 'Paget's disease', 'Paget disease, extramammary' or 'Paget' in title and text. Subsequently, these terms were combined with 'vulva', 'vulvar', 'vulval', 'genitalia', 'perianal' or 'anogenital'. The button 'related articles' in PubMed and reference lists from selected articles were used to identify additional papers. Also, gynaecologic oncology, pathology and dermatology handbooks were used. Overall, 852 studies were found, 324 studies were not available in full-text and after assessment of all titles and abstracts, 298 were considered relevant. Main reasons for exclusion were: extramammary Paget disease in males, or locations other than the vulva. The remaining publications on VPD were considered for inclusion in this review if they reported one of the topics mentioned in this review. Of these 298 studies 230 reported clinical or histopathological data of patients with VPD, including 79 case-reports and 53 case series with <10 patients. We prepared tables of clinical data based on studies that included 10 patients or more, to ensure the size of the tables remained manageable. Studies that reported on both male and female patients with EMPD were considered for inclusion. However, we only used data of female patients with EMPD located on the (ano) genital skin, unless there was no data on VPD available.

2.2. Terminology

In this review, the terms mammary Paget disease (MPD) will be used for Paget disease of the breast, and extramammary Paget disease (EMPD) will be used for other locations, including the anogenital skin in males. The term vulvar Paget disease (VPD) will be used for a disease location in the genital area in females, including the perineal and perianal skin.

3. Clinical characteristics

3.1. Epidemiology

Only one study presents the occurrence of MPD versus EMPD: 90% of all cases of Paget disease are MPD and 10% of all cases of Paget disease are EMPD (Fardal et al., 1964). The overall European incidence of EMPD is 0.7 per 100,000 persons per year, and is slightly higher for women than men. A study in 16 European countries reported 871 cases of invasive EMPD in 13 years, including 231 male and 640 female patients (van der Zwan et al., 2012). Of the 640 female patients, disease was located at the vulva in 533 patients (83%), 3 cases were reported as 'Paget disease of the female genital tract, not otherwise specified' (0.5%), and 21 cases were reported as 'Paget disease of the anal canal and perianal skin' (3%). VPD is reported to occur most often in postmenopausal Caucasian women. In the Asian population, EMPD is seen mostly in males (Chiu et al., 2007), but there is considerable literature describing VPD in Asian women (Hatta, 2006; Takahashi and Yamamoto, 2004; Wang et al., 2004; Xiong et al., 2004; Lee et al., 2009; Liu et al., 2014). However, the exact incidence of VPD is unknown.

EMPD may be associated with underlying vulvar adenocarcinoma. Invasive VPD represents 1–2% of all vulvar carcinomas (Lloyd and Flanagan, 2000). A Dutch epidemiology study including 226 cases of EMPD over a 13-year period found that 178 (79%) cases were invasive and 48 (21%) non-invasive. When the data were categorised by location, invasive VPD (n = 59) was reported twice as often as non-invasive VPD (n = 32) (Siesling et al., 2007). These data were taken from the Netherlands Cancer Registry, which may have resulted in underreporting of non-invasive disease. Most clinical studies used Wilkinson's classification, and report invasion in 16–19% of the cases, and a vulvar adenocarcinoma in 4–17% of all

cases (Niikura et al., 2006; Mendivil et al., 2012; Karam and Dorigo, 2014). Moreover, VPD might not be recognized and thus be underreported if no skin biopsy is performed to confirm the diagnosis.

3.2. Origin of extramammary Paget disease

The origin of EMPD has not been clarified, although there are currently three theories. The first suggests that EMPD has an intraepidermal origin from adnexal structures, like apocrine glands, multipotent stem cells in the epidermal basal layer or infundibular stem cells of the hair follicle (Lloyd and Flanagan, 2000; Kanitakis, 2007; Regauer, 2006). EMPD is typically located in the hair-bearing skin of the axilla or genital area which supports the disease origins from adnexal structures. Although, VPD can also occur in the modified mucosa of the interlabial sulcus, or, in advanced cases, in the glycogenated mucosa without adnexal structures (Abbott and Ahmed, 2006; Lloyd et al., 1999; Mahdi et al., 2011), which supports another theory suggesting that Paget cells originate from mammary-like glands, which are located in the interlabial sulci (van der Putte, 1994). A more recent theory is that Toker cells are precursor cells in MPD as well as in EMPD and VPD (Willman et al., 2005; Toker, 1970). Toker cells have a single round nucleus and pale cytoplasm and are usually found in the nipple and areola (Belousova et al., 2006; Hashemi et al., 2014).

3.3. Signs and symptoms

In the majority of patients, VPD causes symptoms such as irritation, itching, and burning. VPD can be asymptomatic in some patients: about 5–15% of patients have no symptoms at the time of diagnosis (Perez et al., 2014; De Magnis et al., 2013). Upon physical examination, VPD presents as an erythematous plaque with typical white scaling known as “cake-icing scaling”. It is a clinical chameleon as it can present with a variety of colours and macular or plaque-like presentation. The plaque may be ulcerated and crusted with a papillomatous surface, as shown in Figs. 1 and 2. The symptoms experienced by the patient are not always related to the extent of the visible lesion.

Studies have shown that symptoms are typically present for an average of almost 2 years before the diagnosis is made, due to both patient and doctor delays (De Magnis et al., 2013; Chanda, 1985; Fanning et al., 1999). There is limited knowledge regarding the natural course of VPD, as most study reports describe patients who have undergone surgery. The ‘Radiumhemmet series’ of 28 women describes 4 patients with untreated VPD. Of these four women, two women were inoperable and two women refused surgery. Both inoperable patients died of other causes. One of the two women who refused surgery died of a squamous cell carcinoma (SCC) of the vagina, and the other patient had progressive VPD (Baehrendtz et al., 1994).

3.4. Diagnosis

In cases of suspected VPD, an accurate medical history should be taken, including a history of vulvovaginal complaints and gastrointestinal and urological symptoms. In addition, a full gynaecological examination should be performed that includes vulvar, vaginal, and rectal examinations. All raised, pigmented, or otherwise suspicious lesions should be addressed appropriately by a thorough report, digital photography, and histological examination. Digital photographs can help monitoring the course of the disease. Invasive disease should be excluded, preferably by vulvar mapping, including multiple biopsies of the involved and surrounding uninvolved skin. In case of a small unifocal lesion, it can be considered to perform a single biopsy, in which the visible lesion is completely excised. The diagnosis is confirmed by the histological presence of Paget cells.

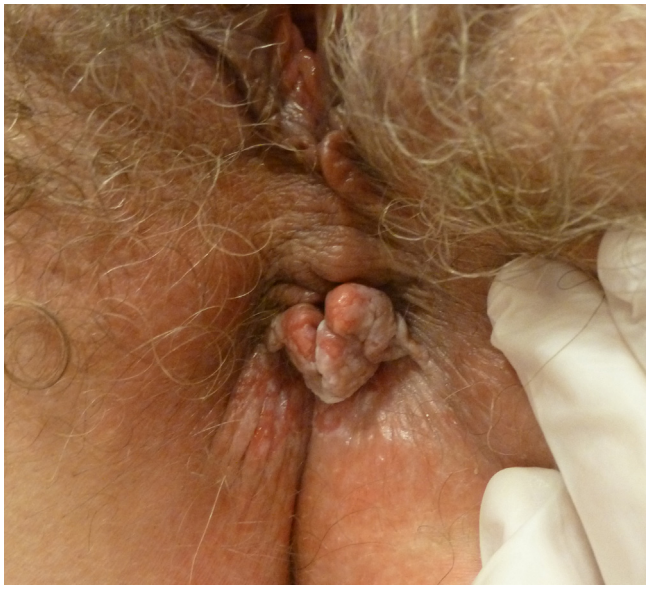

Fig. 1. Peri-anal Paget disease. Poorly demarcerated erythematous perianal plaque with small erosions and white scaling.

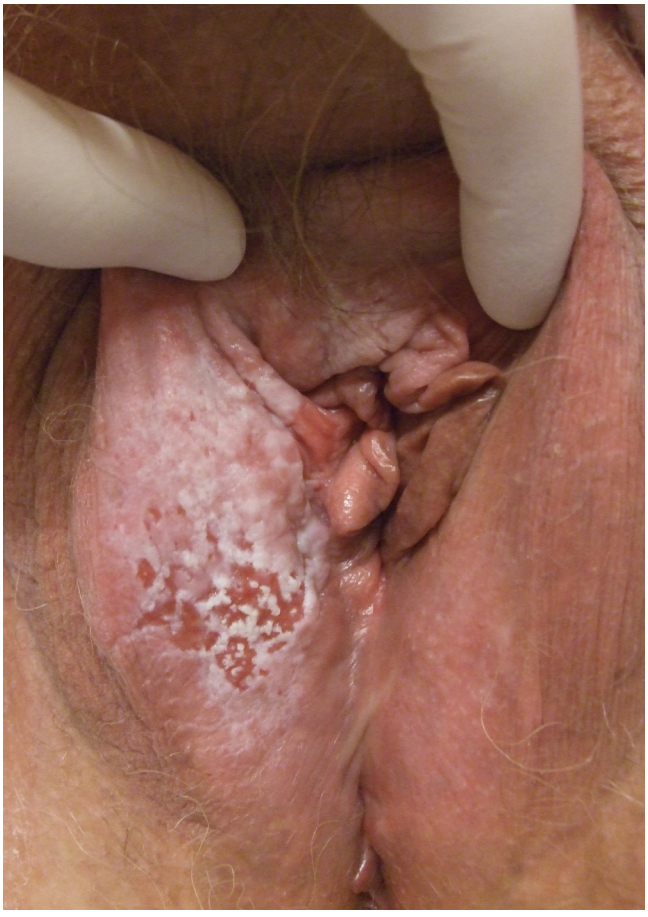

Fig. 2. Vulvar Paget disease. White hyperkeratotic plaque with typical ‘cake-icing’ scaling with small superficial erosions on the right labium majus.

3.5. Differential diagnosis

In addition to eczema and vulvovaginal candidiasis, the differential diagnosis of VPD consists of psoriasis, lichen simplex chronicus, lichen sclerosus, lichen planus, differentiated vulvar intraepithelial neoplasia (VIN) or usual VIN (synonymous: high grade squamous intraepithelial lesion, or H-SIL), SCC, histiocytosis, condylomata acuminata and melanoma. In addition to these clinical diagnoses, a histological differential diagnosis of intraepithelial Pagetoid cells can include the following: melanoma (in situ), pagetoid spitz naevus, sebaceous carcinoma, clear cell papulosis, eccrine porocarcinoma, cutaneous T-cell lymphoma, and Langerhans cell microabscess (Fanning et al., 1999; Shepherd et al., 2005; Delport, 2013).

3.6. Classification

The World Health Organization (WHO) defines VPD as 'an intraepithelial neoplasm of epithelial origin expressing apocrine or eccrine glandular-like features and characterized by distinctive large cells with prominent cytoplasm, referred to as Paget cells' (Crum et al., 2014). In the International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology and Classification of Vulvar Dermatologic Disorders (2011), VPD is assigned to the morphological group 2, described as 'Red lesions, patches and plaques' and to subgroup B, 'Red patches and plaques (no epithelial disruption)' (Lynch et al., 2012).

In 2001, Wilkinson et al. proposed a histopathological classification of VPD that distinguishes primary/cutaneous VPD (type 1) from secondary/non-cutaneous VPD (Wilkinson and Brown, 2002; Wilkinson, 2002). As shown in Table 1, secondary VPD originates from a malignancy of the gastrointestinal tract (type 2) or the urogenital tract (type 3) (Nowak et al., 1998). In cases of pagetoid extension of an urothelial carcinoma, the term pagetoid urothelial intraepithelial neoplasia (PUIN) may be used. The current literature often refers to Wilkinson's classification, which is mainly based on the histopathologic features of VPD. However, this classification is no longer supported by the most recent WHO Classification of Tumours of Female Reproductive Organs (4th edition) (Crum et al., 2014). Moreover, it is a matter of debate whether non-cutaneous EMPD should be regarded as a form of VPD. Some consider it a direct extension ('pagetoid spread') of an intestinal or urothelial malignancy and use immunohistochemistry to distinguish primary from secondary VPD (see Section 4.2) (Crum, 2011). There are no accurate data regarding the distribution of types 2 and 3 versus type 1 VPD. Together with Wilkinson's classification, the subdivision of cutaneous and non-cutaneous EMPD is regularly used in current literature.

Cutaneous VPD (type 1) is further subdivided according to the presence or absence of dermal invasion: type 1a (intraepithelial disease), is reported to account for 75–81% of all primary VPD cases, type 1b in 16–19% and type 1c in 4–17% of all cases (Niikura et al., 2006; Mendivil et al., 2012; Karam and Dorigo, 2014). In contrast, 60% or more of patients with MPD have an underlying breast malignancy (Chaudary et al., 1986). It is hypothesized that Paget cells migrate from the epidermis to the dermis in type 1b and that in type 1c the Paget cells have migrated into the epidermis ("pagetoid spread") from an underlying vulvar adenocarcinoma.

Most studies do not report the definition of 'invasive VPD' or 'vulvar adenocarcinoma' that was used. Some described dermal invasion as 'invasion > 1 mm'. Curtin et al. defined vulvar adenocarcinoma as invasive adenocarcinoma of sweat gland origin (Curtin et al., 1990). Lee et al. defined invasive VPD as Paget disease with in situ involvement of the underlying sweat glands and defined vulvar adenocarcinoma as an invasive adnexal adenocarcinoma (Lee et al., 1977). Because most studies lack clear definitions of invasive VPD and vulvar adenocarcinoma, we are unable to present an overview of the incidence distribution of non-invasive VPD, invasive VPD, and VPD with an underlying adenocarcinoma.

3.7. Associated malignancies

Patients diagnosed with EMPD are reported to have a higher risk of developing a second primary cancer, especially the first year after diagnosis (standardized incidence ratio of 1.39 with a 95% CI of 1.11–1.73) (van der Zwan et al., 2012). VPD is reported to be associated with other malignancies in 11–54% of the cases, including malignancies of the breast, vagina, cervix, uterus, ovary, gallbladder, and liver (Karam and Dorigo, 2014; Lee et al., 1977; Feuer et al., 1990; Taylor et al., 1975). However, some studies consider an underlying vulvar, rectal, or urothelial carcinoma to be an associated malignancy, whereas others reserve this term for distant malignancies. Data need to be interpreted with caution, since most studies reporting on associated malignancies had no adequate age matched control groups.

A total of 15 studies with 10 or more patients, reported intestinal or urological malignancies in patients with VPD (Liu et al., 2014; De Magnis et al., 2013; Baehrendtz et al., 1994; Brown and Wilkinson, 2002; Crawford et al., 1999; Helm et al., 1992; Jones et al., 2011; Pierie et al., 2003; Tebes et al., 2002; Lundquist et al., 1999; Black et al., 2007; Lee et al., 2011; Luyten et al., 2014; Plaza et al., 2009; Press et al., 2011). Of the 456 included patients 10 (2.2%) had intestinal malignancies, and 18 (3.9%) had urological malignancies. Five patients were reported to have VPD and a simultaneous bladder carcinoma (1.1%) and 3 patients (0.7%) had an anal carcinoma that occurred simultaneously with VPD (Brown and Wilkinson, 2002; Pierie et al., 2003; Lundquist et al., 1999; Press et al., 2011). Twenty-six studies with 10 patients or more reported that 51 (3.2%) of the included 1598 patients had a history of breast cancer (Liu et al., 2014; Niikura et al., 2006; Mendivil et al., 2012; Karam and Dorigo, 2014; De Magnis et al., 2013; Fanning et al., 1999; Baehrendtz et al., 1994; Lee et al., 1977, 2011; Feuer et al., 1990; Taylor et al., 1975; Crawford et al., 1999; Helm et al., 1992; Jones et al., 2011; Pierie et al., 2003; Tebes et al., 2002; Black et al., 2007; Plaza et al., 2009; Press et al., 2011; Brainard and Hart, 2000; Cai et al., 2013; Goldblum and Hart, 1997; Gregori et al., 1978; Kodama et al., 1995; Parker et al., 2000; Zollo and Zeitouni, 2000). The time relative to the diagnosis of VPD varied greatly. Based on currently available literature it is not proven that there is a clinical relationship between VPD and breast cancer.

3.8. Excluding other malignancies

There is no current consensus if women with VPD should be screened for associated malignancies, or which additional tests should be performed. Because of the presumed association of VPD with locoregional and distant malignancies, guidelines advise excluding the presence of other malignancies, although the proposed policies vary. The Royal College of Obstetricians and Gynaecologists states that "the gastrointestinal and urinary tracts and the breasts should be checked" (Royal College of Obstetricians & Gynaecologists, 2011) and that "women with VPD should have prolonged follow-up in a multidisciplinary vulvar clinic or by a gynaecological oncologist" (Royal College of Obstetricians & Gynaecologists, 2014). The U.S. Department of Health & Human Services advises, "evaluate the breasts, genitourinary, and gastrointestinal tract (level C evidence: consensus and expert opinion)" (ACOG National Guideline, 2008).

Table 1
Classification of vulvar Paget disease by Wilkinson (Delport, 2013; Crum et al., 2014).

Primary VPD (cutaneous)	Type 1a	Cutaneous vulvar non-invasive Paget's disease
	Type 1b	Cutaneous vulvar invasive disease: dermal invasion of Paget cells
	Type 1c	Cutaneous vulvar disease as a manifestation of an underlying vulvar adenocarcinoma
Secondary VPD (non-cutaneous)	Type 2	VPD originates from rectal or anal adenocarcinoma
	Type 3	VPD originates from urogenital neoplasia

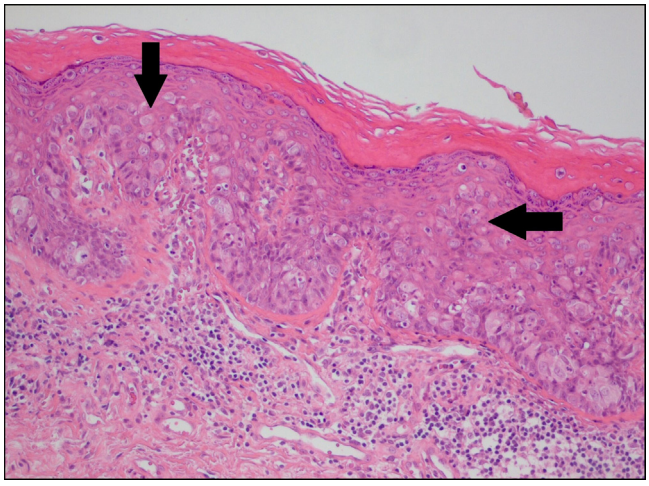

Fig. 3. Non-invasive vulvar Paget disease (HE stain, 100x). Solitary cells and large cell nests are present in the lower parts of the epidermis (arrows). The Paget cells have pale cytoplasm and large rounded atypical nuclei. There is no invasive growth.

4. Histopathological diagnosis

4.1. Histological characteristics

Histologically, VPD is characterized by the presence of large oval or polyhedral intraepithelial cells that have pale cytoplasm and large nuclei with prominent nucleoli, these cells are the so-called Paget cells. Paget cells can be visualised using haematoxylin and eosin (HE) staining. They are arranged either singly or in clusters throughout the epithelium to a variable extent, and may form a lumen or gland-like structures. Sometimes reactive changes are seen in the surrounding epithelial surface, such as acanthosis, papillomatosis, and hyperkeratosis; these changes in themselves are not sufficient for diagnosis. A lichenoid inflammatory infiltrate can be seen in the underlying papillary dermis. The scattered Paget cells are diagnostic, but they are interspersed within the normal epithelium and can be difficult to detect at times (Figs. 3 and 4).

In the pathologic assessment of VPD, it is important to exclude invasive growth. This is challenging because it is not uncommon for VPD to extend into the adnexal structures. An additional problem is the frequent presence of a dense infiltrate that can obscure the epithelial/stromal interface. Invasion is characterized by the presence of dyscohesive neoplastic Paget cells infiltrating the underlying dermis or submucosa (Figs. 5 and 6). In case of invasion, the pathologist is required to report the depth of invasion, as this has proven prognostic significance and determines the type of treatment (Hatta et al., 2008; Ito et al., 2012).

4.2. Immunohistochemistry

A number of immunohistochemical stains can be used to distinguish cutaneous VPD from its histological mimics. Paget cells can be highlighted by PAS reaction and/or by immunohistochemistry, as they are usually positive for cytokeratin (CK) 7 and carcinoembryonic antigen (CEA) (Delport, 2013; Berek and Hacker, 2005; Kuan et al., 2001). They do not express markers of squamous cell differentiation, such as p63 and p40, and these markers can therefore be used to exclude squamous intraepithelial lesions such as uVIN, also known as HPV-induced H-SIL with a pagetoid growth (Yanai et al., 2008; Hoang et al., 2015). However, VPD may over express p16 and mimic uVIN (or: HPV-induced H-SIL), which strongly over express p16 as well (McCluggage et al., 2009; Sah and McCluggage, 2013). In addition, Paget cells do not express melanocyte markers, such as Mel-A, HMB45 or S100, and this can help distinguish VPD from (in situ) melanoma. Paget cells may express androgen receptors, but in general are negative for estrogen and progesterone receptors (Olson et al., 1991; Liegl et al., 2005; Diaz de Leon et al., 2000; Horn et al., 2008).

Immunohistochemistry can also be helpful in determining the primary location of an underlying adenocarcinoma. For example, pagetoid extension of urothelial cancer will likely express CK20, uroplakin-III, and GATA-3 (Delport, 2013; Horn et al., 2008), whereas CK20, CDX2, and MUC2 positivity might indicate an underlying anorectal adenocarcinoma (Delport, 2013; Kuan et al., 2001; Liao et al., 2014). It is therefore recommended that a combination of these markers be used in cases in which pagetoid extension from an

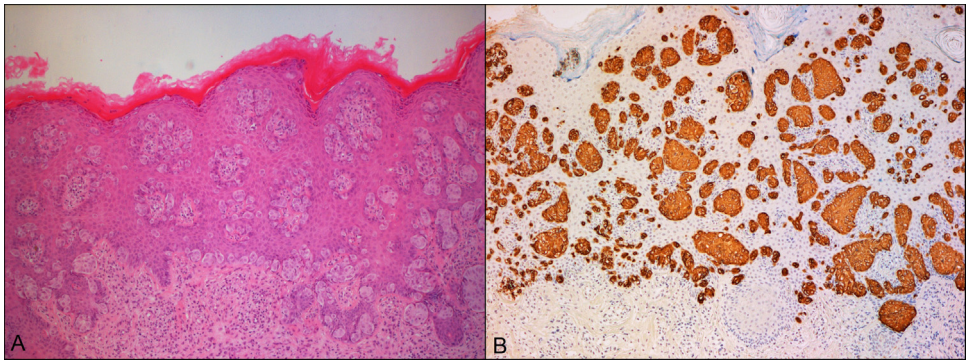

Fig. 4. (A) Non-invasive vulvar Paget disease (HE, 100x), (B) Cytokeratin 7 stained cells (100x). Large pale solitary cells and cell nests are present throughout the thickened hyperplastic epidermis. With CK7 it is clearly depicted that there is no invasive growth in the underlying vulvar stroma.

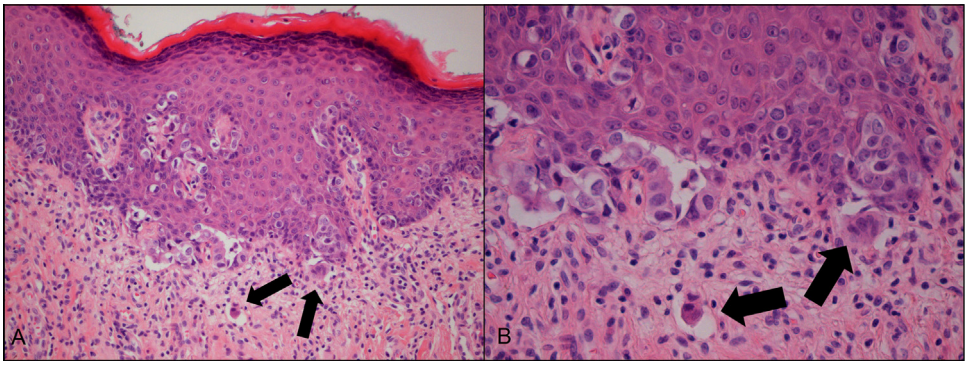

Fig. 5. (A) Micro-invasive vulvar Paget disease (HE, 100x), (B) Detail (HE, 200x). Some large atypical pale cells and cell nests are present in the basal layers of the vulvar epithelium. At magnification it is shown that two smell cell clusters have invaded the underlying vulvar stroma (arrows). The invasive growth is less than 1 mm.

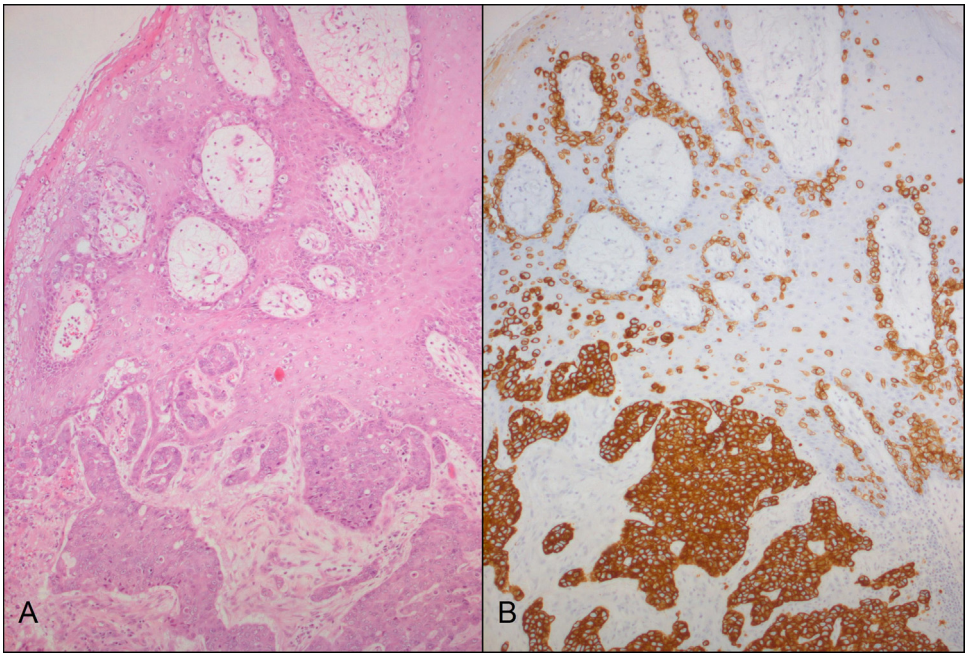

Fig. 6. (A) Invasive Paget disease with underlying anogenital invasive adenocarcinoma (HE, 100x), (B) Cytokeratin 7 stained cells (100x). At left a poorly differentiated adenocarcinoma is present directly under the hyperplastic thickened vulvar epithelium. With cytokeratin 7 immunostaining it is depicted that tumour cells spread alongside the basal parts and rete ridges of the vulvar epithelium.

underlying adenocarcinoma is suspected (Ohnishi and Watanabe, 2000). Because of the rarity of a co-existent intestinal and/or urological (see Section 3.7) we suggest this may be performed in cases in which the patient has a clinical suspicion of an underlying intestinal and/or urological tumour. See Table 2 for an overview of the expression patterns of common markers.

4.3. Tumour microenvironment

Studies of the local tumour microenvironment of VPD are limited and have not investigated the types of cells present in the immune infiltrate, only specific markers have been investigated, such as regulatory T-cells (Tregs) that suppress effector T-cells. Tregs express Foxp3, CD4, and CD25 (or IL-2-*R*α), and high numbers of Tregs are associated with adverse clinical outcomes in several types of cancer (Fujimura et al., 2012; Adeegbe and Nishikawa,

Table 2
Overview of common expression patterns in vulvar Paget disease.

	CEA	p63	CK 7	CK 20	Uro-III	GATA-3	CDX2	MUC2	GCDFP-15
Primary cutaneous VPD (type 1)	+	–	+	–	–	–	–	–	+
Secondary to intestinal malignancy (type 2)	+	–	–	+	–	–	+	+	–
Secondary to urological malignancy (type 3)	+	+	+/–	+	+	+	–	–	–

CEA: carcinoembryonic antigen, CK: cytokeratin, Uro-III: uroplakin-III, MUC2: mucin 2, GCDFP-15: Gross cystic disease fluid protein.

2013; Piersma et al., 2007). A study of Tregs in 44 cases of VPD showed that Tregs are frequently found at the epidermal-dermal junction (Press et al., 2011) whereas the surrounding healthy skin is negative for Tregs. That study also described a correlation between the number of FOXP3+ Tregs and positive surgical margins and recurrence (Press et al., 2011). The percentage of Tregs is significantly higher in non-invasive EMPD than in invasive EMPD, while CD163+ macrophages are detected more frequently in invasive EMPD (Fujimura et al., 2012).

4.4. Genetic profile

Given the rarity of VPD, there are limited data on genetic alterations in VPD, and this field is therefore largely unexplored. Her2/Neu amplification is probably the most studied genetic alteration in VPD, likely because of its therapeutic potential and its association with mammary Paget disease. HER-2/Neu overexpression is found in 70–100% of MPD cases (Wolber et al., 1991; Keatings et al., 1990). However, the reported frequency of Her2/Neu amplification in EMPD varies significantly (Bianco and Vasef, 2006; Reich et al., 2005). Small series and case reports have investigated various genetic abnormalities: mutations in the PIK3CA (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha) gene, divergent DLC1 (Deleted in Liver Cancer 1) methylation, single nuclear polymorphism in the XRCC1 (X-ray repair cross-complementing protein 1) gene, chromosome 7 gains and X chromosome losses have been described (Kang et al., 2012; Chiyomaru et al., 2012; Micci et al., 2003). However, the clinical significance of these abnormalities remains to be determined.

5. Treatment

Traditionally, the treatment of choice for VPD is surgical excision.

5.1. Surgery

Surgical treatment of VPD consists mainly of wide local excision, with or without inguinofemoral lymph node dissection (De Magnis et al., 2013; Fanning et al., 1999; Edey et al., 2013). A inguinofemoral lymphadenectomy is indicated in cases showing invasive VPD (>1 mm). The main clinical challenge of wide local excision is obtaining clear surgical margins; it is unclear what the surgical margin should be in VPD, as Paget disease spreads microscopically throughout the epidermis. This makes it difficult to determine the complete extent and spread of the lesion (Gunn and Gallager, 1980). Paget cells may be difficult to recognize on frozen sections: frozen section evaluation in EMPD is reported to have a false negative rate ranging from 10.4% to 13.2% (Chan et al., 2012; Zhu et al., 2007). The relationship between surgical margin status and recurrence rates remains unclear (see Section 5.3).

In Mohs microsurgery (MMS) the vulvar lesion is excised through the epidermis and dermis, and 100% of the peripheral margins are examined immediately (Mohs and Blanchard, 1979). Excision is repeated, enlarging the circumference each time, until the margins are clear. MMS was reported to be used for VPD for the first time in 1991 (Coldiron et al., 1991), after 90 years of surgical treatment consisting of wide local excision or (hemi) vulvectomy.

For large lesions, different plastic surgery methods for reconstruction of large vulvovaginal defects have been reported and include local fasciocutaneous flaps, gluteal fold flaps, pudendal thigh flaps, and gracilis myocutaneous flaps (Araki et al., 2003; Nakamura et al., 2010; Staiano et al., 2009; Yun et al., 2010).

5.1.1. Sentinel lymph node

There are no studies on the accuracy of sentinel lymph node (SLN) biopsies in invasive VPD. The current literature describes SLN only sporadically in cases with microinvasive VPD (Ewing et al., 2004) and in cases with suspected lymph node metastases (Nakamura et al., 2012; Hatta et al., 2004). However, based on current knowledge of surgery for vulvar SCC, microinvasion is not an indication for SLN, and uni- or bilateral inguinofemoral lymphadenectomy is indicated in cases of invasive VPD (> 1 mm) with clinically suspected lymph node involvement.

5.1.2. Complications of surgery

Vulvar surgery is associated with significant morbidity. Local vulvar complications consist mainly of infection, hematomas, and wound breakdown, with incidence rates for wound breakdown ranging from 9–45% (Gaarenstroom et al., 2003; Senn et al., 2010; Robison et al., 2014). According to quality of life assessments, extensive surgery, such as radical vulvectomy, tends to cause more discomfort than wide local excision (Gunther et al., 2014). The incidence of complications after inguinofemoral lymphadenectomy ranges from 17.5–84%. Early complications (<1 month after surgery) are mainly lymphocyst formation, wound breakdown, and infection of the wound. Late complications (≥1 month after surgery) include lymphedema, leg pain, and erysipelas (Robison et al., 2014; Hinten et al., 2011; Iversen et al., 1980; Walker et al., 2011).

5.1.3. Psychosexual complications

There are no studies concerning the psychosexual effects of vulvar surgery in VPD. One study showed that women with a history of vulvar excision for VIN more frequently reported sexual function impairment and worse quality of life than healthy women (Likes et al., 2007). However, two other studies showed no significant differences in quality of life and sexual function between patients surgically treated for VIN, Bowen's disease, or VPD and a healthy population (Lavoue et al., 2013; Conklin et al., 2009). In patients who underwent vulvar surgery for vulvar carcinoma or carcinoma in situ, there was no correlation between the extent of the surgery, the type of vulvectomy, and sexual dysfunction severity. Elderly women were more likely to stop sexual activity after such surgery, and women with high depression scores more often had sexual aversion disorder, increases in body image disturbance, and sexual dysfunction (Green et al., 2000). Following vulvar surgery for VIN, older women had lower quality of life and lower sexual function according to the Female Sexual Function Index questionnaire compared to younger women (Likes et al., 2007).

5.2. Non-surgical treatment

Surgery for VPD is not always possible or desirable due to the location or size of the lesion or due to patient factors or preferences. In addition, recurrence rates after surgical treatment are high and morbidity is impressive (Perez et al., 2014; Fanning et al., 1999). There is thus a pressing need for alternative treatment options for VPD.

5.2.1. Topical imiquimod cream

Imiquimod is registered for the treatment of condylomata acuminata, superficial BCCs, and actinic keratosis. It has also shown to be effective in the off label treatment of usual VIN in randomized controlled trials (van Seters et al., 2008; Tristram et al., 2014). Imiquimod, a toll-like receptor (TLR) 7 agonist, is an immune response modifier. It triggers immune cells to produce cytokines, including interferon-α, interleukin 1, 6, and 8, and TNF-α (Miller et al., 1999). It also indirectly stimulates the production of pro-inflammatory T helper type 1 cytokines. In the skin, imiquimod

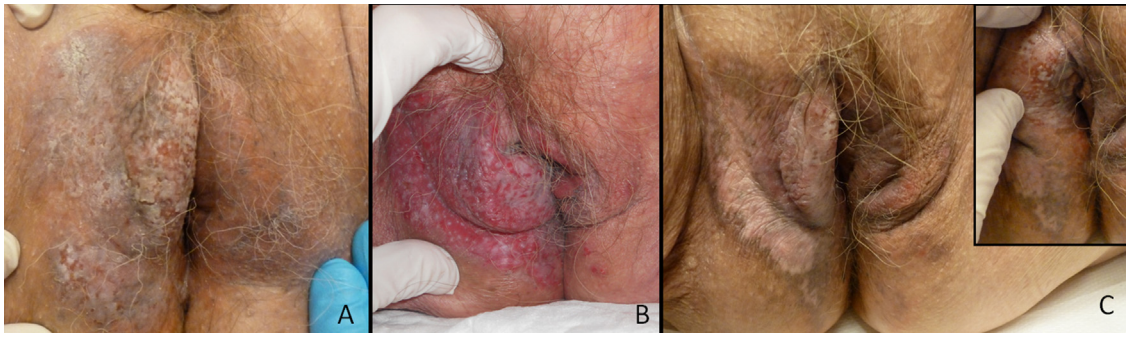

Fig. 7. Extended vulvar Paget disease before (A), after 4 weeks (B) and, after 10 weeks (C) of treatment with topical 5% imiquimod cream.

activates Langerhans cells, which enhance antigen presentation to T cells.

A few observational studies and case reports have shown imiquimod to be effective for the treatment of perineal, scrotal, and inguinal Paget disease (Zampogna et al., 2002). Topical imiquimod cream for the treatment of recurrent VPD was first described by Wang et al. (2003), and subsequently around 25 retrospective case series were published on the use of topical imiquimod cream in non-invasive VPD. The treatment schedules differed widely in these studies, ranging from daily application to application three times a week. The duration of the treatment ranged from 5 to 26 weeks, and follow-up ranged from 2 to 55 months. In these studies, a total of 64 women with VPD were treated with imiquimod cream; 56 (88%) had an objective clinical response, 43 (67%) had a complete response, and 13 (21%) had a partial response. Only 8 women were reported to have residual disease after treatment (Luyten et al., 2014; Bertozzi et al., 2009; Gass et al., 2008; Geisler and Manahan, 2008; Hatch and Davis, 2008; Cecchi et al., 2010; Challenor et al., 2009; Sendagorta et al., 2010; Tonguc et al., 2011; Hiraldo-Gamero et al., 2011; Wagner et al., 2012; Baiocchi et al., 2012; Feldmeyer et al., 2011; Ho and Aw, 2010; Frances et al., 2014; Herranz et al., 2012; Matin et al., 2011; Sanderson et al., 2013; Tanaka et al., 2009; Madnani et al., 2010; Anton et al., 2011; Denehy et al., 2008). Fig. 7 shows a patient from our clinic who has obtained a complete response with topical 5% imiquimod treatment.

A recent observational study examined the effectiveness of imiquimod cream in 10 patients with non-invasive VPD (Marchitelli et al., 2014). The patients were treated for 5–7 months. Nine patients had a complete response, and one patient had a partial response. Local skin reactions like pain and ulceration were reported in this cohort without systemic reaction. We found 16 publications reporting adverse events in 59 patients (Luyten et al., 2014; Geisler and Manahan, 2008; Hatch and Davis, 2008; Cecchi et al., 2010; Sendagorta et al., 2010; Tonguc et al., 2011; Hiraldo-Gamero et al., 2011; Wagner et al., 2012; Baiocchi et al., 2012; Feldmeyer et al., 2011; Frances et al., 2014; Herranz et al., 2012; Matin et al., 2011). A local adverse reaction, such as pain, ulceration, or inflammation, was reported in 16 patients (Luyten et al., 2014; Wang et al., 2003; Sendagorta et al., 2010; Tonguc et al., 2011; Hiraldo-Gamero et al., 2011; Wagner et al., 2012; Baiocchi et al., 2012; Feldmeyer et al., 2011; Frances et al., 2014; Herranz et al., 2012). Five patients reduced the application frequency or stopped for one or more weeks because of these adverse reactions (Wang et al., 2003; Hatch and Davis, 2008; Denehy et al., 2008). In most cases, the severity of adverse effects as reported by the patient was reduced after 4 or 5 weeks of treatment. The recurrence rate after treatment with topical imiquimod cream for VPD is unknown. Overall imiquimod seems to be effective, but treatment schedules differ greatly between the studies, and there may be a high risk of publication bias.

5.2.2. Chemotherapy

Chemotherapy for metastatic EMPD has been reported in one small study (n = 7) (Oashi et al., 2014). The clinical response of 4 patients after FECOM therapy (combination therapy with 5-fluorouracil, epirubicin, carboplatin, vincristine, and mitomycin C) at 4-week intervals showed a partial response according to RECIST (Response Evaluation Criteria in Solid Tumors). One case reports describes a patient with untreated non-invasive VPD who was treated with radiotherapy and FEC100 (fluorouracil, epirubicin, and cyclophosphamide) followed by 3 courses of docetaxel for a lobular breast carcinoma. The VPD clinically disappeared after chemotherapy, but recurred 2 years later (Tauveron et al., 2014). Another case report describes the clinical response and regression of lymph node metastases in a patient with Her2-Neu-overexpressing VPD after treatment with trastuzumab in combination with paclitaxel (Hanawa et al., 2011).

One study describes the topical use of bleomycin for 2 weeks with a resting period of 4–6 weeks in 7 patients with non-invasive VPD. Four patients had a complete response: three after 2 two-week courses and one patient needed 4 courses but had a recurrence after 30 months. The other three patients could not be evaluated: one patient died of intercurrent disease, in one patient therapy was stopped due to adverse events, and one patient refused further therapy after a partial response (Watring et al., 1978).

5.2.3. Other topical treatment

Topical corticosteroids are not proven to be effective for VPD. The current literature includes case reports of women who were treated with topical corticosteroids without success for an irritative vulvar skin lesion. Treatment failure led to further examination of the initially misdiagnosed lesion and resulted in a VPD diagnosis (Tonguc et al., 2011; Hiraldo-Gamero et al., 2011; Moller et al., 2014; O'Connor et al., 2012). Based on clinical experience, topical application of lidocaine (as a cream or ointment) can relieve pain, and emollients with zinc oxide can prevent secondary infection of the lesion. There is no literature available on the symptomatic treatment of VPD.

5.2.4. Radiotherapy

Radiotherapy has been used as a primary treatment option for patients with invasive and non-invasive VDP who were not eligible for surgery or who refused surgery, as a treatment option for patients with recurrence after surgery, and as adjuvant postoperative therapy (Karam and Dorigo, 2012; Son et al., 2005). Son et al. described a case series of 3 patients with VPD that included 1 patient with invasive VPD (Son et al., 2005). All 3 patients had a clinical complete response. Karam et al. performed a large retrospective study of 1439 patients with EMPD, 781 of whom had VPD. In total, 92 patients received radiotherapy, but these were not ana-

Table 3
Local recurrences after surgical treatment.

Author	Number of patients with local recurrence in non-invasive VPD	Number of patients with local recurrence in invasive VPD
Black et al. (2007)	17/28 (60.7%)	0
Cai et al. (2013)	7/22 (31.8%)	1/5 (20%)
Crawford et al. (1999)	5/10 (50%)	3/10 (30%)
Creasman et al. (1975)	0/7 (1[b])	0/5 (3[b])
Curtin et al. (1990)	6/28 (21.4%)	2/5[a] (2[b]) (40%)
De Magnis et al. (2013)	13/30 (43.3%)	2/4 (50%)
Fanning et al. (1999)	30/84 (35.7%)	3/12 (25%)
Feuer et al. (1990)	7/14 (50%)	2/3 (1[b]) (66.7%)
Goldblum and Hart (1997)	4/13 (30.8%)	1/6 (16.7%)
Gregori et al. (1978)	2/13 (15.4%)	0
Jones et al. (1979)	7/32 (21.9%)	4/9 (44.4%)
Lee et al. (1977)	1/5 (20%)	2/7 (28.7%)
Liu et al. (2014)	7/23 (30.4%)	4/8 (50%)
Mendivil et al. (2012)	8/13 (61.5%)	1/3 (33.3%)
Scheistrøen et al. (1997)	6/15 (40%)	2/4 (50%)
Shaco-Levy et al. (2010a, 2010b)	15/46 (32.6%)	3/10 (30%)
Tebes et al. (2002)	4/14 (28.6%)	2/6 (33.3%)
Zollo and Zeitouni (2000)	5/15 (33.3%)	2/6 (33.3%)
Total	144/402 (35.8%)	34/103 (33.0%)

VPD: vulvar Paget disease.
[a] 1 patient had metastases in LN.
[b] Number of patients that died of Paget disease.

lysed by sex or by lesion location (Karam and Dorigo, 2012). The invasion depth was not reported. Adjuvant postoperative radiotherapy was given to 51 patients (55.4%), and 40 patients received radiotherapy as primary treatment. A dose of 40–50 Gy is recommended for intraepithelial EMPD and 55–65 Gy is recommended for invasive EMPD or for an associated adenocarcinoma (Besa et al., 1992; Moreno-Arias et al., 2001; Burrows et al., 1995). Long-term follow-up shows that recurrence rates after radiotherapy are less than 20% (Son et al., 2005). Lower doses may be less effective and may thus have a higher recurrence rate (Brierley and Stockdale, 1991). One case report described the use of high-dose-rate superficial brachytherapy, also known as plesiotherapy, for VPD. A total dose of 54 Gy was administered in 3 weekly fractions for 4 weeks. The patient had a complete response and was free of disease during 18 months of follow-up (Marcos et al., 2012).

5.2.5. Photodynamic therapy

Photodynamic therapy (PDT), also known as photochemotherapy, is mainly prescribed by dermatologists (Tidy et al., 1996). A photosensitizer such as 5-aminolevulinic acid (5-ALA) or methyl 5-amnoplevilunate (MAL) is applied to the lesion. After an incubation period of several hours, the photosensitizer is washed off and the lesion is irradiated with visible red light, destroying proliferating tumour cells that have absorbed the photosensitizer (Al Yousef et al., 2011; Raspagliesi et al., 2006). PDT has shown clinical efficacy for treating superficial cutaneous (pre-) malignancies such as superficial BCCs, actinic keratosis, and usual VIN (Winters et al., 2008). PDT can be painful and can cause inflammation.

Several case reports have evaluated PDT for VPD. Three case reports of three patients all reported complete responses to PDT therapy (Al Yousef et al., 2011; Magnano et al., 2013; Zawislak et al., 2004). The reports described using topical antibiotics, tretinoin 0.05%, and vitamin E ointment at the lesion site. The patients received 2–3 sessions of 5-ALA or MAL PDT, and all were free of disease for the follow-up periods of 3–6 months (Magnano et al., 2013; Zawislak et al., 2004). As side effects, one case reported minimal pain and mild erythema for several days after a session. She had a partial response and refused surgical treatment. During the 3-year follow-up period, there was no invasion of the lesion (Al Yousef et al., 2011). Raspagliesi et al. reported a case series of 7 patients who were treated with PDT; 4 had a complete response, 1 had a partial response, and 2 patients had stable disease after 1–5 months of follow-up. The patients, who were premedicated with benzodiazepine and NSAIDs, received 3 sessions of MAL PDT with a 3-week intervals. Two patients reported having pain for several days after the treatment (Raspagliesi et al., 2006).

5.2.6. Laser therapy

CO_2 laser therapy has been used as a treatment for recurrent VPD after surgery. One case report described the use of 30-W CO_2 laser therapy for recurrence after multiple extended surgeries. Invasion was not reported. After the laser treatment, there was no recurrence during the 12 months of follow-up, and the clinical response was satisfactory (Valentine et al., 1992). Laser therapy has also been used in combination with PDT and surgery. One case series describes additional 10 W CO_2 laser vaporization after surgery. One patient had a vulvar adenocarcinoma and was primarily treated with a radical vulvectomy. The other patients underwent wide local excision prior to laser therapy. All patients were free of disease 4 months to 4.5 years after treatment (Ewing, 1991). A trial that included 3 patients with recurrent VPD after surgery subsequently treated the patients with CO_2 laser therapy and 5-ALA PDT. Invasion was not reported. All patients showed complete response during 12 months of follow-up, although 1 died due to other causes (Fukui et al., 2009).

5.3. Recurrence rates

Reported local recurrence rates after surgical treatment of VPD vary from 34–56% (Perez et al., 2014; Fanning et al., 1999). Recurrences have also been reported in reconstructive skin grafts and flaps (Misas et al., 1990; Geisler et al., 1995; Chin et al., 2004). Table 3 presents an overview of the local recurrence rates of invasive and non-invasive VPD in surgically treated patients (Liu et al., 2014; Mendivil et al., 2012; De Magnis et al., 2013; Fanning et al., 1999; Curtin et al., 1990; Lee et al., 1977; Feuer et al., 1990; Crawford et al., 1999; Tebes et al., 2002; Black et al., 2007; Cai et al., 2013; Goldblum and Hart, 1997; Gregori et al., 1978; Zollo and Zeitouni, 2000; Creasman et al., 1975; Jones et al., 1979; Scheistrøen et al., 1997; Shaco-Levy et al., 2010a, 2010b).

Some studies report high recurrence rates regardless of the surgical margin status (Tebes et al., 2002; Black et al., 2007; Bergen et al., 1989), whereas others found a significant correlation between negative margins and lower recurrence rates (Pierie et al., 2003).

Table 4
Local recurrences in relation to margin status after surgical treatment of vulvar Paget disease.

Author	Number of patients with recurrence in patients with positive surgical margins	Number of patients with recurrence in patients with negative surgical margins
Black et al. (2007)	14/20 (70%)	3/8 (37.5%)
Cai et al. (2013)[a]	N/A (38.5%)	N/A (18.8%)
Crawford et al. (1999)	7/13 (53.8%)	1/7 (14.3%)
Curtin et al. (1990)	2/6 (33.3%)	3/11 (27.2%)
De Magnis et al. (2013)	10/15 (66.7%)	5/19 (26.3%)
Lee et al. (1977)	0/1 (0%)	3/11 (27.3%)
Liu et al. (2014)	9/15 (60%)	11/31 (35.5%)
Mendivil et al. (2012)	5/11 (45.5%)	4/5 (80%)
Scheistrøen et al. (1997)	1/8 (12.5%)	0/6 (0%)
Shaco-Levy et al. (2010a, 2010b)	20/50 (40%)	3/17 (17.6%)
Tebes et al. (2002)	6/16 (37.5%)	2/7 (28.6%)
Zollo and Zeitouni (2000)	1/6 (16.7%)	5/12 (41.7%)
Total[b]	75/161 (46.6%)	40/134 (29.8%)

N/A: not available
[a] Percentages available only.
[b] Excluding Cai et al. (2013).

Table 5
Overview of literature reporting patients who died of extramammary Paget's disease.

Author	Death of disease in patients with non-invasive EMPD	Death of disease in patients with microinvasive EMPD (≤1 mm)	Death of disease in patients with invasive EMPD (> 1) and/or malignancy
Crawford et al. (1999)	0/11	0/7	1/3 (33.3%)
Creasman et al. (1975)	1/10 (10%)	N/A	3/5 (60.0%)
Curtin et al. (1990)	0/28	N/A	2/5 (40.0%)
De Magnis et al. (2013)	1/29 (3.4%)[a]	0/3	0/2[b]
Feuer et al. (1990)	0/14	NA	1/3 (33.3%)
Ito et al. (2012)	0/18	0/9	5/8 (62.5%)
Jones et al. (2011)	0/38	N/A	2/5 (40.0%)
Mendivil et al. (2012)	0/15	N/A	0/1
Niikura et al. (2006)	0/18	N/A	0/4
Shaco-Levy et al. (2010a, 2010b)	0/46	N/A	1/10 (10%)
Zollo and Zeitouni (2000)	0/19	N/A	1/9 (11.1%)
Total	2/246 (4.9%)	0/19	16/55 (29.1%)

When studies reported cases with invasion ≤1 mm, they are reported separately in the 'micro-invasion' column. Otherwise we assumed cases with invasion ≤1 mm are classified as 'non-invasive'. EMPD: Extramammary Paget disease. N/A: not available.
[a] Patient that died of disease was also diagnosed with vulvar squamous cell carcinoma.
[b] Both patients had non-invasive VPD with a vulvar adenocarcinoma.

Table 6
Overview of number of patients with invasive vulvar Paget disease or metastases after treatment for initial non-invasive vulvar Paget disease.

Author	N	Number of patients with invasive VPD after treatment for initial non-invasive VPD	Number of patients with metastases after treatment for initial non-invasive VPD
Baehrendtz et al. (1994)	28	3	0
Black et al. (2007)	28	1	0
Fanning et al. (1999)	88	1	2
Goldblum and Hart (1997)	19[a]	1	0
Jones et al. (1979)	39	0	2
Total	202	6 (2.9%)	4 (1.9%)

N: Total number of patients with non-invasive vulvar Paget disease, VPD: vulvar Paget disease.
[a] Includes 5 cases of micro-invasion (<1 mm), the patient with an invasive recurrence did not have micro-invasive disease at time of first diagnosis.

Table 4 presents an overview of studies that looked at associations between recurrence rates and surgical margin status.

Gunn et al. performed a topographical study of VPD in 1980 (Gunn and Gallager, 1980). Four specimens from affected vulvas were examined, and it was found that the histological presence of disease extended far beyond the visible lesion. This may contribute to the difficulties in obtaining a clear margin. Multifocality of the disease may also play a part in recognising the extend of the disease.

The type of surgery may also influence the recurrence rate. It is well known that Paget cells are present in hair follicles and bulbs, which can be found deeper into the adipose tissue of the mons pubis and labia minora. A skinning vulvectomy may leave diseased hair bulbs in the patient, and it is known that laser ablation does not reach this deep.

There are no data available on the recurrence rates according to type of VPD, invasion depth or location of the disease. Topical treatment of VPD is relatively new. Therefore, publications on this topic do not report sufficient follow up for recurrence rates. Other treatment modalities have been described in such small sample sizes, that we are unable to explore this topic.

6. Prognosis and follow up

The overall 5-year survival rate for EMPD in male and female patients is 75–91% (van der Zwan et al., 2012; Hatta et al., 2008;

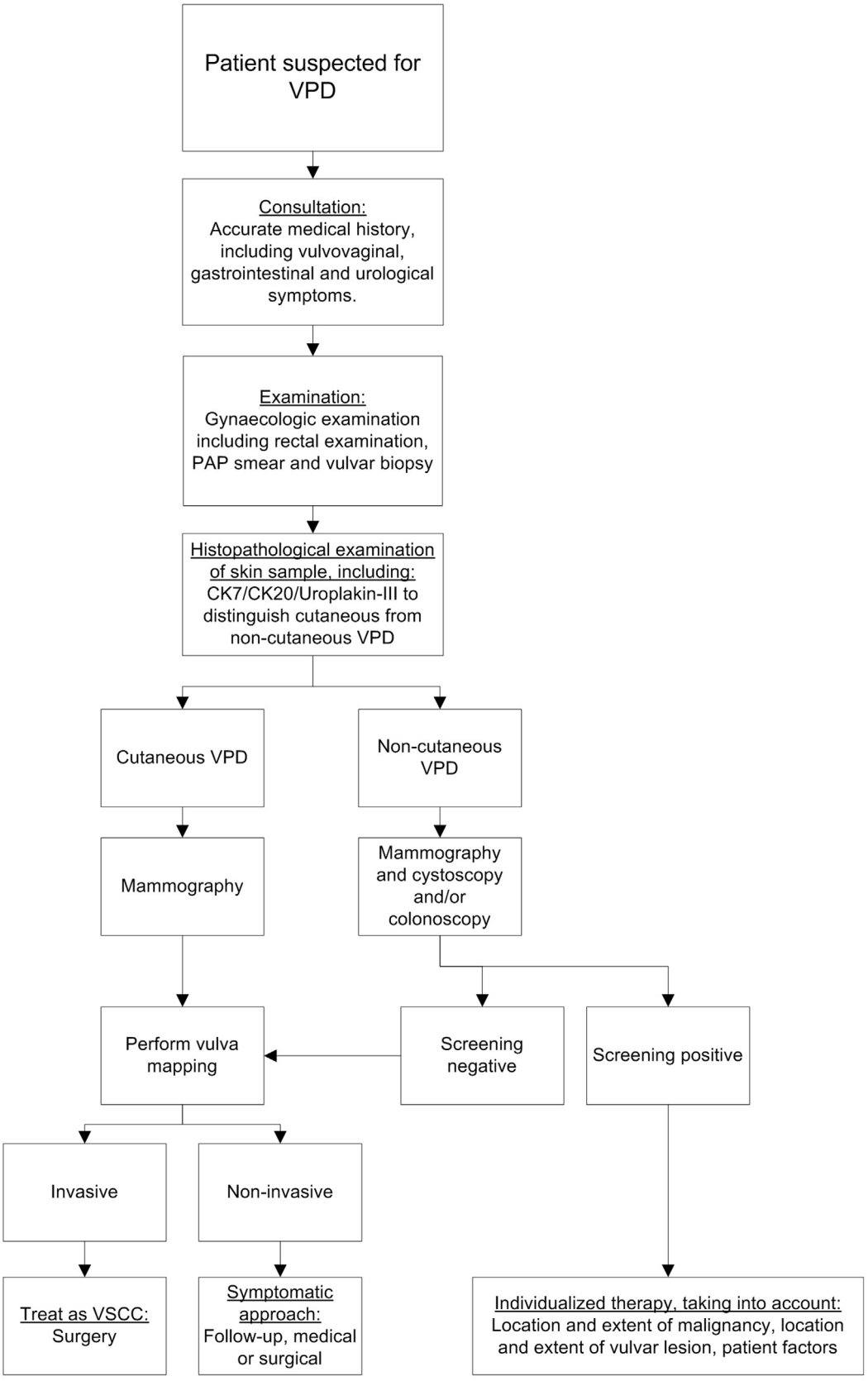

Fig. 8. Flowchart for diagnostic procedures and treatment of patients with VPD.

Ito et al., 2012). Patients with invasive Paget disease or with an associated malignancy seem to have significantly shorter survival. As a comparison, the overall 5-year survival rate for vulvar cancer is reported to be 70% (Lai et al., 2014). Hatta et al. reported on 76 male and female patients with EMPD and found that 5-year survival was 100% in the 43 patients with intraepithelial disease and 88.2% in the patients with microinvasion to the papillary dermis. Eleven patients with deep invasion did not survive for 5 years (Hatta et al., 2008). Ito et al. reported 30 patients with EMPD and showed that survival was 100% for intraepithelial disease and dermal invasion ≤1 mm. The 5-year survival rate for patients with dermal invasion >1 mm was 15% (Ito et al., 2012). Table 5 presents an overview of studies that report the number of patients who died from EMPD based on invasion depth.

Based on the currently available literature, the risk of developing invasive VPD disease or metastases after treatment for non-invasive VPD is very low (Table 6). Fanning et al. describe 2 patients with extravulvar adenocarcinoma metastases after initial non-invasive VPD (Fanning et al., 1999). Jones et al. describe 2 patients with metastases, but do not specify the location and histological type (Jones et al., 1979). Lesions with nodules, elevated CEA, deeper invasion depth, and lymph node metastases all correlate with a shorter survival time and patients with intraepidermal disease or microinvasion had significantly longer survival time than patients with invasive EMPD (Hatta et al., 2008; Ito et al., 2012).

7. Conclusion and discussion

VPD is a rare skin disease that typically occurs in elderly women. Its origin remains unclear. Wilkinson's classification is used most frequently to distinguish primary or cutaneous VPD from secondary VPD; the latter is associated with an intestinal or urological malignancy. This separation, however, has been omitted in the 2014 WHO classification (Crum et al., 2014).

The majority of patients with VPD have non-invasive cutaneous disease. About 20% of the cases involve invasive VPD, and 5.7% are associated with an underlying vulvar adenocarcinoma. There is no consensus on how to distinguish between invasive VPD, VPD with an underlying associated intestinal/urological malignancy, or vulvar adenocarcinoma. Intestinal and urological malignancies might spread to the vulva in a pagetoid pattern, or Paget cells might cause an underlying malignancy.

VPD is reported to be associated with other malignancies, in our review we found that 3.2% of patients with VPD were reported to have been diagnosed with breast cancer, 2.2% with an intestinal malignancy, 3.9% with an urological malignancy. Based on these low figures, we want to raise the question on the association with breast, intestinal, and urological malignancies, as there are no studies with age matched control groups. We especially question the association with concurrent intestinal and urological malignancies, as they are reported in 1.1% of VPD patients and in 0.7% respectively. Therefore screening for all associated malignancies might be superfluous. However, as 12% of women will develop breast cancer during their lifetime, we do think that all women with VPD should undergo mammography, which is an easy and affordable test (UK, C.R., 2014). More research on this topic should be conducted to support a screening protocol.

A diagnosis of VPD is confirmed by the presence of Paget cells on histological examination. Immunohistochemical markers can be used to differentiate between cutaneous and non-cutaneous VPD, and may serve as a decision aid in the work-up of patients with VPD. Invasive disease should be excluded by accurate histological examination or by vulvar mapping. The risk of progression into invasive VPD or to metastasis after treatment for non-invasive VPD is low (2.8% and 1.9%, respectively), and the prognosis of non-invasive VPD is excellent. We therefore suggest that aggressive surgical treatment can be avoided in cases of non-invasive VPD. There seems to be a place for topical treatment, and sometimes more symptomatic treatment could be considered. Because of the lack of literature on SLN in VPD, there is no place for SLN procedures in VPD. In case of invasive VPD >1 mm, standard treatment of the groin area should consist of uni- or bilateral inguinofemoral lymphadenectomy.

The risk of recurrence after standard surgical treatment is high i.e. about 35% for non-invasive VPD. The use of topical imiquimod cream for the treatment of VPD shows promising results in small case series, but more research is needed before definite conclusions can be drawn. One ongoing study on this topic is registered at clinicaltrials.gov (NCT00504023); which is currently not recruiting. Our group has started an observational trial in 20 patients with non-invasive VPD and is currently recruiting patients (NCT02385188).

Based on the results of this review, we suggest that the work-up of VPD patients should include a consultation that addresses symptoms that could indicate an underlying intestinal or urological malignancy. A full gynaecological examination should be performed, including rectal examination. A pap smear can be performed if no recent results are available, and a vulvar biopsy should be performed to confirm the VPD diagnosis. The immunohistochemical expression pattern can be used to distinguish primary from secondary VPD. Screening for an associated locoregional malignancy should be performed in non-cutaneous VPD, or if the patient has symptoms of a malignancy elsewhere. Even though the risk of progression into invasive VPD is small, invasion should be excluded in all patients by vulvar mapping.

Given its aggressive clinical behaviour, invasive VPD should be treated similarly to vulvar SCC. However, patients with non-invasive VPD can be treated with a symptomatic approach that should be individualized. In case of non-cutaneous VPD with an underlying intestinal or urological malignancy, individualized therapy should be provided. The location and extent of the malignancy and skin lesion should be taken into account along with symptoms and patient factors. We therefore propose a flowchart, based on the information reported in this review, which is intended to function as a supportive decision aid (Fig. 8). The treatment of patients with VPD should be individualized, taking into account the size and location of the lesion, the symptoms it causes, and individual patient factors.

Conflict of interest

The authors declare no conflicts of interest.

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None.

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Biographies

Michelle van der Linden attended Medical School at the Radboud University in Nijmegen, the Netherlands. She has done research on luteal phase support at the Menstrual Disorder and Subfertility Group of the Cochrane Collaboration as a part of her Masters degree. After her graduation in 2014 she started working as a Ph.D.-student at the Department of Obstetrics and Gynaecology (subdivision Gynaecologic Oncology) of the Radboud University Medical Centre in Nijmegen, the Netherlands.

Kim A. P. Meeuwis completed the first academic year of Medical Biology in 2002 and finished Medical School in 2008 at the Radboud University Nijmegen. Thereafter, she started working as a Ph.D.-student on a collaborative research project of both the departments of Dermatology and Obstetrics & Gynaecology (subdivision Gynaecologic Oncology) of the Radboud University Nijmegen Medical Centre in Nijmegen. In 2014, she successfully defended her thesis "Clinical studies on genital psoriasis and HPV-related lesions, a multidisciplinary approach". She currently works as a resident at the department of Dermatology of the Radboud University Medical Center in Nijmegen, the Netherlands. Genital skin pathology is her field of particular interest.

Hans Bulten attended Medical School at the Radboud University in Nijmegen, the Netherlands. He defended his thesis "Hyperproliferation and genetic instability in cervical lesions" successfully in 2000. After finishing his training as a pathologist in the Radboud University Medical Center, Nijmegen, the Netherlands in 1993 (Prof. Dr. G. P. Vooijs and Prof. Dr. D. J. Ruiter) he started working at the Department of Pathology of the Radboud University Medical Center, Nijmegen, the Netherlands. His field of interest is the pathology of the female genital tract and cytology, cervical pathology in particular. He is one of the Dutch coordinating pathologists within the National Screening Program for cervical cancer.

Tjalling Bosse attended Medical School at the University of Amsterdam (UvA). During his medical school he was trained in basic research and molecular biology at Children's Hospital Boston, Harvard Medical School (Prof. R.J. Grand). He obtained his Ph.D. degree in 2006 for his thesis: "Intestinal specific gene regulation of transcription factors Gata4 and Hnf1a in vivo". After finishing his training as a surgical pathologist in 2008 he followed a fellowship in gynaecologic pathology at Brigham and Women's Hospital, Boston (supervision Prof. Dr. Crum and Nucci). After this he was appointed as an associate professor in pathology of the female genital tract at the Leiden University Medical School (LUMC). He currently is consultant pathologist for the PORTEC trials and head of the translational studies related to these clinical trials.

Mariëtte I.E. van Poelgeest attended Medical School at Leiden University, the Netherlands. In 2007 she successfully defended her thesis "HPV16-specific cellular immunity in health and disease". After finishing her training as a gynaecologist in 2008, she followed a fellowship in gynaecologic oncology at the Department of Gynaecologic Oncology of the Leiden University Medical Center, the Netherlands (Prof. Dr. J.B.M.Z. Trimbos and Prof. Dr. A.A.P. Peters). Since 2013 she works as a gynaecologic oncologist at the Department of Gynaecologic Oncology of the Leiden University Medical Center. Het fields of special interest and research include vulvar pathology and immunotherapy of HPV16-induced genital disease.

Joanne A. de Hullu attended Medical School at the State University in Groningen, the Netherlands. After finishing her training as a gynaecologist in 1998, she followed a fellowship in gynaecologic oncology at the Department of Gynaecologic Oncology of the University Medical Centre Groningen, the Netherlands (Prof. Dr. J.G. Aalders and Prof. Dr. A.G.J. van der Zee) and the Royal Adelaide Hospital, Australia (Dr. M. Davy). In 2002 she successfully defended her thesis "Innovations in treatment of vulvar cancer". Until 2003 she worked as a gynaecologic oncologist at the Department of Gynaecologic Oncology of the University Medical Centre Groningen. From 2003 onwards, she is working as a gynaecologic oncologist at the Department of Obstetrics & Gynaecology (subdivision Gynaecologic Oncology) of the Radboud University Medical Center in Nijmegen, the Netherlands. Currently, she is an associate professor (UHD). Her fields of special interest and research include vulvar pathology and hereditary cancer.